Hungry for life

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Atherosclerosis, reduced insulin sensitivity, hypertension, aortic stenosis: these are some of the many conditions that comprise the penultimate disease that afflicts us all. Life is that disease; it has absolute mortality and no cure. The existential angst imbued in this idea is not meant to be depressing; it is merely meant to illuminate an often forgotten, yet ever-present, adversary. For if life is the disease, aging is the weapon it uses to fell its victim. In this light, health care practitioners do not directly address the master disease itself, but only its consequences. Intuitively, we all appreciate the temporal dichotomies of aging. A 'good 85-year-old' may be accepted for bypass surgery, yet a 'frail 85-year-old' may be denied, despite having similar comorbidities. We sanitize and label the discrimination as experience or clinical judgement, but what makes the two patients so different? Is it all genetics, in that they were destined to arrive at this state of health at this point in time, or is there more to the story?

How do we even begin to understand and 'treat' aging? The first randomized controlled clinical trials would only be published in our children's lifetimes! However, a beginning dawns in observations made from long-lived societies and animal data. The common link seems to be a calorie-restricted diet, such as the one consumed by the residents of Okinawa. This Japanese island is home to one of the highest numbers of centenarians on earth (40 times more than on any other Japanese island). Residents not only enjoy an exceptional quantity of life, but also an extraordinary quality of life by having a delayed onset of heart disease and many types of cancer. There are also tantalizing clues from animal experiments. By consuming 30% to 50% fewer calories, a white rat extends its average life span from 23 to 33 months and its maximum life span from 33 to 47 months, a guppy extends its average life span from 33 to 46 months and its maximum life span from 54 to 59 months, and a Bowl and Doily Spider extends its average life span from 50 to 90 days and its maximum life span from 100 to 139 days. Investigators have ruled out the confounder of variable dietary composition as the cause of longevity. Rodents that are fed limited quantities of specific dietary constituents (protein, carbohydrate and fat) without caloric restriction, or ones that have diets supplemented with multivitamins, antioxidants or specific types of fat, do not have an increase in life span.

Primate data, although encouraging, are not yet definitive. Early work suggests that calorie-restricted monkeys have lower body temperature, blood pressure, glucose and insulin levels, but whether these surrogate markers translate into longevity is yet to be determined.

It is important to qualify what is meant by caloric restriction as a means to longevity. The most significant is that nutrition is not compromised; intake of essential amino acids, vitamins, minerals and fats is preserved. It is for this reason that studies of caloric restriction and longevity cannot be undertaken in poverty-stricken societies, in which both nutritional and caloric intakes are reduced. Similarly, caloric restriction must also be distinguished from the eating disorder of anorexia, which is characterized by poor nutrition. Furthermore, the focus of anorexia is weight loss and a negative self-image. Although weight loss is frequently associated with caloric restriction, it is not the prime focus, and practitioners concentrate positively on health rather than appearance.

If caloric restriction is truly the fountain of youth, it offers some insight into the mechanisms of aging. Contemporary views deal primarily with cellular metabolism and respiration. Caloric restriction is thought to limit the generation of free radicals, which damage cellular mitochondria and reduce their efficiency. A more tantalizing mechanism comes from genetic studies. Although several candidate genes controlling aging have been studied, the best known and studied is the silent information regulator 2 (*Sir2*) gene. *Sir2* has been found in organisms such as yeast, worms, rodents and humans. It prevents the transcription of certain seemingly redundant genes that lead to the production of ribosomal DNA (ultimately to undergo ribosomal translation). *Sir2* prevents the accumulation of ribosomal DNA copies seen with each cell division. Therefore, the cell does not have to expend energy in translating these proteins. Adding one copy of *Sir2* to yeast increases its life span by 30%. The link to caloric restriction was established by finding that it increased the activity of nicotinamide adenine dinucleotide (NAD) and reduced the activity of NADH (the reduced form of NAD). A reduced NAD to NADH ratio profoundly increases the activity of *Sir2*. Studies on *Sir2* have challenged the notion of caloric restriction being merely a slowing of metabolism, with a resultant reduction in accumulation of toxic products. Instead, caloric restriction is seen as a low-grade biological stressor that shifts the balance from cellular apoptosis to repair and regeneration through the activity of *Sir2*.

Not surprisingly, there has been considerable effort in developing drugs that mimic caloric restriction. One potential candidate is 2-deoxy-D-glucose, which blocks the uptake of glucose into the cells and reduces ATP synthesis. However, it has an extremely narrow therapeutic window and a low toxicity threshold. Another drug, known as resveratrol, also holds promise. This small molecule is found in some plants, as well as in red wine, of all things! Giving this molecule to yeast, worms and flies extends their life spans by 30% without the need for caloric restriction. It is thought that resveratrol activates *Sir2*. An added benefit to the drug is the avoidance of reduced fertility, which is a side effect of caloric restriction.

An excellent series of papers further detailing caloric restriction and longevity is found in a recent publication of Scientific American Reports (1). While the idea of caloric restriction has existed for over 70 years, it is not surprising to see why it has not caught on, given the difficulties with changing human behaviour. It is not suitable for everyone, including children and women who are or may become pregnant. Nonetheless, it provides invaluable lessons on the importance of a high-value diet. Whether intermittent fasting provides similar benefits to caloric restriction remains to be seen. If nothing else, it shows us that longevity is not a place we seek to be, but rather a journey shaped by the decisions we make every day of our lives.

REFERENCES

1. DiChristina M. Eating to Live. Scientific American Reports, December 2006. <www.sciam.com/special/toc.cfm?issueid=49&sc=rt_nav_list> (Version current at January 15, 2007).

Selected sites

1. Wikipedia
< en.wikipedia.org/wiki/Calorie_restriction > | 2. The Okinawa Centenarian Study
< www.okinawaprogram.com > | 3. The Calorie Restriction Society
< www.calorierestriction.org > |
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For comments or to suggest a Web site for discussion in a future column, write to pgmalik@hotmail.com