caloric restriction for *longevity* (CRL).

http://www.answers.com/topic/calorie-restriction

Calorie restriction, or **caloric restriction** (CR), is a dietary regimen that, when not associated with malnutrition,[1]improves age related health and slows the aging process in some animals and fungi by limiting dietary energy intake. The baseline for the restriction varies, usually being the previous, unrestricted, intake of the subjects. CR is the only dietary intervention that has been documented to increase both the median and maximum lifespan in a variety of species, among them yeast, fish, rodents, dogs and non-human primates. The life extension is varied, for mice and rats there is a 30-40% increase [2]. Even though there has been research on CR for over 70 years the mechanism by which CR works is still not well understood.[3][4] There are currently ongoing studies on primates to show if CR works on primates, and even though they are showing positive indications[3][5] it is still not certain if CR has a positive effect on longevity for primates and humans.[3][5] The effect of CR on IGF-1 serum levels seen in rodents has not been replicated in human trials.[6]

Recent research has been in favour of the hypothesis that CR works by decreasing insulin levels and thereby upregulating autophagy,[7] but CR affects many other health indicators and whether insulin is the main concern is still undecided.[2]

Calorie restriction is a common measure found in several dietary regimens, including the Okinawa diet [8] and the CRON-diet.

Contents

[hide]

Effects on humans

Positive effects

In human subjects, CR has been shown to lower cholesterol, fasting glucose, and blood pressure. In CR, energy intake is minimized, but sufficient quantities of vitamins, minerals and other important nutrients must be eaten. Vitamins and minerals can be taken in pills, which contain no calories.

A small-scale study in the US at the Washington University School of Medicine in St. Louis studied the effects following a calorie-restricted diet of 10-25% less calorie intake than the average Western diet. Body mass index (BMI) was significantly lower in the calorie-restricted group when compared with the matched group; 19.6 compared with 25.9. The BMI values for the comparison group are similar to the mean BMI values for middle-aged people in the US.[9]

All those on calorie-restricted diets experienced reductions in BMI after starting their diet. Their BMIs decreased from an average of 24 (range of 29.6 to 19.4) to an average of 19.5 (range of 22.8 to 16.5) over the course of their dieting (3-15 years). Nearly all the decrease in BMI occurred in the first year of dieting. It was found that the average total cholesterol and LDL (bad) cholesterol levels for calorie-restricted individuals were the equivalent of those found in the lowest 10% of normal people in their age group. It was found that the average HDL (good) cholesterol levels for calorie-restricted individuals were very high—in the 85th to 90th percentile range for normal middle-aged US men. These positive changes in calorie-restricted individuals were found to occur mainly in the first year of dieting.[9]

"The calorie-restricted group also fared much better than the control group in terms of average blood pressure (100/60 vs. 130/80 mm Hg), fasting glucose, fasting insulin (65% reduction), body mass index (19.6 ± 1.9 vs. 25.9 ± 3.2 kg/m^2), body fat percentage (8.7% ± 7% vs. 24% ± 8%), C-reactive protein, carotid IMT (40% reduction), and platelet-derived growth factor AB."[10]

It was found that the calorie-restricted group had remarkably low triglyceride levels. In fact, they were as low as the lowest 5% of Americans in their 20s. This is more remarkable when it is noted that the calorie-restricted individuals were actually aged between 35 and 82 years. Both systolic and diastolic blood pressure levels in calorie-restricted group were remarkably low, about 100/60, values normally found in 10-year-old children. Fasting plasma insulin concentration was 65% lower and fasting plasma glucose concentration was also significantly lower in the calorie-restricted group when compared with the comparison group." The comparison group's statistics aligned approximately with the US national average on the dimensions considered.[11] Fasting plasma insulin levels[12] and fasting plasma glucose levels[13] are used as tests to predict diabetes. The researchers also found that "excessive calorie restriction causes malnutrition and can lead to anemia, muscle wasting, weakness, dizziness, lethargy, fatigue, nausea, diarrhea, constipation, gallstones, irritability and depression". The study was published in the March 2007 issue of the Journal of American Medical Association.[9]

While compelling, these studies used borderline overweight (BMI>25) subjects as controls, which is the average in some countries but not in others. It remains unclear whether the same effects would also be observed if non-overweight subjects were used as controls.

Improved memory

A 2009 research paper showed that a calorie restricted diet can improve memory in normal to overweight elderly. The diet as well resulted in decreased insulin levels and reduced signs of inflammation.[14] Scientists believe that memory improvement in this experiment was caused by the lower insulin levels, because high insulin levels are usually associated with lower memory and cognitive function.[15] However, that relation seems to be age-specific since another study, when analyzing people older than 65, those who were underweight had a higher dementia risk than normal or overweight people.[16]

Attenuation of age-related sarcopenia

Moderate CR attenuates age-related sarcopenia in primates.[17]

Negative effects

Mortality

By persistently consuming fewer calories than the body needs to maintain itself, an individual can become underweight. One study has shown that having a BMI lower than 18, for women, is associated with significantly increased mortality from noncancer, non−cardiovascular disease causes. The results were the same when not accounting for those who were underweight because they might have been already sick or were smokers. However, the study focused solely on BMI and did not look specifically at diet.[18]

Starvation

Severe calorie restriction may result in starvation, unless metabolism is also slowed by some means. The concept of a reduced calorie diet should not be confused with anorexia nervosa or other eating disorders. If such a pattern is repeated for prolonged periods of severe caloric restriction, the body may burn lean tissue (including but not limited to muscle and collagen) along with its remaining fat reserves.[19]. The combination of starvation and the associated

lethargy and decreased physical activity can result in muscular atrophy which leads to lower quality of life.[20][21]

Beyond using lean tissue as energy source, the presence of catabolic hormones, such as cortisol, and lack of anabolic ones, such as insulin, disrupts protein synthesis, amino acid uptake and weakens the immune system.

Lack of essential nutrients

When reducing calorie intake, intake of essential nutrients may also be reduced, especially fat-soluble vitamins, which require fat for proper absorption and others nutrients generally associated with high calorie foods, such as oils, nuts, meat and dairy products.

Abnormal hair growth

When undernourished, the body slows the growth rate of hair and nails.[22]

Neuroglycopenia

Hypoglycemia can lead to neuroglycopenia.

Research history

In 1934, Mary Crowell and Clive McCay of Cornell University observed that laboratory rats fed a severely reduced calorie diet while maintaining micronutrient levels resulted in life spans of up to twice as long as otherwise expected. These findings were explored in detail by a series of experiments with mice conducted by Roy Walford and his student Richard Weindruch. In 1986, Weindruch reported that restricting the calorie intake of laboratory mice proportionally increased their life span compared to a group of mice with a normal diet. The calorie-restricted mice also maintained youthful appearances and activity levels longer and showed delays in age-related diseases. The results of the many experiments by Walford and Weindruch were summarized in their book *The Retardation of Aging and Disease by Dietary Restriction* (1988) (ISBN 0-398-05496-7).

The findings have since been accepted and generalized to a range of other animals. Researchers are investigating the possibility of parallel physiological links in humans. In the meantime, many people have independently adopted the practice of calorie restriction in some form.

Trials were set up at Washington University in 2002 and involved about thirty participants. Dr. Luigi Fontana, clinical investigator, says CR practitioners seem to be aging more slowly than the rest of us. "Take systolic blood pressure," he says. "Usually, that rises with age reliably, partly because the arteries are hardening. In my group, mean age is 55, and mean systolic blood pressure is 110: that's at the level of a 20-year-old."

A study conducted by the Salk Institute for Biological Studies and published in the journal *Nature* in May 2007 determined that the gene PHA-4 is responsible for the longevity behind calorie restriction in animals, '***with similar results expected in humans***'.[23] The discovery has given hope to the synthesising of future drugs to increase the human lifespan by simulating

the effects of calorie restriction. However, MIT biologist Leonard Guarente cautioned that "(treatment) won't be a substitute for a healthy lifestyle. You'll still need to go to the gym".[24]

The most recent study conducted by Ricki J. Colman and Richard Weindruch at the University of Wisconsin used rhesus monkeys that live an average of 27 years and a maximum of 40, found that the dieting monkeys show many beneficial signs of caloric resistance, including significantly less diabetes, cancer, and heart and brain disease. However, as some of the monkeys are expected to live another 20 years, the findings are still inconclusive. [25]

Effects of CR on different organisms

Primates

A study on rhesus macaques, funded by the National Institute on Aging, was started in 1989 at the University of Wisconsin-Madison. This study showed that caloric restriction in rhesus monkeys blunts aging and significantly delays the onset of age related disorders such as cancer, diabetes, cardiovascular disease and brain atrophy. The monkeys were enrolled in the study at ages of between 7 and 14 years; at the 20 year point, 80% of the calorically restricted monkeys were still alive, compared to only half of the controls.[26] These results bore out earlier preliminary results that showed lower fasting insulin and glucose levels as well as higher insulin sensitivity and LDL profiles associated with lower risk of atherogenesis in dietary restricted animals.[27]

Researchers at New York's Mount Sinai School of Medicine reported in 2006 that compared to monkeys fed a normal diet, squirrel monkeys on a life-long calorie-restrictive diet were less likely to develop Alzheimer's-like changes in their brains.[28] Since squirrel monkeys are relatively long-lived, definitive conclusions regarding whether or not they are aging slower are not yet available.

Mice

Studies in female mice have shown that estrogen receptor-alpha declines in the pre-optic hypothalamus as they age. The female mice that were given a calorically restricted diet during the majority of their lives maintained higher levels of ERα in the pre-optic hypothalamus than their non-calorically restricted counterparts.[29] Studies in female mice have shown that both Supraoptic nucleus (SON) and Paraventricular nucleus (PVN) lose about one-third of IGF-1R immunoreactive cells with normal aging. Old caloricly restricted (CR) mice lost higher numbers of IGF-1R non-immunoreactive cells while maintaining similar counts of IGF-1R immunoreactive cells in comparison to Old-Al mice. Consequently, Old-CR mice show a higher percentage of IGF-1R immunoreactive cells reflecting increased hypothalamic sensitivity to IGF-1 in comparison to normally aging mice.[30][31]

Rats

Seventy years ago, McCay CM, *et al.*, discovered that reducing the amount of calories fed to rats nearly doubled their lifespan. For the last seventy years, scientists have proposed hypotheses as to why. Some explanations included reduced cellular divisions, lower metabolism rates, and reduced production of free radicals generated by metabolism.

Yeast

Fungi model are very easy to manipulate and many crucial steps toward the understanding of aging has been done with it. Many studies were published in budding yeast and fission yeast to analyse the cellular mechanisms behind the increased longevity due to calorie restriction. First, calorie restriction is often called dietary restriction because the same effects on life span can be reached only by changing the nutrient quality without changing the amount of calorie. The data from Dr Guarente, Dr Kennedy, Dr Jazwinski, Dr Kaeberlein, Dr Longo, Dr Shadel, Dr Nyström, Dr Piper and others showed that genetic manipulations in nutrient signaling pathways could mimic the effects of dietary restriction. In some case dietary restriction needs mitochondrial respiration to increase longevity (chronological aging) and in some other case not (replicative aging). Nutrient sensing in yeast controls stress defense, mitochondrial functions, Sir2 and others. These functions are all known to regulate aging. Genes involved in these mechanisms are : TOR, PKA, SCH9, MSN2/4, RIM15, SIR2,... [32][33][34][35][36]

Drosophila

Research in 2003 by Mair et al. showed that calorie restriction extends the life of fruit flies of any age with instantaneous effects on death rates.[37]

Caenorhabditis elegans

Recent work in *Caenorhabditis elegans* has shown that restriction of glucose metabolism extends life span by primarily increasing oxidative stress to exert an ultimately increased resistance against oxidative stress, a process called (mito)hormesis.[*citation needed*]

Why might CR increase longevity?

There have been many theories as to how CR works, and many of them have fallen out of favor or been disproved. These include reduced basal metabolic rate, developmental delay, the control animals being gluttons, and decreased glucocorticoid production.

(Mito)hormesis

Main article: Hormesis

A small number of researchers in the CR field are now proponents of a new theory known as the "Hormesis hypothesis of CR" also known as the "Mitohormesis hypothesis of CR" due to the likely involvement of mitochondria. Southam and Ehrlich (1943) reported that a bark extract that was known to inhibit fungal growth, actually stimulated growth when given at very low concentrations. They coined the term "hormesis" to describe such beneficial actions resulting from the response of an organism to a low-intensity biological stressor. The word "hormesis" is derived from the Greek word "hormaein" which means "to excite".

The (Mito)hormesis hypothesis of CR proposes that the diet imposes a low-intensity biological stress on the organism, which elicits a defense response that helps protect it against the causes of aging. In other words, CR places the organism in a defensive state so that it can survive adversity, and this results in improved health and longer life. This switch to a defensive state may be controlled by longevity genes (see below).

While the (Mito)hormesis hypothesis of CR was a purely hypothetical concept until late 2007, recent work by Michael Ristow's group in a small worm named Caenorhabditis elegans has shown that restriction of glucose metabolism extends life span by primarily increasing oxidative stress to exert an ultimately increased resistance against oxidative stress.[38] This is probably the first experimental evidence for hormesis being an essential cause for extended life span following CR.

Insulin signaling

See also: Insulin#Physiological effects

Lowering of the concentration of insulin and substanses which are related to insulin, e.g Insulin-like growth factor 1 and Growth hormone has been shown to upregulate autophagy, the repair mechanism of the cell [4]

Early work in *C. elegans* (see Cynthia Kenyon) and more recent research in mice has suggested (see Matthias Bluher, C. Ronald Kahn, Barbara B. Kahn, *et al.*) that it is not only reduced calorie intake which influences longevity. This was done by studying animals which have their metabolism changed to reduce activity of the hormone insulin or downstream elements in its signal transduction, consequently retaining the leanness of animals in the earlier studies. It was observed that these animals can have a normal dietary intake, but have a similarly increased lifespan. This suggests that lifespan is increased for an organism if it can remain lean and if it can avoid any excess accumulation of adipose tissue: if this can be done while not diminishing dietary intake (as in some minority eating patterns, see e.g. Living foods diet or Joel Fuhrman) then the 'starvation diet' anticipated as an impossible requirement by earlier researchers is no longer a precondition of increased longevity.[*citation needed*]

The extent to which these findings may apply to human nutrition and longevity is as noted above under investigation. A paper in the Proceedings of the National Academy of Sciences, U.S.A. in 2003 showed that practitioners of a CR diet had significantly better cardiovascular health.[39] Also in progress are the development of CR mimetic interventions.[40]

Sir2/SIRT1 and resveratrol

Sir2 or "silent information regulator 2" is a longevity gene, discovered in baker's yeast cells, that extends lifespan by suppressing DNA instability (see Sinclair and Guarente, Cell, 1997).[41] In mammals Sir2 is known as SIRT1. Recent discoveries have suggested that the gene Sir2 might underlie the effect of CR. In baker's yeast the Sir2 enzyme is activated by CR, which leads to a 30% lifespan extension. David Sinclair at Harvard Medical School, Boston, showed that in mammals the SIRT1 gene is turned on by a CR diet, and this protects cells from dying under stress.[42] An article in the June 2004 issue of the journal *Nature* showed that SIRT1 releases fat from storage cells.[43]. Sinclair's lab reported that they have found small molecules (e.g. resveratrol) that activate Sir2/SIRT1 and extend the lifespan of yeast,[44] nematode worms, fruit flies,[45] and mice consuming a high caloric diet.[46] The effect of resveratrol on lifespan in C. elegans and Drosophila was recently re-investigated by D. Gems and L. Partridge. After performing the experiment numerous times, it was concluded that the lifespan extending effects of resveratrol are not consistent, and the previously reported lifespan increases were in fact due to natural variability in C. elegans lifespans (Effects of resveratrol on lifespan in Drosophila melanogaster and Caenorhabditis elegans.Mech Ageing Dev. 2007 Oct;128(10):546-52. Epub 2007 Aug 14.PMID: 17875315 [PubMed - indexed for MEDLINE). No lifespan extension in Drosophila was reported. A more recent study from Sinclair and De Cabo also concluded that resveratrol does not extend

lifespan of normal mice (Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span.Cell Metab. 2008 Aug;8(2):157-68. Epub 2008 Jul 3.) An Italian group headed by Antonio Cellerino showed that resveratrol extends the lifespan of a vertebrate fish by 59%.[47] In the yeast, worm, and fly studies, resveratrol did not extend lifespan if the Sir2 gene was mutated. A group of researchers headed by Matthew Kaeberlein and Brian Kennedy (who just like Sinclair, were trained in the lab of L. Guarente) at the University of Washington Seattle believe that Sinclair's work on resveratrol is an artifact and that the Sir2 gene has no relevance to CR.[48]

Gurarente has recently published that behavior associated with caloric restriction did not occur when Sirt1 knockout mice were put on a calorie restricted diet, the implication being that Sirt1 is necessary for mediating the effects of caloric restriction. However, the same paper also reported that the biochemical parameters thought to mediate the lifespan extending effects of calorie restriction (reduced insulin, igf1 and fasting glucose), were no different in normal mice and mice lacking Sirt1. Whether the lifespan-extending effect of CR was still evident in Sirt1 knockout mice was not reported in that study.

According to Sinclair's data, Sirtuins (SirT1, Sir2, ...) are involved in calorie restriction-mediated effects on longevity and so are beneficial for longevity [49] but in some case these enzymes can be pro-aging and appeared detrimental for longevity. That was seen by Valter Longo and coworkers in yeast and mammals. [50][51][52]

Sirtris Pharmaceuticals, Inc., a GlaxoSmithKline-owed biotechnology company based in Cambridge, MA co-founded by Sinclair, is developing resvertrol and other SIRT1 activators for human use. Because life-span extension is not an FDA-approvable indication, the company is developing SIRT1 activators for the treatment of diseases associated with aging including type 2 diabetes and cancer.

DHEA

While calorie restriction has been shown to increase DHEA in primates (PMID 12543259), it has not been shown to increase DHEA in post-pubescent primates (PMID 15247063).

Free radicals and glycation

Two very prominent theories of aging are the free radical theory and the glycation theory, both of which can explain how CR could work. With high amounts of energy available, mitochondria do not operate very efficiently and generate more superoxide. With CR, energy is conserved and there is less free radical generation. A CR organism will be less fat and require less energy to support the weight, which also means that there does not need to be as much glucose in the bloodstream. Less blood glucose means less glycation of adjacent proteins and less fat to oxidize in the bloodstream to cause sticky blocks resulting in atherosclerosis. Type II Diabetics are people with insulin insensitivity caused by long-term exposure to high blood glucose. Obesity leads to type 2 diabetes. Type 2 diabetes and uncontrolled type 1 diabetes are much like "accelerated aging", due to the above effects. There may even be a continuum between CR and the metabolic syndrome.

In examining Calorie Restriction with Optimal Nutrition, it is observed that with less food, and equal nutritional value, there is a higher ratio of nutrients to calories. This may lead to more ideal essential and beneficial nutrient levels in the body. Many nutrients can exist in excess to their need, without side effects as long as they are in balance and not beyond the

body's ability to store and circulate them. Many nutrients serve protective effects as antioxidants, and will be at higher levels in the body as there will be lower levels of free radicals due to the lower food intake.

Calorie Restriction with Optimal Nutrition has not been tested in comparison to Calorie Excess with Optimal Nutrition. It may be that with extra calories, nutrition must be similarly increased to ratios comparable to that of Calorie Restriction to provide similar antiaging benefits.

Stated levels of calorie needs may be biased towards sedentary individuals. Calorie restriction may be no more than adapting the diet to the body's needs.

Although aging can be conceptualized as the accumulation of damage, the more recent determination that free radicals participate in intracellular signaling has made the categorical equation of their effects with "damage" more problematic than was commonly appreciated in years past.

Papers on CR in yeast: dismissing increased respiration

In late 2005 Matt Kaeberlein and Brian Kennedy published two important papers on calorie restriction in yeast. In the first, they show that calorie restriction does not increase respiration in yeast (in contrast with the model proposed by Lenny Guarente). In the second, calorie restriction decreased the activity of TOR, a nutrient-responsive signaling protein already known to regulate aging in worms and flies. This paper is the first to directly link TOR to calorie restriction.

Papers on CR in *C. elegans*: promoting increased respiration

In late 2007 Michael Ristow published a paper on calorie restriction in *C. elegans*.[38] Here the authors show that calorie restriction does increase respiration in *C. elegans* as previously described for yeast (in support of the model proposed by Lenny Guarente, although independent of Sir2.1).

Evolution

It has been recently argued that during years of famine, it may be evolutionarily desirable for an organism to avoid reproduction and to upregulate protective and repair enzyme mechanisms to try to ensure that it is fit for reproduction in future years. This seems to be supported by recent work studying hormones.[53]

Objections

No benefit to houseflies, overfed model organisms

A significant opposition to caloric restriction comes from experiments that show that it has no benefits in the housefly.[54] The authors claim that the widely purported effects of calorie restriction may be because a diet containing more calories can increase bacterial proliferation, or that the type of high calorie diets used in past experiments have a stickiness, general composition, or texture that reduces longevity.

Another related theory says that some of the calorie-restriction effects are artifacts, because the laboratory model organisms are kept at non-physiological high calorie diets. This would mean, that calorie restriction simply means mimicking a natural environment energy supply [55]

Catabolic damage

A major conflict with calorie restriction is that adequate calorie intake is needed to prevent catabolizing the body's tissues. A body in a catabolic state promotes the degeneration of muscle tissue, including the heart.

Physical activity testing biases

While some tests of calorie restriction have shown increased muscle tissue in the calorie-restricted test subjects, how this has occurred is unknown.[*citation needed*] Muscle tissue grows when stimulated, so it is possible that the calorie-restricted test animals exercised more than their companions on higher calories. The reasons behind this may be that animals enter a foraging state during calorie restriction. In order to control this variable, such tests would need to be monitored to make sure that levels of physical activity are equal between groups.

Insufficient calories and amino acids for exercise

Exercise has also been shown to increase health and lifespan and lower the incidence of several diseases. Calorie restriction comes into conflict with the high calorie needs of athletes, and may not provide them adequate levels of energy or sufficient amino acids for repair, although this is not a criticism of CR per se, since it is certainly possible to be an unhealthy athlete, or an athlete destined to die at a young age due to poor diet, stresses, etc. Moreover, in experiments comparing CR to exercise, CR animals live much longer than exercised animals.[56]

Benefits only the young

There is evidence to suggest that the benefit of CR in rats might only be reaped in early years. A study on rats which were gradually introduced to a CR lifestyle at 18 months showed no improvement over the average lifespan of the Ad libitum group.[57] This view, however, is disputed by Spindler, Dhahbi, and colleagues who showed that in late adulthood, acute CR partially or completely reversed age-related alterations of liver, brain and heart proteins and that mice placed on CR at 19 months of age show increases in lifespan.[58] The Wisconsin rhesus monkey study showed increased survival rates and decreased diseases of aging from caloric restriction even though the study started with adult monkeys.[59]

Possible contraindications

Both animal and human research suggest BUD CR may be contraindicated for people with amyotrophic lateral sclerosis (ALS). Research on a transgenic mouse model of ALS demonstrates that CR may hasten the onset of death in ALS. Hamadeh *et al.* therefore concluded: "These results suggest that CR diet is not a protective strategy for patients with amyotrophic lateral sclerosis (ALS) and hence is contraindicated."[60] Hamadeh *et al.* also note two human studies[61][62] that they indicate show "low energy intake correlates with death in people with ALS." However, in the first study, Slowie, Paige, and Antel state: "The reduction in energy intake by ALS patients did not correlate with the proximity of death but

rather was a consistent aspect of the illness." They go on to conclude: "We conclude that ALS patients have a chronically deficient intake of energy and recommended augmentation of energy intake." (PMID 8604660)

Previously, Pedersen and Mattson also found that in the ALS mouse model, CR "accelerates the clinical course" of the disease and had no benefits.[63] Suggesting that a calorically dense diet may slow ALS, a ketogenic diet in the ALS mouse model has been shown to slow the progress of disease.[64] More recently, Mattson *et al.* opine that the death by ALS of Roy Walford, a pioneer in CR research and its antiaging effects, may have been a result of his own practice of CR.[65] However, as Mattson *et al.* acknowledge, Walford's single case is an anecdote that by itself is insufficient to establish the proposed cause-effect relation.

Negligible effect on larger organisms

Another objection to CR as an advisable lifestyle for humans is the claim that the physiological mechanisms that determine longevity are very complex, and that the effect would be small to negligible in our species.[66]

Intermittent fasting as an alternative approach

Main article: Intermittent fasting

Studies by Mark P. Mattson, Ph. D., chief of the National Institute on Aging's (NIA) Laboratory of Neurosciences, and colleagues have found that intermittent fasting and calorie restriction affect the progression of diseases similar to Huntington's disease, Parkinson's disease, and Alzheimer's disease in mice (PMID 11119686). In one study, rats and mice ate a low-calorie diet or were deprived of food for 24 hours every other day (PMID 12724520). Both methods improved glucose metabolism, increased insulin sensitivity, and increased stress resistance. Researchers have long been aware that calorie restriction extends lifespan, but this study showed that improved glucose metabolism also protects neurons in experimental models of Parkinson's and stroke.

Another NIA study found that intermittent fasting and calorie restriction delays the onset of Huntington's disease-like symptoms in mice and prolongs their lives (PMID 12589027). Huntington's disease (HD), a genetic disorder, results from neuronal degeneration in the striatum. This neurodegeneration results in difficulties with movements that include walking, speaking, eating, and swallowing. People with Huntington's also exhibit an abnormal, diabetes-like metabolism that causes them to lose weight progressively.

This NIA study compared adult HD mice who ate as much as they wanted with HD mice who were kept on an intermittent fasting diet during adulthood. HD mice possess the abnormal human gene huntingtin and exhibit clinical signs of the disease, including abnormal metabolism and neurodegeneration in the striatum. The mice on the fasting program developed clinical signs of the disease about 12 days later and lived 10 to 15% longer than the free-fed mice. The brains of the fasting mice also showed less degeneration. Those on the fasting program also regulated their glucose levels better and did not lose weight as quickly as the other mice. Researchers found that fasting mice had higher brain-derived neurotrophic factor (BDNF) levels. BDNF protects neurons and stimulates their growth. Fasting mice also had high levels of heat-shock protein-70 (Hsp70), which increases cellular resistance to stress.

Another NIA study compared intermittent fasting with cutting calorie intake. Researchers let a control group of mice eat freely (ad libitum). Another group was fed 60% of the calories that the control group consumed. A third group was fasted for 24 hours, then permitted to free-feed. The fasting mice didn't cut total calories at the beginning and the end of the observation period, and only slightly cut calories in between. A fourth group was fed the average daily intake of the fasting mice every day. Both the fasting mice and those on a restricted diet had significantly lower blood sugar and insulin levels than the free-fed controls. Kainic acid, a toxin that damages neurons, was injected into the dorsal hippocampus of all mice. Hippocampal damage is associated with Alzheimer's. Interestingly, the scientists found less damage in the brains of the fasting mice than in those that ate a restricted diet, and most damage in mice with an unrestricted diet. But the control group which ate the average daily intake of the fasting mice also showed less damage than the mice with restricted diet.[67]

Another Mattson study[68] in which overweight adult asthmatics followed alternate day calorie restriction (ADCR) for eight weeks showed marked improvement in oxidative stress, inflammation, and severity of the disease. Evidence from the medical literature suggests that ADCR in the absence of weight loss prolongs lifespan in humans[69].

See also

- Calorie Restriction Society
- Intermittent fasting
- Fasting
- Resveratrol
- Starvation
- Very Low Calorie Diet
- Okinawa diet
- Mitohormesis
- Life extension
- Lloyd Demetrius
- CRON-diet

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v • d • e

Longevity

Terminology	Centenarian · Supercentenarian · Maximum life span · Life extension · Life expectancy
Issues	Longevity claims · Longevity myths
Lists	Oldest people · Oldest people by year of birth · 100 verified oldest people (100 verified oldest men · 100 verified oldest women) · Centenarians · National longevity recordholders · Living national longevity recordholders · Oldest people by U.S. state · Oldest living people by U.S. state · Life extension-related topics · Living supercentenarians Supercentenarians by continent (African · European) · By nation or subregion (American · Australian · British · Canadian · Dutch · French · German · Italian · Japanese · Nordic · Portuguese · Spanish)
War-related Lists	Last living war veterans · Last war veterans (European · United States · Canadian) · World War I (Surviving veterans · Last surviving veterans by country) · Surviving veterans of the Spanish Civil War
Non-human	Long-living organisms · List of oldest trees

See also Gerontology · Ageing · Extreme longevity tracking

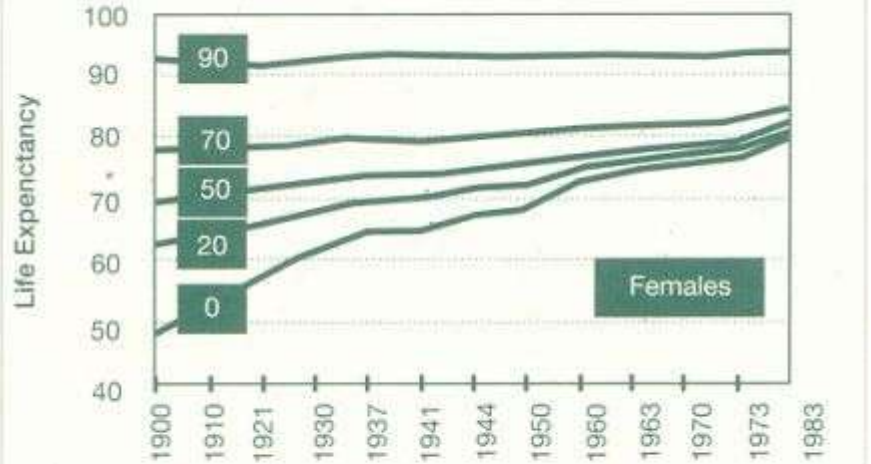
Diet, Lifestyle and Life Expectancy …

Reliable data from a number of sources, such as the World Health Organization and the Swiss Federal Office of Statistics, concerning changes in population life expectancy in various countries of the world shows that life expectancy, which is defined as the age to which half the

population of a given age can expect to live, has been increasing for many years and is higher today than it has ever been in the recorded past. This is a very positive development for all who share the ever increasing interest in diet, health and lifestyle.

To illustrate this, the changes in life expectancy for Swiss women, from the beginning of this century is shown in Figure 1. The data shows that, since 1900, life expectancy in Switzerland has increased appreciably and consistently in all but the highest age group (at 90 years of age). Similar increases have also occurred for men over the same period.

Figure 1



Changes in Life Expectancy in Switzerland since 1900: from Birth, and at 20, 50, 70 and 90 Years of Age

Changes in Life Expectancy in Switzerland since 1900

These improvements that have occurred in Switzerland during this century are not exceptional. Figures 2, 3 and 4, based on data from WHO, show that similar changes have occurred in other European countries (such as Italy and the United Kingdom), as well as in non-European countries (such as Japan and the USA).

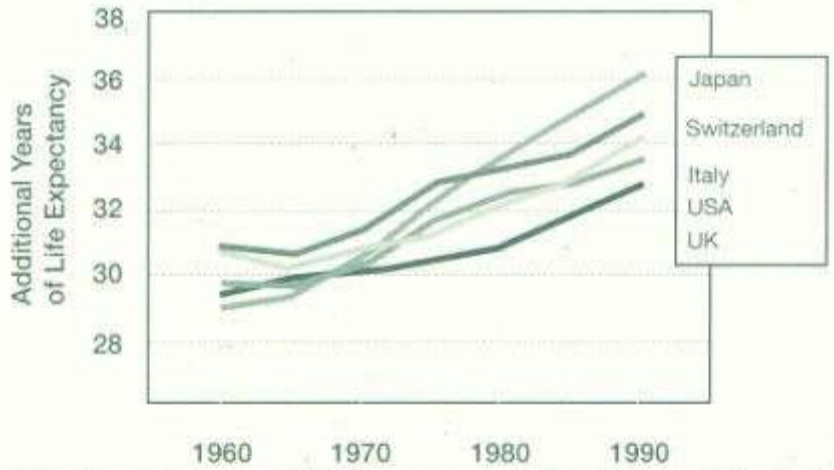
Figure 2 shows that the prospects from birth for living longer have increased in all five countries by around 5 years. Over the same period, life expectancy at the age of 45 has also increased in each country by more than 3 years (Figure 3), and by a similar amount among people aged 65, (Figure 4). The interesting feature of this data is that the increase in life expectancy of adults, at 45 and 65 is not a great deal less

than the increase from birth (5 years at birth versus around 3 years for the adult age groups).

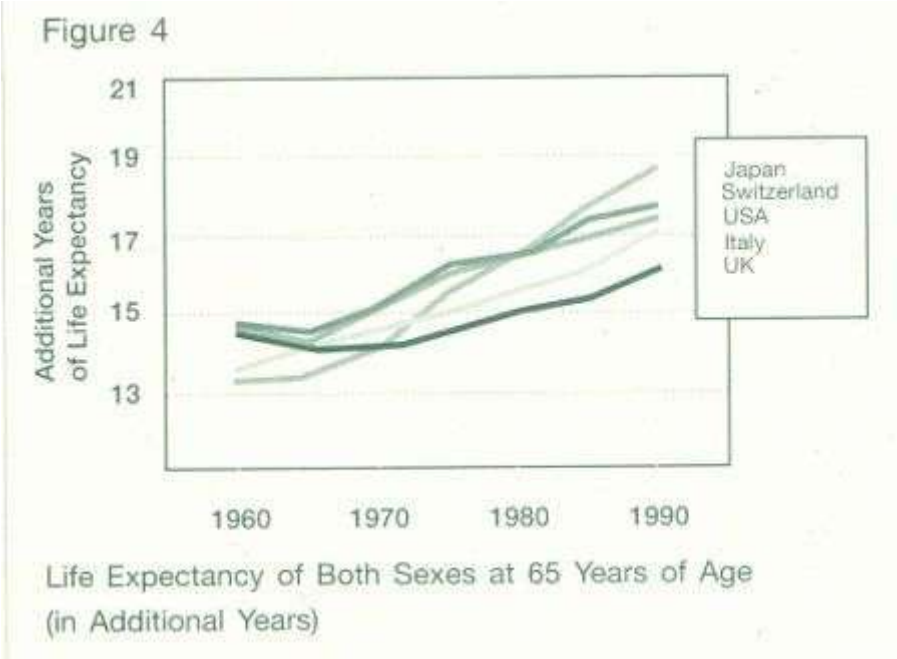
Figure 2

Life Expectancy of Both Sexes at Birth (in Years)

Figure 3

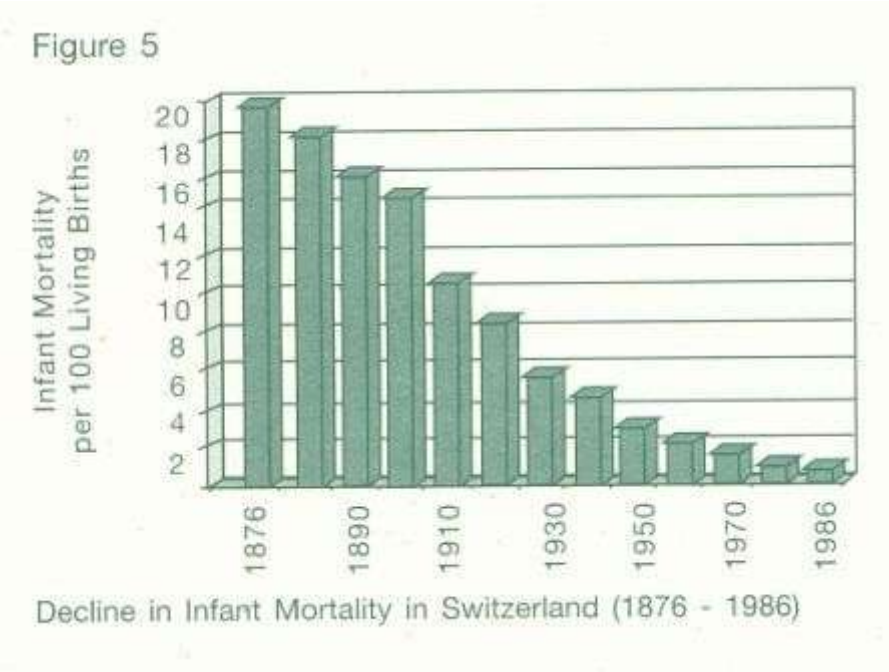


Life Expectancy of Both Sexes at 45 Years of Age (in Additional Years)



The Major Components

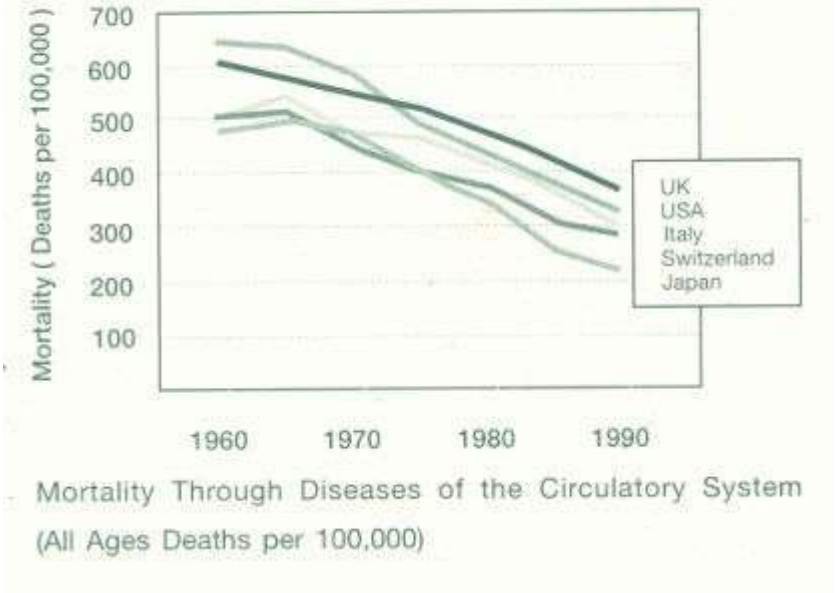
With respect to infants, the increase in life expectancy has come about because of a marked decline in infant mortality during the first year of life. This is illustrated in Figure 5, by data for Swiss infants. The rate has decreased from 19.7% of total live births in 1876, to 0.7% in 1986 and is now probably nearing its limit.



In adults, the significant change is a decline in the incidence of circulatory diseases, the most notable of which is heart disease. Heart disease is the principal cause of death in the world. The mortality rate from this type of disease has declined substantially over the last 30 years in many countries

(Figure 6). In absolute numbers this is a decrease of around 240 deaths per 100,000 of the population per year during the thirty-year period. It is likely that the trend will continue.

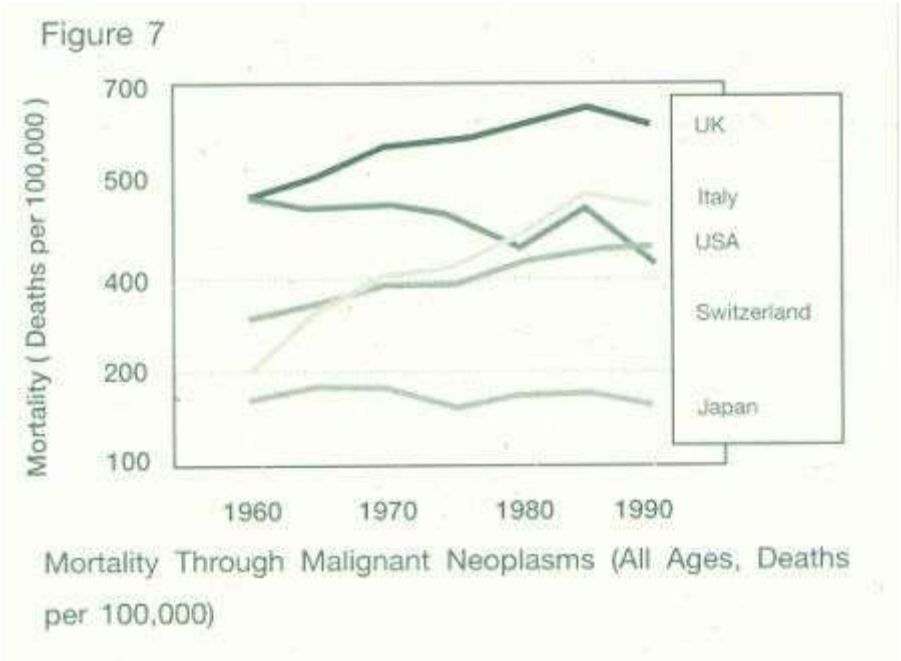
Figure 6



Mortality Through Diseases of the Circulatory System (All Ages Deaths per 100,000)

The second principal cause of death is cancer. Mortality over the last 30 years from cancer has either stabilised (e.g. Japan and Switzerland) or is increasing slightly (e.g., Italy, USA and UK). In absolute terms, the overall situation for the five countries shown in Figure 7 is a slight increase in mortality of around 11 deaths per 100,000 of the population between 1960 and 1990.

Figure 7



Mortality Through Malignant Neoplasms (All Ages, Deaths per 100,000)

The reason why

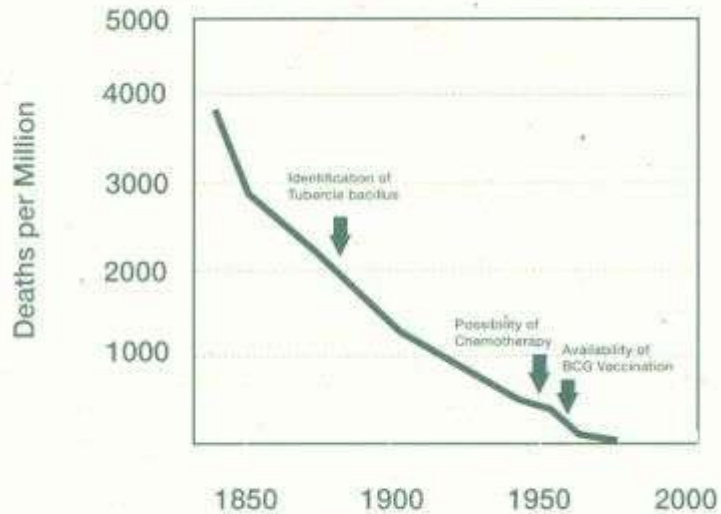
It is, of course, impossible to attribute the increase in life expectancy during the last 100 years or so to any one particular reason or factor. Improvement in medical care has without doubt played a prominent part in the decline of infant mortality. More advanced obstetric techniques, better perinatal and postnatal care, as well as increased vaccination against fatal infant diseases such as measles, diphtheria, polio and whooping cough, have all contributed to the overall improvement.

With adults, as for infants, there has also been a significant, and undeniable, contribution from better medical treatment but the situation is not as clear. Several studies have been done to evaluate the relative contribution of preventive and therapeutic practices to the reduction of, for example, cardiovascular mortality. Most of them have concluded that prevention and treatment have had almost equal impact. Factors in prevention have included, better food availability, variety and balance, more appropriate nutrition, recognition of the benefits of physical activity and a reduction in smoking habits.

The genetic aspect is also important as illustrated by the fact that in virtually every population in the world, women live longer than men - by an average of 7.0 years when estimated from birth and 5.4 years at 50 years of age. The exact explanation for this phenomenon is not known. Since this occurs almost universally, it would seem to be irrespective of differences in culture, diet or lifestyle.

Non-medical factors, such as better living conditions and hygiene, better food availability, variety and balance and improved nutrition, have also played a significant role but direct and clear evidence for their individual importance is difficult to obtain. Indirectly, however, their potential importance can be judged by the fact that declines in mortality from certain diseases have preceded medical advances in the treatment of the particular diseases. An example of this is tuberculosis (McKeown, 1976). Figure 8 shows that the mortality from tuberculosis in England and Wales, which was very high at the beginning of the 19th century, had declined by about 50% by 1880, the year that the causative tubercle bacillus itself was first identified. Mortality had substantially declined even further by the mid 20th century, when the first effective treatment and vaccines were developed.

Figure 8



The Fall in Deaths from Tuberculosis from 1838 to 1970

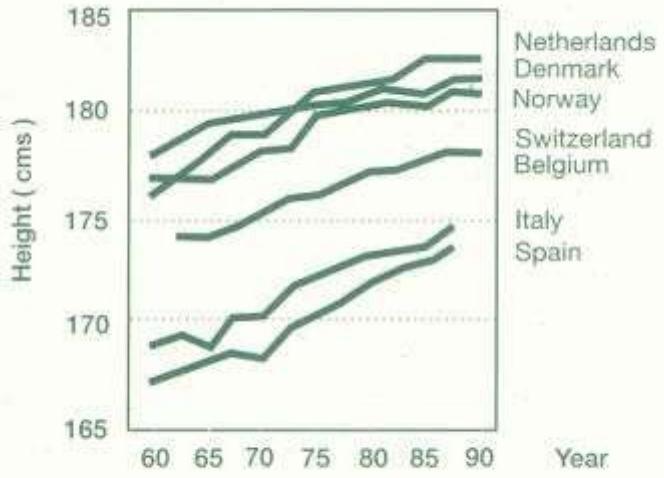
In the case of tuberculosis, therefore, the advancement of medicine was obviously secondary to that of other changes occurring within this particular population. Among the likely explanations for the decline in tuberculosis before the advent of medical treatment, are improved housing conditions and better hygiene.

The influence of food availability and nutrition in promoting health is no longer news and it is generally accepted that these factors have also played some role in the observed increases in life expectancy.

Again direct evidence for this is very difficult to find but there certainly have been improvements in nutritional status in many populations over the same period of time. Changes of body height may suggest a correlation.

The height of army conscripts in Europe, for example, has increased markedly since 1960 (Figure 9). Although a difference in height has always existed between the countries (north-south bias), in all of them the average height of the conscripts increased between 5-8 cm during the 30 year period shown in the figure.

Figure 9



The Increase in Height of 18-Year Old Army Conscripts (1960-1990)

The Future

The question for the future is whether there is an upper limit to human life expectancy and, if there is, when it will be reached-in the next decade, some- time during the 21st century, or perhaps even never? Theoretical estimations (Olshansky et al., 1990), how- ever, put the maximum life expectancy from birth at 85 years of age for any population of both men and women. Today, the average for many European populations stands at between 77-79 years. Are Europeans nearing their maximum limit? Only time will tell.

Some Conclusions

It is obvious that many components have been involved in making our lives safer and healthier. This conclusion is by no means new. Hippocrates, stated something similar over 2,000 years ago - in the 5th century BC:

"Positive health requires knowledge of man's primary constitution and the powers of various foods, both those natural to them and those resulting from human skills. But eating alone is not enough for health. There must be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the seasons of the year, the changes of the winds, the age of the individual and the situation of his home".

Interestingly, Hippocrates incorporates almost every element that we now consider important for improving health and increasing our chances of longer life - namely, genetic makeup, food availability (both fresh and

processed), nutrition, exercise, sanitation and hygiene, the weather and a subtle reference to medicine.

In conclusion, it would appear that, when judged by changes in life expectancy, health in our modern society is improving all the time and is not, as is often suggested, getting worse. Progress in medical care, better living conditions and hygiene, better food supply, improved nutrition and the importance of physical activity can be associated with this development.

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Effect of caloric restriction in non-obese humans on physiological, psychological and behavioral outcomes

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Abstract

The focus of this review is on current research involving long-term calorie restriction (CR) and the resulting changes observed in physiological and behavioral outcomes in humans. Special emphasis will be given to the first completed clinical studies which are currently investigating the effects of controlled, high-quality energy-restricted diets on both biomarkers of longevity and on the development of chronic diseases related to age in humans. Prolonged CR has been shown to extend both the median and maximal lifespans in a variety of lower species such as yeast, worms, fish, rats, and mice. Mechanisms of this CR-mediated lifespan extension are not fully elucidated, but possibly involve significant alterations in energy metabolism, oxidative damage, insulin sensitivity, and functional changes in both the neuroendocrine and sympathetic nervous systems. In this brief report, we review some of the major physiological, psychological and behavioral changes after 6 months of CR in

overweight otherwise healthy volunteers. Ongoing studies of prolonged CR in humans are now making it possible to analyze changes in “biomarkers of longevity” to unravel some of the mechanisms of its anti-aging phenomenon. With the incremental expansion of research endeavors in the area of energy or calorie restriction, data on the effects of CR in animal models and human subjects are becoming more accessible. Detailed analyses from controlled human trials involving long-term CR will allow investigators to link observed alterations from body composition down to changes in molecular pathways and gene expression, with their possible effects on the biomarkers of aging.

Keywords: Calorie restriction; Longevity; Metabolic adaptation; Quality of life; Physical activity

Article Outline

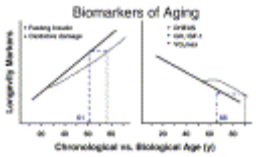

Fig. 1. Can calorie restriction improve biological age and extend chronological age? This figure summarizes some of the temptative biomarkers of aging. It is hypothesized that calorie restriction will change the biological trajectory of these biomarkers and therefore improve biological age and extend chronological age. For example, the left panel shows an individual aged 75 years. With prolonged calorie restriction it is hypothesized that fasting insulin and oxidative damage will be reduced in this individual. Therefore an individual although 75 will have a biological age 17 years younger. Similarly the individual on the right at 90 years with prolonged calorie restriction will be biologically similar to an individual aged 66 years.

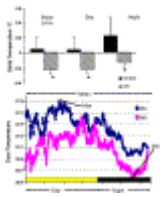

Fig. 2. The effect of calorie restriction on core body temperature. Core body temperature, a possible biomarker of longevity, was significantly reduced after six months of calorie restriction [6]. Not only did calorie restriction decrease mean 24-h temperature, minimal and maximal temperatures and the average through day and night times were also reduced. The top panel shows the mean change in 24-h temperature as well as mean temperature change during the day and night and also the mean minimal and maximal temperatures. The bottom panel shows a typical core temperature trace before and after six months of calorie restriction.

Table 1.

Summary of the physiological and psychological/behavioral responses to six months of calorie restriction in humans

Results are for the Pennington CALERIE randomized clinical trial [6].

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Caloric Restriction –

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