# ISAGENIXSCIENCE

## Isagenix for Life

*Living a healthier life with Shake Days and Cleanse Days*

*When Isagenix Pillars of Health are used within an Isagenix system combining Shake Days and Cleanse Days, they offer a straightforward, effective way to optimize health based on scientific studies.*

Isagenix products work, almost magically. This is a sentiment felt by thousands of satisfied customers who have found their products of choice for achieving weight loss, improved health, and feeling better using our signature Pillars of Health—Cleanse for Life, IsaLean Shake, Ionix Supreme, and Ageless Essentials Daily Pack. These products are used within a nutritionally sound program involving Shake Days and Cleanse Days and represent a convenient pathway toward maintaining healthy weight and optimal health.

Why do the products work so enchantingly well? How do they amaze people with weight loss, muscle building, and more energy? You could say *The World Leader in Nutritional Cleansing, Replenishing, and Youthful Aging* has a few tricks up its sleeves backed by the science of cleansing, minimized calories, and maximized nutrition.

Most low-calorie diets are strictly catabolic (causing tissue breakdown): fat *and muscle* break down, hunger is continuous, and feelings of fatigue are normal. Furthermore, these types of diets provide less than optimal nutrition to power the body or quality protein necessary to prevent long-term muscle loss. Micronutrient intake falters and cells begin to function less efficiently. Similarly, water (or even juice) fasting is short-term starvation, is catabolic, and puts the body into "slower metabolism" to conserve energy. In addition there are little if any nutrients provided by fasting including the ones necessary for detoxification and guarding against toxins and oxidative stress.

In contrast, Cleanse Days provide a "jump start" for people so they can take control of their health and see wonderful results. Cleanse Days stimulate reduction

### Special Issue

I'm delighted to be part of a company with a system of products that clearly offers an effective, straightforward approach to health and wellness. In this issue of *Isagenix Science,* we present why Cleanse Days and Shake Days are key parts of our system to gain each of the following health benefits:

- Reduce body weight, body fat, and waist circumference
- Improve insulin sensitivity and other metabolic markers
- Reduce oxidative stress and inflammatory markers
- Improve heart health by reducing cardiovascular risk factors
- Promote a longer life

Live well and adventurously!

*- Suk Cho, Ph.D.*

"ISAGENIX FOR LIFE" *CONTINUED...*

of fat deposits that release stored toxins. The smaller the fat cells become, the less pro-inflammatory cytokines (signaling molecules) they produce—further reducing ill effects on the body. Cleanse for Life facilitates a healthier body by encouraging detoxification of these toxins whether they be endogenous (produced by the body) or exogenous (from our diets or environment). Cleanse Days provide some fuel and nutrients, thus allowing the digestion processes to rest and promoting detoxification in the liver and kidneys.

Shake Days include IsaLean Shake, a nutrient-dense meal with low calories for weight management, but that stimulates protein synthesis producing an anabolic state. The shake feeds the body whey protein shown to outperform other proteins for satiety (keeping you feeling fuller longer, reducing total amount of calories in later meals), decreasing abdominal and total body fat, and increasing thermogenesis and fat oxidation. The shake also helps restore glutathione levels to youthful levels and fights oxidative stress related to obesity. The healthy meal replacement shakes provide essential vitamins and minerals, often depleted in dieting but necessary to maintain normal cellular activity. In addition, Ionix Supreme, a tonic of adaptogens, helps reduce stress associated with weight loss and helps with the "feel good" effects of our program.

Cleanse Days appear to re-set the "food intake" center within our brains since data show less food is eaten the following day after food is restricted (1). Various enzymes are activated that are beneficial to health. Mitochondria are shown to increase in number and become more efficient with lowering oxidative stress (2), which mimics results seen in mice following calorie restriction diets. Sirtuin 1, the enzyme found in various species shown to extend life, may also be activated (3). Of course, fat is mobilized and used for fuel in the muscle and liver—even more so when followed by whey protein on Shake Days. Insulin becomes more sensitive to plasma glucose—one of the key markers for longevity. Oxidative stress and inflammatory markers are reduced, other hallmarks for longevity (4-7). These are the biochemical changes thought to confer longer, healthier living.

The magic of Shake Days and Cleanse Days is that customers achieve dietary goals with exciting results matching those seen in well-designed, published studies on restricting food intake without undernutrition (calorie restriction) and fasting in animals and in humans. Not only does the program reduce caloric intake, but also provides optimal nutrition and detoxification—with the highest-quality macro- and micronutrients, botanicals, and supporting ingredients.

The Isagenix system's combination of Shake Days and Cleanse Days is intriguing because it encompasses these benefits documented by studies while advantageously providing optimal nutrition and botanicals to assist the body's detoxification and cleansing process.

The Isagenix system has been in the forefront of longevity—now, research is beginning to support what Isagenix has delivered for the last nine years.

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## CLEANSING MAY ACTIVATE "LONGEVITY GENE"

Harvard researchers at Massachusetts General Hospital have found that withholding food temporarily causes SIRT1, "the longevity gene," to shut down fat production, which could open up scientific explanations into new approaches for weight loss and improving cardiovascular health.

Absence of food was previously shown to suppress proteins called SREBPs, which are responsible for controlling fat synthesis and storage, but the mechanism was not well understood. However, after a series of experiments in worms, fruitflies, and mice, the researchers reported that fasting acts directly on SIRT1, one of a family of sirtuin enzymes, thereby down-regulating these SREBPs.

Sirtuins have grown as an active area of research since the early 2000s because of findings that stimulation of sirtuin activity—via calorie restriction, intermittent fasting, and compounds such as resveratrol—protected mice fed a high-calorie diet against weight gain. Furthermore, it increased the lifespan in nematode worms, fruitflies, fish, and rodents.

Geneticists and medical researchers are only just beginning to understand how genes encode sirtuins, how the enzymes influence energy metabolism, and how certain drugs may act as possible stimulators of SIRT1.

These studies may potentially offer new insights into the science behind Isagenix products and systems.

"The biological mechanism by which fasting turns off the proteins that stimulate fat and cholesterol synthesis may explain partially our success with our two weight-loss programs, where we incorporate one to two days per week of Cleanse Days, which we've shown successfully produce healthy weight loss in adults," says Susie Rockway, Ph.D., director of Isagenix Research and Science.

She adds, "Similarly, the new study is interesting as it could have other implications because it offers support to intermittent fasting, or Cleanse Days, as a potential alternative to caloric restriction for stimulating SIRT1."

**Reference:** Walker AK, et al. Conserved role of SIRT1 orthologs in fasting-dependent inhibition of the lipid/cholesterol regulator SREBP. *Genes Dev* 2010;24:1403-17.

## DOES TAKING RESVERATROL MIMIC CUTTING CALORIES?

Resveratrol is considered as a calorie restriction (CR) mimetic because it stimulates genetic expression of Sirt1, "the longevity gene," similar to that of CR. Like CR, resveratrol extends lifespan in the fruit fly, the nematode worm, yeast and rodents. Even in studies where resveratrol didn't increase lifespan, it still appeared to reduce those unwanted changes that can come with age.

According to a recent review, there may be something to the claim that resveratrol delays aging, or at least has the potential of "softening" the effects of aging on the body.

The review examined laboratory animal and cell culture studies to clarify what is well-understood, what is possible, and what is yet to be determined regarding resveratrol and human health.

"We believe the evidence is sufficiently strong to conclude that a single dose of resveratrol is able to induce beneficial physiologic responses, and that either weeks or months of resveratrol supplementation produces physiologic changes that are predictive of improved health," the authors wrote.

In part, resveratrol keeps cells healthy by reducing oxidative stress and by promoting blood vessel dilation, increasing circulation throughout the body and to the brain.

Reference: Smoliga JM, et al. Resveratrol and health—A comprehensive review of human clinical trials. *Molecular Nutrition & Food Research*. 2011.

## THE SCIENCE OF REDUCING CALORIES ASSOCIATED WITH LONGEVITY

Since the 1930s when Cornell University researcher Clive McCay reported that a reduction in calories extended mammalian lifespan, hundreds of subsequent studies conducted found it could extend lifespan and delay the onset of age-related diseases in a variety of species.

Research over the past 80 years brings hope that the same results could transfer to humans, although, calorie restriction (CR) studies in humans are lacking. However, there are already exciting results suggesting that CR very well may extend life and protect against age-related diseases.

### Okinawa

One group of humans that have provided evidence from a "natural experiment" in long-term CR is the older generation of Okinawans from Japan. Because of poverty when they were younger, these Okinawans were so deprived of calories that it stunted their growth, but, even so, their quality of diet was adequate enough to keep them free of nutritional deficiencies and infectious diseases that afflict most of the third world.

To this day, there are more people who have lived over 100 years of age in Okinawa than in any other part of the world—leading researchers to believe this may be evidence that CR slows aging in humans.

### Biosphere 2

There are relatively few actual studies on long-term CR in humans. A famous one that was accidental was as part of an entirely different experiment, Biosphere 2. Eight volunteers were sealed inside an enclosed three-acre space meant to be an "ecological mini-world". They ran into problems when their food supply unexpectedly dwindled to meager portions.

Coincidentally, the crew's physician, Roy Walford, M.D., (see "Remembering Roy" on Page 4) was one of the pioneers in CR, so he convinced his fellow biospherians to embark on their own CR experiment. Their results showed that CR decreased BMI, blood pressure, fasting blood glucose, insulin, and cholesterol.

*The older generation of Okinawans from Japan are a "natural experiment in long-term calorie reduction and among the longest-living people in the world.*

### Calorie Restriction Society

Another source for information on humans restricting their food intake is from the Calorie Restriction Society (CRS) whose members adhere to a CR regimen because of evidence from animal studies.

Data collected show the CRS members exhibited similar results as the subjects in Biosphere 2. Of particular notice was their low blood pressure and reduced incidence of chronic inflammation compared to similarly aged individuals.

### CALERIE

The growing interest in the effects of CR in humans has led to a multi-collaborative research program, CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Calorie Intake). This program is a joint effort of the National Institute on Aging along with several other research centers (Tufts University, Pennington Biomedical Research Center, Washington University, and Duke University) whose goal is to research the effects of long-term CR in humans.

Phase I of CALERIE consisted of three pilot studies that examined healthy, overweight men and/or women (BMI 25-29.9 kg/m) and restricted

"THE SCIENCE..." *CONTINUED*

*Eight volunteers took part of an accidental calorie restriction experiment in Biosphere 2 in Tucson.*

their calories by varying degrees for six or 12 months.

Results showed that CR led to decreases in body weight, fat mass, core body temperature, visceral and subcutaneous fat mass. The study also showed decreased fasting glucose and improved insulin sensitivity.

Phase 2 is already in the works and future studies will target younger individuals with lower BMI (not overweight or obese).

Although the research on CR in humans is still in its infancy, what has been found so far suggests reduced risk of age-related diseases and similar life-extending benefits as previously demonstrated in animal studies.

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REMEMBERING ROY WALFORD

One of the leading advocates for calorie restriction (CR) as a method of extending life and improving health was Roy Walford, M.D. (1924-2004). A pioneer in the field of anti-aging, Walford performed extensive research addressing the role of calorie restriction, body temperature, and genetic influence in slowing aging and promoting longer lifespan.

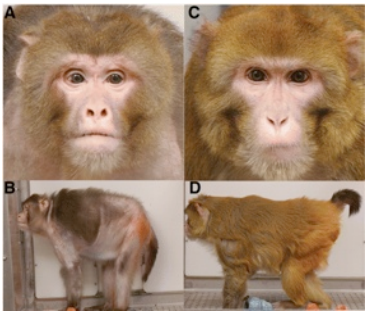
His work is credited with significantly advancing CR research after the discovery that lab mice fed a diet restricting their caloric intake by 50 percent, yet maintaining nutritional requirements, had nearly double their expected life span.

Walford received his medical degree from the University of Chicago in 1948, and joined the faculty at UCLA in 1954 as part of the Pathology and Laboratory Medicine Department.

He also served as an expert advisor to immunology in the World Health Organization (1969-1984), as a senatorial delegate to the White House Conference on Aging (1981), and as a member of the National Institute on Aging.

After leaving UCLA, Walford joined the crew of Biosphere 2 where he served as team physician for their two years in the enclosed experiment. In Biosphere 2, Walford was able to conduct the first completely monitored CR experiment in humans mimicking those performed in rodents and other species documenting life-extending benefits of CR. The results of Biosphere 2 have been extensively reported in the scientific literature.

## A NON-HUMAN PRIMATE MODEL OF CALORIE REDUCTION




*A and B photographs of a typical control animal at 27.6 years of age (about average lifespan). C and D photographs of an age-matched animal on calorie restriction.*

Could reducing calories really promote a longer lifespan in humans as it has in other species?

Because of lack of long-term studies, we can't know for sure; but the strongest evidence to date of long-term health benefits comes from results of a 20-year-long study in our close cousins. Scientists at Wisconsin National Primate Research Center aimed to find out if rhesus monkeys fed a diet 30 percent lower in calories than normal and with adequate nutrition would have fewer age-related diseases. The study's results, published in *Science* in 2009, found that monkeys on low-calorie diets were about three times less likely to die from age-related diseases than monkeys fed a normal diet.

Age-related diseases in rhesus monkeys are much like those experienced by humans—the most common being type 2 diabetes, cancer and cardiovascular disease.

For two decades (beginning in 1989 and ending in 2009), the researchers evaluated adult monkeys at least twice daily for food intake, body weight and composition, glucose regulation, energy expenditure, blood pressure and brain function.

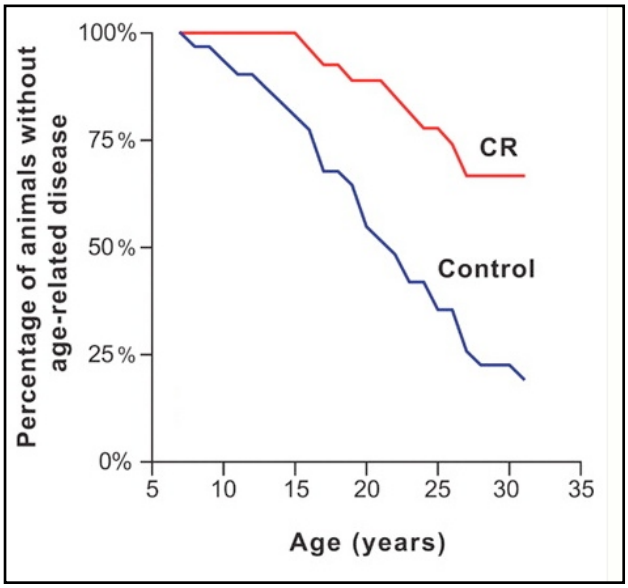



*Figure 2. Longitudinal study design and mortality curves showing age-related mortality. Animals that died from non-age-related causes are excluded. Reference: Colman et al.*

Their continual evaluation allowed for disease conditions to be recognized and treated as soon as they appeared.

As expected, the monkeys on restricted calories had lower body weights and more lean body mass than those in the control group.

The authors noted that increases in metabolic function were "consistent and striking."

The CR group showed sustained improvement in insulin sensitivity. In the control group, five of the animals developed diabetes and 11 more were considered pre-diabetic. In comparison, all animals in the CR group—including those with less-than-perfect metabolic function at the start of the trial—showed no alterations to glucose homeostasis.

As with humans, cancer occurs in rhesus monkeys increasingly as they age. In the study, the incidence of new pre-cancerous lesions was reduced by 50 percent in the CR monkeys.

Similarly, there was a 50 percent reduction in frequency of cardiovascular disease compared to the control.

Finally, the CR monkeys had reduced age-related brain atrophy (shrinking) in regions that play a part in motor and executive function.

"Given the obvious parallels between rhesus monkey and human, the beneficial effects of CR may also occur in humans," the authors conclude.

**Reference:** Colman RJ, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 2009;325:201-4.

## CLEANSING REGULARLY MAY BOOST HEART HEALTH

Regularly abstaining from food for at least one day each month may lower the risk of cardiovascular disease, according to research cardiologists from Salt Lake City (1). Their findings suggest greater advantages from Cleanse Days.

They observed 200 subjects, most being members of the Church of Jesus Christ of Latter-day Saints (LDS), whose monthly religious ritual involves fasting, or abstaining from two consecutive meals.

The study found that subjects who fasted regularly had a 58 percent reduction in risk of coronary artery disease.

These findings may explain why Utah LDS routinely have lower risk of death from cardiovascular disease compared to other Utahns and the United States population.

The same research team conducted a smaller experiment observing metabolic markers on 30 subjects instructed to fast with water for 24 hours. The researchers observed increases in HDL and LDL cholesterol and found that human growth hormone (HGH) increased 20 times in men and 13 times in women. The surge of HGH stimulates fat burning as it prevents muscle breakdown.

"This probably occurred because the body stopped metabolizing glucose and switched over to fat," said Benjamin Horne, Ph.D., MPH, director of cardiovascular and genetic epidemiology at Intermountain Medical Center Heart Institute, and the study's principal investigator.

The findings were presented April 3 at the American College of Cardiology's annual scientific sessions in New Orleans and confirms evidence from their larger 2007 study conducted on 448 Utahns (most of whom were LDS) published in the *American Journal of Cardiology* (2).

"These new findings demonstrate that our original discovery was not a chance event," Dr. Horne said.

The earlier study evaluated routine fasting among other LDS behaviors including social support, religious observance patterns, and abstinence from smoking, alcohol, tea, and coffee.

"In conclusion," the authors wrote, "not only proscription of tobacco, but also routine periodic fasting was associated with lower risk of [cardiovascular disease]."

Routine periodic "fasting was also associated with lower diabetes prevalence," the authors wrote.

They explain that the "likely explanation" is that fasting influences metabolic health by assisting weight loss and improving insulin sensitivity. They also suggested that fasting may "reset cellular sensitivity to glucose and/or insulin by periodically resting the system."

Finally, the authors point out that new findings suggest fasting also activates self-protective, cellular stress-resistance mechanisms.

Cleanse Days may work in the same way to boost heart health, but with the added advantage of optimal dosages of vitamins, minerals, and botanicals for optimal detoxification.

| | Univariable | | Modeled with Fasting | |
|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Fasting | 0.55 (0.35, 0.87) | 0.010 | ----- | ----- |
| *LDS-proscribed Beverages* | | | | |
| Alcohol | 1.63 (0.98, 2.72) | 0.06 | 1.40 (0.82, 2.39) | 0.22 |
| Tea | 1.44 (0.87, 2.38) | 0.15 | 1.23 (0.73, 2.08) | 0.43 |
| Coffee | 1.42 (0.88, 2.28) | 0.15 | 1.14 (0.68, 1.90) | 0.62 |
| *Religious Observance* | | | | |
| Religious Worship | 0.54 (0.31, 0.93) | 0.027 | 0.63 (0.35, 1.13) | 0.12 |
| Day of Rest | 0.92 (0.51, 1.65) | 0.78 | 1.05 (0.58, 1.93) | 0.87 |
| *Receipt of Social Support* | | | | |
| Talk about Health | 0.90 (0.18, 4.53) | 0.90 | 0.84 (0.16, 4.29) | 0.83 |
| Talk about Personal Problems | 1.40 (0.55, 3.56) | 0.48 | 1.36 (0.53, 3.50) | 0.53 |
| Financial Support | 0.87 (0.55, 1.39) | 0.56 | 0.88 (0.55, 1.41) | 0.60 |

*Figure 3. Among LDS behaviors, only fasting retained significance at $p<0.05$ in models for an association with cardiovascular disease.*

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## CLEANSING KEEPS WEIGHT OFF AFTER FEASTING

Most people who've ever embarked on a diet know how hard it is to "stick to it" and restrict calories day after day. For one, it requires steel-hard self-discipline to refrain from overeating. Needless to say, many people don't successfully adhere to a weight-loss diet nearly as long as they set out to.

The occasional feast—it's a pitfall many of us fall into, but one not to worry about. If you take a cue from a recent study, a Cleanse Day may help. Cleansing the day after feasting, in fact, may even put you right back on track to achieving all your health and weight-loss goals.

The study involved obese subjects alternating between "feed days" and "fast days." Each "feed day," participants were allowed to eat normally, then on "fast days" they cut calories to only a quarter of their energy needs. Sound familiar? The "fast days" resemble Cleanse Days only without supplementation with detoxification and cleansing ingredients from Cleanse for Life. The "feed days" resemble Shake Days only without the high-nutrient density and high-quality protein found in IsaLean Shake.

After a total of 10 weeks, the modified alternate-day fasting plan helped the subjects lose considerable weight. The subjects also showed significant drops in total cholesterol, LDL cholesterol, and triglycerides. High compliance was maintained throughout the study.

Krista Varady, Ph.D., who led the study along with other University of Illinois at Chicago researchers, told Isagenix, "I was surprised by how low some of the numbers dropped."

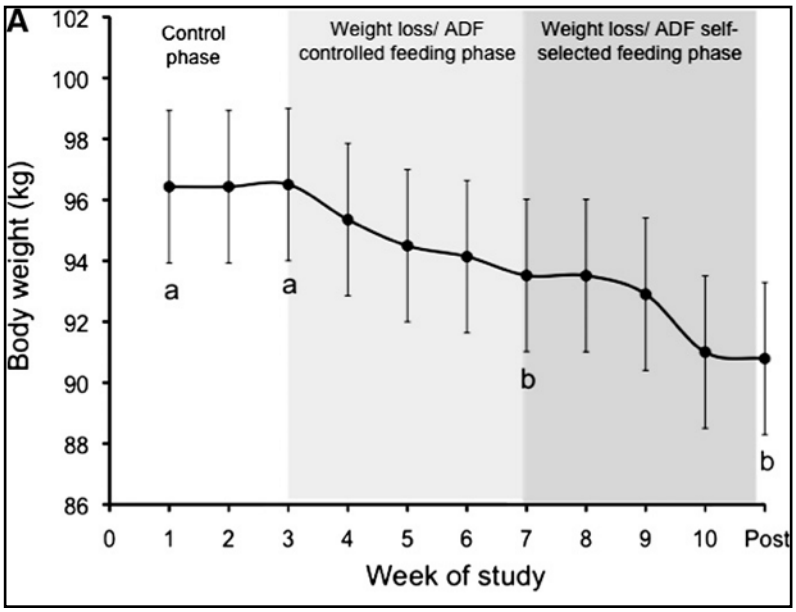


*Figure 4. Mean body weight of subjects (n=16) each week during the 10-week trial. There was no difference in percentage adherence between weeks during the trial.*

She added, "What really got me interested in alternate-day fasting was its potential in mice for reducing risk of cardiovascular disease. It's never clear how these things translate to humans."

Does the study suggest people who feast and fast continually lose weight over time? Why does she think the plan was successful?

"Yes, that's the idea," she said. "I think there is compensation on the 'feed days' as you continue. You're shrinking the stomach on the 'fast days'. By the time the 'feed days' come around, people are hungry, but they don't eat as much."

**Reference:** Varady K, et al. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. *Am J Clin Nutr* 2009.

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