

Caloric Restriction For Improved Health and Longer Life Updated: 01/18/2006

How long we live may not be determined by what we eat so much as how much we eat. Of all the potential anti-aging approaches, none have so far shown the promise of caloric restriction. Over the past 75 years, many studies have shown that caloric restriction extends life span in a wide variety of species, from invertebrates to rodents, to mammals. So far, no long-term studies have been completed in primates or conducted in humans because of the sheer length of any proposed study (perhaps a century or more for human studies!). However, several ongoing studies are looking at caloric restriction in primates, and the early results are promising.

Despite its promise to extend life, caloric restriction remains a misunderstood lifestyle. People imagine that caloric restriction is associated with near-starvation and constant hunger, or malnutrition due to inadequate intake of dietary nutrients. In fact, caloric restriction, if undertaken correctly, is a healthy lifestyle that is accompanied by weight loss, only occasional hunger, optimal nutrition, and other health benefits. To stress the importance of a healthy lifestyle, caloric restriction will henceforth be referred to as "caloric restriction with optimal nutrition" or CRON.

Practicing CRON means decreasing caloric intake by 30 percent to 40 percent while following the principles of a healthy diet and greatly limiting the consumption of calorie-dense, nutrient-poor foods such as white flour and refined sugar. It is also important that additional vitamins and minerals be added to any caloric restriction program to supply any missing nutrients. Only calories, not nutrients, should be limited (Nicolas AS et al 1999).

CRON IN ANIMAL STUDIES

Caloric restriction is the most effective and well-documented pathway to longevity in animal studies. Both the mean and maximum life spans of yeast, rotifers, water fleas, nematodes, fruit flies, spiders, fish, hamsters, rats, mice, and dogs have been extended significantly by decreasing normal caloric consumption by 30 percent to 40 percent (Weindruch R et al 1988).

When CRON is begun in young animals, they remain smaller and leaner than their free-feeding counterparts (Weindruch R et al 1988). They also withstand a number of stressors better than their free-feeding counterparts (Berg TF et al 1994; Heydari AR et al 1993; Masoro EJ 1998).

Young rodents consuming 40 percent fewer calories than their free-feeding counterparts will generally experience about a 50 percent increase in their life spans. Regardless of when CRON is started, its benefits appear to be proportional to both the degree and duration of caloric restriction (Merry BJ 2002). Thus, health benefits might be expected even when CRON is started late in life (Rae M 2004). Since the longevity response to CRON appears to be conserved across the animal kingdom, primates and humans will likely benefit from CRON as well.

THE PROMISE OF CRON IN PRIMATES AND HUMANS

The National Institute on Aging (NIA), the University of Wisconsin, and the University of Maryland are currently conducting CRON studies on primates. Statistically significant differences in longevity will not be available until 2010, but preliminary results are encouraging. In the NIA study, the number of deaths in the CRON group is approximately half that of those fed at will. For example, 33 percent of the CRON squirrel monkeys have died compared with 54 percent of the free-feeding controls. For rhesus monkeys, mortality is 13 percent for the CRON group and 23 percent for the free-feeding group (Lane MA et al 2002). So far, the CRON longevity trends are in a positive direction.

Although life span CRON studies have not been conducted on humans, there is anecdotal evidence and short-term data to suggest that CRON might work in humans as well. For example, the island of Okinawa has up to 40 times as many centenarians as does the rest of Japan. The caloric intake of adult Okinawans is 20 percent lower than their mainland counterparts. Children in Okinawa consume only about 60 percent of the recommended intake of food as their mainland counterparts (Kagawa Y 1978). The longevity of this subpopulation may be because of their restricted diet, although other factors cannot be ruled out.

Similarly, data from the Baltimore Longitudinal Study of Aging suggests that long-lived humans exhibit some of the same physiological and biochemical changes that accompany caloric restriction in animals. Survival rates are highest in those with low body temperatures and low levels of circulating insulin (Roth GS et al 2002). In addition, levels of serum dehydroepiandrosterone (DHEA), a presumed longevity marker (Kalimi M et al 1999), are also higher in long-lived individuals (Roth GS et al 2002). In primates

undergoing CRON, DHEA levels are also conserved (Lane MA et al 1997).

CRON: LOWERING RISK FACTORS FOR DISEASE

Although scientists haven't yet identified a single global marker of aging, there are a number of widely accepted measures used to gauge health and longevity. CRON has been shown to positively affect many of them including:

Cardiovascular risk factors

Cardiovascular risk factors such as obesity, high blood pressure, and high cholesterol and triglycerides are rapidly lowered once adult animals or humans are placed on CRON. Cholesterol and triglyceride levels were lowered in animals on CRON (Lane MA et al 1999; Liepa GU et al 1980), and primates on CRON exhibited decreased blood pressure compared to their free-feeding counterparts (Lane MA et al 1999) .

The eight people living in Biosphere 2, an enclosed ecosystem, underwent involuntary caloric restriction during their 2-year stay because they were unable to grow enough food for their needs. They consumed 1800 calories per day during the first 6 months and 2200 calories thereafter. Their diet was nutrient rich and high in vegetables. Body weight decreased by 15 percent and serum cholesterol dropped 38 percent. Blood pressure fell from an average of 110/74 millimeters of mercury (mm Hg) to 90/59 mm Hg. A group outside Biosphere 2, who ate without restriction but who took the same nutritional supplements as those inside Biosphere 2, did not exhibit these same positive health alterations (Walford RL et al 2002).

Many of the changes seen in the Biosphere 2 group are readily observable in humans just 10 weeks after modest CRON. In a study of eight subjects who were unrestricted in their eating habits and 16 people who ate 20 percent less than they usually ate, significant weight loss, decrease in body fat mass, and lower blood pressure were observed in the latter group. As expected, high-density lipoprotein (HDL) cholesterol, the so-called good cholesterol, increased in proportion to the weight loss experienced (Velthuis-te WEJ et al 1994).

Risk of type 2 diabetes

The relationship between insulin and diabetes (and heart disease) is well established. Insulin is a critical hormone that enables the transport of blood sugar (glucose) into our cells, where it is used to generate energy. As people age, their cells become resistant to insulin, a condition called insulin resistance. In response, blood levels of insulin rise, along with blood levels of glucose. This condition of elevated glucose and insulin is a major risk factor for type 2 diabetes. CRON not only prevents these changes but can substantially reverse them. In fact, some researchers believe that CRON's ability to extend life span is related to its ability to modulate insulin and glucose levels.

In rats, CRON significantly reduces fasting and after-meal glucose levels by 10 percent to 20 percent, and reduces plasma insulin by about 50 percent (Kalant N et al 2001; Masoro EJ et al 1992; Wetter TJ et al 1999). This is also true in mice (Dahbi JM et al 2001), dogs (Kealy RD et al 2002), and primates (Lane MA et al 1999). The inhabitants of Biosphere 2 experienced a 20 percent drop in blood sugar (Walford RL et al 2002). Decreases in plasma insulin and glucose can be observed even after 1 month of 10 percent restriction in primates, before any weight loss has occurred (Lane MA et al 2001).

Insulin and glucose levels are lower during CRON. Glucose uptake, which measures the cell's ability to absorb available glucose, remains healthy (Masoro EJ et al 1992), suggesting that CRON enhances insulin sensitivity.

Oxidative damage

In addition to lowering risk factors for cardiovascular disease and diabetes, animals on CRON exhibit less oxidative damage than their free-feeding counterparts. Oxidative damage is caused by reactive oxygen species (ROS), which cause serious damage within cells and cell membranes.

CRON counters this free radical damage by accelerating the repair of damaged cell structures, quenching free radicals, breaking free radical chains, and making cell membranes more resistant to ROS. Consequently, some researchers believe caloric restriction to be "the most effective modulator of free radical-induced oxidative stress" (Yu BP 1996; Yu BP et al 2001).

CRON'S BENEFICIAL EFFECTS ON CELLS

Researchers initially speculated that animals who consumed fewer calories would also expend less energy. However, careful measurements of the energy expenditures of animals on CRON indicate that they use as much or more energy than their free-feeding counterparts (Duffy PH et al 1991; Masoro EJ et al 1982; Masoro EJ et al 1992; McCarter RJ et al 1992).

In spite of the comparable energy expenditure, however, CRON reduces the cellular damage that is typically associated with higher energy expenditure, including accumulation of ROS products, lipid peroxidation, oxidized proteins, and other measures of cellular aging (Cook CI et al 1998; Dubey A et al 1996; Matsuo M et al 1993).

CRON stimulates cellular repair

Macroautophagy is a major repair process for membranes and cell structures damaged by ROS (Stevens A et al 2000; Yokota S 2003). During this process, the damaged cell structure is surrounded by pieces of cell membrane and its molecular components are recycled. This process is reduced after eating, however, because insulin and amino acids rise, meaning that cellular repair likely only occurs during fasting (Mortimore GE et al 1987; Mortimore GE et al 1989; Seglen PO et al 1992). By reducing insulin levels, CRON sets the stage for more cellular repair (Bergamini E et al 2003; Droge W 2004).

CRON protects cells

CRON increases the ability of the body to defend against ROS damage in other ways. In fruit flies and rodents on CRON, the levels of internal antioxidant enzymes such as superoxide dismutase and catalase are protected from age-related decline (Lin YJ et al 1998; Van Remmen H et al 1995).

Aging rats on CRON have an antioxidant capacity comparable to that of younger animals (Kim JW et al 2002). This is at least partly because of elevated levels of glutathione, a powerful internal antioxidant (Armeni T et al 1998).

CRON AND CANCER

The antitumor effects of caloric restriction are well documented in experimental animals, and epidemiological studies in humans suggest a protective effect (Nkondjock A et al 2005). CRON protects rats and mice from both spontaneous tumors and tumors induced by carcinogenic chemicals or radiation (Tannenbaum A 1944; Tannenbaum A 1945; Weindruch R et al 1988). Studies show that:

- Breast cancer tumors (which developed after 2 months in laboratory rats who were administered a carcinogen) stopped growing when the rodents were put on CRON (Kritchevsky D et al 1984).
- CRON's cancer-limiting effects may also be due to its ability to limit cyclooxygenase 2 (COX 2), which is a major player in promoting the growth and spread of tumors (Chang SH et al 2004; Cianchi F et al 2004; Foslien E 2000; Ristimaki A et al 2002; Rose DP et al 2000).

HOW DOES CRON PROMOTE LONGEVITY?

Because caloric restriction decreases body weight, especially dangerous abdominal fat, researchers originally thought its ability to prolong life was associated with decreased fat.

However, this hypothesis was questioned after a study showed that genetically obese Zucker rats experienced no change in body fat percentage while on CRON compared to free-feeding controls, even though the restricted animals weighed less (Harrison DE et al 1984; Johnson PR et al 1997; Keenan KP 1996). Clearly, there were some other mechanisms at play.

Mounting evidence suggests that CRON acts, at least in part, by improving insulin sensitivity, thereby reducing insulin and glucose levels.

The data suggest that most people consume too many calories for optimal health. Part of the problem may be evolutionary. Stone Age humans consumed few calories from simple carbohydrates and more from complex carbohydrates, which are rich in natural fiber. High-fiber foods tend to be more filling than simple refined sugars and refined carbohydrates such as white flour.

The establishment of agriculture about 10,000 years ago (Eaton SB et al 1997) dramatically changed the nature of the human food supply. Carbohydrate-rich grains became available in large quantities. Then, in the past century, the grains were stripped of their fiber by processing, resulting in a steady dietary supply of refined carbohydrates. These refined carbohydrates are a dense source of calories, although not a great source of nutrition.

People who live in North America are advised to eat about 55 percent of their calories as carbohydrates (Anderson GH 1994), most of which realistically are consumed as refined sugar and grains that are depleted of fiber.

By relying on complex carbohydrates and dramatically reducing intake of calories, CRON produces dramatic weight loss, which

improves insulin sensitivity and insulin action. It is worth noting, however, the CRON animal studies have generally shown that CRON counteracts aging and prevents the diseases of aging regardless of the composition of the diet if adequate nutrients are consumed.

CALORIC RESTRICTION IN TODAY'S WORLD

Even if our genes are still living in the Stone Age, we are not. To maximize our longevity, we need to find a way to have the benefits of caloric restriction without being constantly distracted by hunger. One of the persistent problems with people and CRON is low compliance. Maintaining a dramatically reduced caloric intake over the long-term can be very demanding, especially in a culture surrounded by inexpensive, plentiful, calorie-rich, nutrient-poor food. Realistically, few people are willing to reduce their caloric consumption by 30 percent to 40 percent (Roth GS 2005).

Two approaches are currently being explored to make the benefits of CRON more accessible. The first is the most direct: reducing calories by 30 percent to 40 percent. This requires a careful diet that is rich in nutrients, complex carbohydrates, soluble fiber, and lean protein. Soluble fiber has been shown to decrease hunger, although hunger cannot realistically be eliminated completely during a dedicated CRON diet. Consuming fiber before meals can reduce the rapid absorption of simple carbohydrates and help decrease the post-meal surge in insulin (Anderson JW et al 1993).

The second approach is the development of drugs that alter body biochemistry to mimic the benefits of CRON.

LIFE EXTENSION IN A PILL

Many individuals find radical caloric restriction difficult and are unable to sustain the lifestyle. Consequently, a number of attempts have been made to develop a pill that would substitute for, or be used in conjunction with, caloric restriction. Although there is no such pill yet, researchers are pursuing several promising avenues.

2-deoxy- D-glucose

One of the first candidates for "life extension in a pill" was 2-deoxy-D-glucose (2DG). 2DG reduced plasma insulin, body temperature, heart rate, and blood pressure in rats when it was included in the diet at a concentration of 0.4 percent. Although the animals initially lost weight, after 6 months their body mass did not differ significantly from controls (Ingram DK et al 2004).

2DG appeared to strengthen the ability of both rats and mice to withstand a number of stressors, similar to the protection afforded by caloric restriction. In one rat study, 2DG was directly compared to caloric restriction and found to have a similar spectrum of activity (Ingram DK et al 2004). Unfortunately, when longevity studies were undertaken, 2DG proved too toxic to be given for the entire life of the animal (Ingram DK et al 2004).

Blocking insulin receptors in fat tissue

Researchers found they could extend the life spans of mice by 18 percent by blocking insulin receptors located in fat tissue. These mice ate more than their normal counterparts, yet had 70 percent less body fat at 3 months of age (Blüher M et al 2003).

These studies suggest a pharmaceutical agent that downregulates or blocks only the insulin receptors in fatty tissue that might mimic some of the effects of caloric restriction.

Scientists at the University of California at Riverside found that giving the drug metformin (a gluco-regulatory agent used to treat diabetes) to mice produced many of the gene expression changes found in long-lived mice on CRON (Dhahbi JM et al 2005). A recent study by scientists at the N. N. Petrov Research Institute of Oncology in Saint Petersburg, Russia, found that metformin extended the mean life span of transgenic mice by 13.1 percent and their maximum life span by 1 month. In this study, metformin also significantly decreased the incidence and size of mammary tumors (Anisimov VN et al 2005). A large life span study of long-lived mice funded by the Life Extension Foundation is underway at the BioMarker Pharmaceuticals laboratory in northern California.

Resveratrol

Increased life span in yeast can be induced by adding resveratrol, an antioxidant found in red wine, to their growth medium. These results have been replicated in both worms (*Caenorhabditis elegans*) and pomace flies (*Drosophila melanogaster*) (Wood JG et al 2004), suggesting that the action of resveratrol may be equivalent to that of caloric restriction. Whether resveratrol will prove to be a caloric restriction agent in mammals, primates, and humans remains to be seen.

Recent studies at the BioMarker Pharmaceuticals laboratory have shown that a nutrient formula from the Life Extension Foundation that contains extracts of grape seed and skin, a whole red grape resveratrol extract, vitamin C, and calcium (from calcium ascorbate) can produce many of the gene expression effects found in mice on CRON. Studies funded by the Life Extension Foundation at the

Chinese Academy of Sciences in Beijing have shown that this formula can improve the strength and coordination of pomace flies (*D melanogaster*) afflicted with a motor disorder that is similar to Parkinson's disease in humans. This formula can protect mitochondria (the energy-generating power plants in the cell) isolated from rat livers from damage caused by exposure to carcinogens (unpublished data). A life span study with this formula is underway at the BioMarker Pharmaceuticals laboratory.

OPTIMAL NUTRITION

It appears that caloric restriction works by slowing biological aging in many ways, including decreasing ROS damage to cells, limiting inflammation, enhancing insulin sensitivity, and repairing damaged cells. Certain nutrients have demonstrated similar effects, leading one group of researchers (Lemon JA et al 2005) to attempt to mimic CRON with a formula containing 31 ingredients that included a wide range of antioxidants and nutrients that have been extensively studied in humans (such as vitamin E, vitamin C, coenzyme Q10, glutathione precursors, and essential fatty acids).

This formula was given to normal mice and mice that over-expressed growth hormone. The mice that over-expressed growth hormone were larger and had a shorter life span than the normal ones, presumably because they aged faster.

The results were dramatic. Supplementation extended the life span of the growth hormone mice by 28 percent, to 431 days. In normal mice, supplementation extended life span by 11 percent on average, from 688 days to 765 days (Lemon JA et al 2005).

How does this 11 percent increase in longevity in normal mice compare to caloric restriction? Although a CRON group was not included in the study described above, other investigators have reported that 40 percent restriction in calories increased survival in the same strain of mice about 19 percent (Forster MJ et al 2003). Thus, supplementation yielded about half as much longevity as caloric restriction.

Unfortunately, this mix of nutrients was developed for mice and isn't available for humans. However, the Life Extension Foundation is able to offer many of the same nutrients that were used in this study at doses more appropriate to humans.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Although there are no studies confirming that CRON extends life span in primates or humans, there is plenty of evidence to suggest that it works in other life forms (including invertebrates, mice, rats, dogs, and other animals tested in laboratories) by increasing markers of longevity or by actually increasing longevity.

Before going on a CRON program, the Life Extension Foundation recommends that you obtain a blood chemistry profile. This will allow you to monitor your progress through subsequent blood tests. During CRON, fasting blood glucose and insulin levels should fall, as should insulin-like growth factor-I (IGF-I) levels. HDL should rise. Blood pressure, which can be measured at most pharmacies without charge, should fall. For more information on blood testing, call 1-800-544-4440 or visit www.lef.org. If you intend to practice severe caloric restriction (30 percent to 40 percent), we recommend that you do so under the care of a knowledgeable physician.

The Life Extension Foundation suggests that you reduce calories by eating plenty of fresh organic fruits and vegetables, soluble fiber, and lean protein. For more advice on a healthy diet, see your physician or a qualified nutritionist, or call 1-800-544-4440.

Before each meal, take one of the following:

- 8 to 9 grams (g) of Enhanced Fiber Food Powder (flavored or unflavored)
- 8 to 9 g of high lignan flaxseed powder
- 3 to 6 capsules of PGX soluble fiber blend

With each meal, take one to four capsules of Super Digestive Enzymes to ensure efficient absorption of nutrients.

Supplement with the following nutrients:

- **Life Extension Mix**—Follow label directions (some supplements listed above are already contained in the Mix).
- **Acetyl-L-carnitine**—300 milligrams (mg) of acetyl-L-carnitine hydrochloride and 320 mg of acetyl-L-carnitine arginate dihydrochloride
- **R-dihydro-lipoic acid**—150 mg daily
- **Fish oil**—700 mg of eicosapentaenoic acid (EPA) and 500 mg of docosahexaenoic acid (DHA) twice daily with meals
- **Coenzyme Q10**—100 mg daily
- **DHEA**—Blood testing is required to determine optimal dosage.
- **Garlic**—600 to 1200 mg daily
- **Ginkgo biloba**—120 mg daily
- **Ginseng**—As recommended on label.

- **L-glutathione with cysteine and vitamin C**—One to three capsules daily
- **Melatonin**—500 micrograms (mcg) (total of 3 mg daily)
- **Gamma E mixed tocopherols**—359 mg daily with 20 mg sesame lignans daily
- **Low-dose aspirin**—80 mg daily
- **Digestive enzymes**—Follow label directions.
- **Resveratrol**—20 mg daily

CALORIE RESTRICTION SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Acetyl-L-Carnitine

- Acetyl-L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Fiber

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

Flaxseed

- Flaxseed has blood-thinning, anticlotting properties.
- Discontinue using flaxseed before any surgical procedure.
- Consult your doctor before taking flaxseed if you have hemophilia or if you take warfarin (Coumadin).
- Flaxseed can cause gastrointestinal symptoms such as nausea and diarrhea.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Ginkgo biloba

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.

- Avoid concomitant use of ginkgo with NSAIDs, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

Ginseng

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level.
- Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

Lipoic Acid

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a "heavy head," or gastrointestinal symptoms such as nausea and diarrhea.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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