Caloric Restriction and Longevity

The Science and the Ascetic Experience

Linda Hotchkiss Mehta[a] **and George S. Roth**[b]

[a]*New York Academy of Sciences, New York, New York, USA*

[b]*GeroScience, Inc., Pylesville, Maryland, USA*

Aging involves a gradual increase in disorder of the systems that sustain living. Although stress is a major driver of this process, one stressor, caloric restriction (CR), is the only intervention proven to extend life span in multiple species as well as extend the persistence of those characteristics that are associated with youth. CR has been used since ancient times to enhance many of those characteristics: principally, increased activity levels and heightened levels of mental acuity. Religious ascetics, often living in monastic communities, have provided long-term opportunities to observe the effects of CR, or fasting, in humans. Tibetan medicine has made use of observations, which include that of enhanced immune function, in its dietary prescriptions. In the hopes of reaping these benefits for the general population, scientists focusing their research on the aging process have sought mimetics that will deliver the benefits of CR without requiring the discipline of fasting. The search begins with discovering the processes that make CR work.

Key words: **caloric restriction; fasting; ascetics; asceticism; aging; mimetics; longevity; sirtuins; Tibetan medicine**

Think of aging as entropy slowly at work, a gradual increase in disorder of the various systems that sustain living, and that make life worth living, which for humans in particular include systems that make cognitive processes possible.[1] Driving the devolution of somatic order is a lifetime's accumulation of stress, including such stressors as oxygen radicals, glycation, and gene repression. Both intuitively and experimentally, stress has been observed to cause damage to biological systems, so it was counterintuitive to discover that one stressor has the capacity to extend youthful qualities and life itself. This stressor is called "caloric restriction" in the laboratory and "fasting" in the monastery.

Address for correspondence: Linda H. Mehta, Senior Medical Editor, People's Medical Publishing House–USA, 2 Enterprise Drive, Suite 509, Shelton, CT 06484. Voice: 203-402-0646. lmehta@pmph-usa.com

Caloric Restriction Research—An Overview

What does make sense about caloric restriction (CR) reducing the aging effects of other stressors is that aging is a multifaceted process, so it is not surprising that something with a broad impact on the body, that is, caloric and nutritional intake, might offer an effective means of modulating its progress. Since 1935, when the effect of CR on longevity and on the retention of youthful characteristics was first observed in a scientific laboratory and reported on by Clive McKay,[2] it has been observed in several very different species: yeast,[3] fruit flies,[4,5] worms,[6] fish,[7] spiders,[8] mice,[9] hamsters,[10] and dogs.[11] Two continuing studies in monkeys are showing similar results, which suggests more strongly that it may work in humans.[12,13] For obvious reasons, it is impossible to conduct similarly controlled studies in human populations, but demographic studies

Longevity, Regeneration, and Optimal Health: Ann. N.Y. Acad. Sci. 1172: 28–33 (2009).
doi: 10.1111/j.1749-6632.2009.04409.x

have helped to answer some of the questions about the factors involved in determining human longevity.[14] It appears, for example, that human longevity is only about 25 to 30% dependent on genetic inheritance. Exercise extends median, but not ultimate, life span. So far, only caloric restriction has been demonstrated to extend both median and maximum life span in multiple species.[1,15]

Caloric restriction seems also to confer benefits beyond that of extending life span. Immune reactions in rats begin to slow down with age, but immune function retains the robustness of youth in rats kept on a calorie-restricted diet. Likewise, older rats (beginning at about one year of age) metabolize glucose less efficiently, synthesize proteins more slowly, lose muscle mass more rapidly, and even learn more slowly. These functions remain in a youthful state much longer in genetically identical CR animals. The monkey studies show similar results. The early observations by McKay and others did not include these metabolic analyses, but the animals *looked* younger—their coats were healthier and they were more active than their age-cohort of animals fed *ad libitum*. Later studies demonstrated the retention of learning skills characteristic of younger animals through CR.[16]

Fasting in Human History

Simple observation led to McKay's discovery that rats on a low-calorie, yet nutritionally optimal diet lived longer than rats fed *ad libidum*. Before modern times, the only scientific method available was direct experience, simple experimentation, and observation, but our forebears honed those tools to a fine edge. Their conclusions based on those methods have often turned out to be surprisingly accurate, at least in broad terms, thanks to their patient observational skills.

The first observations of the effects of fasting surely came naturally enough to early *Homo sapiens* through direct experience; or maybe it was the effects of *feasting* on the first truly large-animal kills that made them aware of the contrast between full-stomach lethargy and the heightened alertness and enhanced energy of the fast. These benefits of fasting offer clear advantages for the next successful hunt. Fasting, or caloric restriction, would need to have clear and rather immediate benefits, otherwise few would willingly subject themselves to it. Eating is pleasurable, and a more fundamental requirement for sustaining life than that other great drive, sexual reproduction; both responses are centered in brain regions associated with endogenous reward, but also with euphoric and other pleasant emotion.[17]

The discipline of fasting was likely first practiced by hunters and warriors as part of their regimen to prepare for the hunt or for battle and was adopted later by ancient athletes and religious ascetics. The origin of the word *ascetic* is the Greek word *asketikos*, and the root meaning is "laborious, fr. *asketes*, one who exercises." Robert Thurman defines asceticism as "the impulse in human beings to attempt consciously to improve control over their habitual life processes, with a view to bettering their situation at least in a relative, and, if possible, an ultimate, way."[18] Before modern science, religion was the most systematic means by which humans explained their world and sought the means to exert control over the human condition. Culturally established religion also provided a means of communicating those insights and explanations across widespread populations and through the generations. Early Buddhists achieved this transfer of knowledge in a surprisingly modern way: during the Gupta period in India (4^{th} and 5^{th} centuries), Buddhist monasteries taught the "spiritual sciences," or *adhyatmavidya*, as well as other studies. They functioned like modern universities in disseminating cultural knowledge and attracted students from as far away as Iran and China.[19,20] Fasting, or CR, was among the religious–medical insights taught in ancient India.

Fasting is a common practice among world religions even today, with examples of its use

ranging from the milder restrictions of Lenten fasts among Christians to the more severe, near-starvation fasts of Hindu ascetics. The Buddha found the more extreme practices of asceticism to be just as obsessive and futile as hedonism, and famously preached a middle path. In the monastic community he established, monks and nuns ate only one main meal and fasted from noon to dawn.[21] This form of fasting most closely meets the criteria of the scientific definition of caloric restriction without nutritional deficit, and simple but patient observation of their own direct experience led the Buddha and his followers to embrace moderate fasting.

The therapeutic value of the reduction of stressors is one common thread connecting the observations and discoveries of modern science and those of the religious ascetics such as those who developed the Tibetan system of medicine. The psychophysiological manifestations of stress reduction are evident in both CR animals and ascetic monks, and they include efficient use of caloric intake, the evidence for which can be found in body weight measurements and activity/energy levels, as well as in enhanced immunity.[22] Not only does the sensation of hunger eventually recede, but fasting may also increase a sense of tranquility and even euphoria, both of which are associated with elevated levels of opioid substances produced naturally by the body. Unfortunately, before these beneficial effects are felt, often hunger manifests itself as an intensely uncomfortable set of sensations.[22]

Probably the most counterintuitive outcome of fasting is the increased activity levels observed among individuals whose caloric intake is restricted. This is one of the most robust outcomes in the laboratory and one that human ascetics experience and report. Likewise, human ascetics report enhanced alertness, just as laboratory rats have been demonstrated to show enhanced learning skills.[16] Enhanced immunity is also something that medical practitioners in early monastic communities could observe among monks practicing caloric restriction over time.

Longer Living through Mimetics

Regardless of what the long-term benefits are, most modern people are unlikely to adopt the ascetic life; in fact, most of us cannot even stick with a basic weight-loss diet long enough to reach a goal weight in spite of the clear health, social, and even economic rewards of doing so. For this reason, scientists studying longevity and the processes that contribute to the disorder of aging are looking for CR mimetics that would serve as agents of "manipulation of energy metabolism creating the metabolic shift seen in CR without the requirement for reduced food intake to obtain the health, function, and longevity-producing effects of CR."[23] The focus placed on energy metabolism is in recognition of research establishing energy intake as essential in producing the health and longevity effects observed in CR.[24] Metabolic rate had long been thought to be linked to longevity, but the work in Lloyd Demetrius's lab has led him to conclude that metabolic *stability* may be more important than metabolic *rate* in influencing life span.[25]

The first compound tested as a CR mimetic (in rats) was 2-deoxyglucose, a glycolytic inhibitor, which reduces glucose flux through cells through the enzyme phosphohexose isomerase. It worked reasonably well in that it did produce physiological effects similar to those of CR without the need for reduced food intake, but toxic levels were too close to the effective dose for this to be a safe approach in humans.[26]

Other compounds being investigated include iodoacetate and phenformin (also glycolytic inhibitors), a variety of antioxidants, sirtuin regulators such as resveratrol (also an antioxidant), lipid regulators (e.g., carnitine), autophagic enhancers, and insulin sensitizers. Each of these mimics one or more of the actions of CR, but so far none have produced all of the beneficial effects. Ultimately, it may be that a combination of mimetic compounds will be the most effective strategy for extending an optimally healthy life span.[24]

Seeking mimetics and the best combinations of mimetics relies heavily on research elucidating the mechanisms by which an organism is able to extend life span under the CR regime. Understanding what these regulatory pathways are and how they work together in response to energy intake will help us target those elements that will yield the most effective means of activating these pathways without the rigors of CR or causing unwanted side effects. For example, some research shows a link between CR mechanisms and reproductive function. Cynthia Kenyon found that *Caenorhabditis elegans* in the dauer state is longer lived, although they neither eat nor reproduce.[6] Clearly, few people would want to trade reproductive maturity for longevity. It turns out that if the gene *daf-2* is knocked out in adults, they will enter the dauer state and live longer,[6] so it may be that a longevity-enhancing intervention can be found that could be prescribed in early middle age. A link to one of the pathological processes of aging (increased blood glucose) as well as to caloric restriction was discovered by Gary Ruvkun when he demonstrated that *daf-2* encodes an insulin receptor.[27]

Leonard Guarente's lab found that in yeast the *Sir2* gene is involved in stabilizing chromosomes, particularly in yeast cells under stress. If the chromosomes of yeast cells are stable, both average and maximum life span increases.[28] *Sir2* is part of the ancient sirtuin family of genes found in all complex life forms. Furthermore, sirtuins are part of an insulin-signaling pathway and are controlled by insulin and another hormone, insulin-like growth factor-1 (IGF-1).[29,30]

Another part of the longevity machinery appears to be provided by neuron-endocrine interactions in *C. elegans* that may be signaling increased metabolic activity in peripheral tissues. Bishop and Guarente have recently reported that dietary restriction activates the *skn-1* gene in two neurons, the ASIs, which "turns on" the metabolic increase. This is the first evidence of dietary restriction triggering neuronal mediation of a hormonal response. The ASIs may be sensing energy availability and regulating the organism's energy intake and metabolism accordingly.[31]

A simultaneous publication by Panowski et al. describes a link between the transcription factor PHA-4, which regulates glucagon production and glucose homeostasis in fasting adult *C. elegans*, and longevity resulting from CR.[32]

Since the late 20th century, chronic degenerative diseases have overcome infectious disease as the major causes of death in the 21st century, so an increase in human longevity will depend on finding an intervention that inhibits the development of these diseases and slows their progress.[33] Caloric restriction remains the most promising intervention, either by reduction in the intake of calories through food, or by mimicking CR's effects with a pharmacologic intervention. Dietary prescriptions have long been a staple of traditional systems of medicine, and Tibetan medicine in particular relies on "the therapeutics of diet and behavior without any more elaborate treatment."[34]

Until safe, reliable mimetics are discovered, the modern, scientific prescription for extending one's healthy life span and that of the practitioners of Tibetan medicine are remarkably close: eat a moderate diet of high-nutrient, low-calorie foods. Specifically, Tibetan medicine recommends meals that leave the stomach one-third full with food, one-third full with liquids, and one-third empty in order to maintain good health and promote mental clarity.[34] The *Gheranda Smahita* prescribes a slightly less austere approach: "Half the stomach should be filled with food, one-quarter with water, and one-quarter should be kept empty for practicing *pranayama*."[35] Furthermore, the diet should consist principally of "*sattvic*" (alkaline) foods, such as vegetables, fruit, grains, and milk. "*Rajasic*" (or acid-forming) foods can be ingested in moderation; these include starches, sugars, meats, fish, and eggs.[36] The monastic dietary prescription did get one thing wrong according to the best current science: butter was considered a beneficial *sattvic* source of fat in the diet. It is true that oils/fats are essential to a

nutritionally complete diet, but modern science is demonstrating that we are better off with olive oil. Of course, olive oil may not have been known of or readily available when this diet was being developed.[a] Buddhist tradition also emphasizes the influence of the mind on promoting general good health and longevity and teaches methods (e.g., meditation) through which free will is exercised to shape events that in turn will influence one's destiny, including the length of one's life span.[37]

Conclusions

The beneficial claims for fasting found in Tibetan medicine—longevity, disease resistance, mental acuity, retention of youthful vigor, capacity for vigorous activity—are all supported to some degree by the scientific work. One great value of the type of meeting that produced these proceedings is the opportunity to share the scientific findings of the mechanisms of action that lead to the phenotypic qualities that observation has brought to our attention. But shedding scientific light on ancient observation is not the whole story: it benefits scientists to be reminded that we cannot discard the observational skills, borne of patience and quiet receptiveness that the ancient, as well as modern, ascetics and medical practitioners have developed. Caloric restriction is a good example of how we have taken simple, astute observation to the next level, measurement of hormonal actions, and to the level after that—genetics. But it is a good thing to be reminded that these exacting high-tech methods are revealing the processes and mechanisms behind something observed, recorded, and used hundreds of years ago, which receded from our awareness (at least in the West) until McKay observed it anew in 1935 and only now is revealing its secrets to molecular science. Nevertheless, in terms of practical application of the knowledge, we are no farther along than the Buddha was when he taught his followers to fast moderately. Even with CR mimetics, it is unlikely that the hedonistic lifestyle will be cancelled out by taking a pill, but mimetics will eventually unlock the benefits of the ancient prescription for the less disciplined among us.

[a]Even now, olive oil is not commonly used for cooking in India. Annual olive oil consumption in India averages just 2.5 g per person, a situation that the International Olive Council hopes to remedy. (Source: *Commodity Online*, July 23, 2007). A 2004 article in *The Hindu* touted the health benefits of using olive oil, which has always been more popular for massage than for cooking in India. (Source: *The Hindu*, June 14, 2006).

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Roth, G.S. 2005. Introduction. In *The Truth about Aging: Can We Really Live Longer and Healthier?* pp. 15–18. Windstorm Creative. Port Orchard, WA.
2. McKay, C.M., M.F. Crowell & L.A. Maynard. 1935. The effect of retarded growth upon the length of the lifespan and ultimate body size. *J. Nutr.* **10:** 63–79.
3. Kennedy B.K., M. Gotta, D.A. Sinclair, *et al*. 1997. Redistribution of silencing proteins from telomeres to the nucleolus is associated with extension of life span in *S. cerevisiae*. *Cell* **89:** 381–391.
4. Pletcher, S.D., S.J. MacDonald, R. Marguerie, *et al*. 2002. Genome-wide transcript profiles in aging and calorically restricted *Drosophila melanogaster*. *Curr. Biol.* **12:** 712–723.
5. Arkin, R. 2001. Gene expression and regulation in the extended longevity phenotypes of Drosophila. *Ann. N. Y. Acad. Sci.* **928:** 157–167.
6. Kenyon, C. 1996. Ponce d'elegans: genetic quest for the fountain of youth. *Cell* **84:** 501–504.
7. Gerhard, G.S. & K.C. Cheng. 2002. A call to fins! Zebrafish as a gerontological model. *Aging Cell* **1:** 104–111.
8. Austad, S.N. 1989. Life extension by dietary restriction in the bowl and doily spider, *Frontinella pyramitela*. *Exp. Gerontol.* **24:** 83–92.
9. Blüher, M., M.D. Michael, O.D. Peroni, *et al*. 2003. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. *Eur. J. Endocrinol.* **148:** 489–490.
10. Gerritsen, G.C. 1982. The Chinese hamster as a model for the study of diabetes mellitus. *Diabetes* **31:** 14–23.
11. Wang, Y., D. Lawler, B. Larson, *et al*. 2007. Metabonomic investigations of aging and caloric

restriction in a life-long dog study. *Proteome Res.* **6:** 1846–1854.
12. Kemnitz, J.W., R. Weindruch, E.B. Roecker, *et al.* 1993. Dietary restriction of adult male rhesus monkeys: design, methodology, and preliminary findings from the first year of study. *J. Gerontol.* **48:** B17–26.
13. Roth, G.S., J.A. Mattison, M.A. Ottinger, *et al*. 2004. Aging in rhesus monkeys: relevance to human health interventions. *Science* **305:** 1423–1426.
14. Gavrilova, L.A. & N.S. Gavrilova. 1999. Season of birth and human longevity. *J. Anti-Aging Med.* **2:** 365–366.
15. Weindruch, R. & R.L. Walford. 1988. *The Retardation of Aging and Disease by Dietary Restriction*. Charles C. Thomas. Springfield, IL.
16. Hashimoto, T. & S. Watanabe. 2005. Chronic food restriction enhances memory in mice—analysis with matched drive levels. *Neuroreport* **16:** 1129–1133.
17. Zatorre, R.J. 2003. Music and the brain. *Ann. N. Y. Acad. Sci.* **999:** 11–12.
18. Thurman, R.A.F. 1995. Tibetan Buddhist perspectives on asceticism. In: V.L. Wimbush & R. Valantasis, (eds.), with the assistance of Gay L. Byron & William S. Love. *Asceticism*. p. 108. Oxford University Press, New York.
19. Ibid, p. 114.
20. Nehru, J. 1960. In: R.I. Crane, (ed.). *The Discovery of India* pp. 123–134. Anchor Books/Doubleday, Garden City, NY.
21. Thurman, ibid. p. 132.
22. Bushell, W.C. 1995. Psychophysiological and comparative analysis of ascetico-meditational discipline: toward a new theory of asceticism. In: V.L. Wimbush & R. Valantasis, with the assistance of Gay L. Byron & William S. Love (eds.), *Asceticism*. p. 554. Oxford University Press, New York.
23. Roth, G.S., D.K. Ingram & M.A. Lane. 2005. Caloric restriction in primates and relevance to humans. *Ann. N. Y. Acad. Sci.* **1057:** 365–371.
24. Sohal, R.S. & R. Weindruch. 1996. Oxidative stress, caloric restriction, and aging. *Science* **273:** 59–63.
25. Demetrius, L. 2004. Caloric restriction, metabolic rate, and entropy. *J. Gerontol.* **59:** B902–915.
26. Lane, M.A., D.K. Ingram & G.S. Roth. 2006. The serious search for an antiaging pill. *Sci. Am. Rpts.* **16:** 63–67.
27. Kimura, K.D., H.A. Tissenbaum, Y. Liu & G. Ruvkun. 1997. daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. *Science* **277:** 942–946.
28. Sinclair, D.A., S.J. Lin & L. Guarente. 2006. Life-span extension in yeast. *Science* **312:** 195–197.
29. Michan, S. & D. Sinclair. 2007. Sirtuins in mammals: insights into their biological function. *Biochem. J.* **404:** 1–13.
30. Guarente, L. 2005. Calorie restriction and SIR2 genes—towards a mechanism. *Mech. Ageing Dev.* **126:** 923–238.
31. Bishop, N.A. & L. Guarente. 2007. Two neurons mediate diet-restriction-induced longevity in *C. elegans*. *Nature* **447:** 545–549.
32. Panowski, S.H., S. Wolff, H. Auilaniu, *et al*. 2007. PHA-4/Foxa mediates diet-restriction-induced longevity of *C. elegans*. *Nature* **447:** 550–555.
33. De Flora, S., A. Quaglia, C. Bennicelli, *et al*. 2005. The epidemiological revolution of the 20^{th} century. *FASEB* **10:** 892–897.
34. Clifford, T. 1984. *Tibetan Buddhist Medicine and Psychiatry: The Diamond Healing*. p. 98. Samuel Weiser, Inc. York Beach, ME.
35. Hewitt, J. 1977. *The Complete Yoga Book: Yoga of Breathing, Yoga of Posture, and Yoga of Meditation*. p. 154. Shocken Books. New York.
36. Ibid, p. 155.
37. Mullin, G.H. 1986. *Death and Dying: The Tibetan Tradition*. p. 149. Arkana-Penguin Books. London.