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Foundation for the
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VitaLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

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Life Span Extension by Diet

The goal of medical care has always been to extend life either by preventing or treating individual diseases on a disease-by-disease basis. In fact, though, the overall effect of completely eradicating a single age-related disease like atherosclerosis or cancer would be an increase of only a few years in average life expectancy in the population. Imagine instead that the rate of aging itself could be slowed, so that all diseases occurred later in life. The result would be a radical increase in life span far beyond that which could be achieved by curing some single disease.

Extending Life Span to 168 Years

Surprisingly, scientists have known for almost 100 years how to slow aging sufficiently to extend life span by approximately 40%. That corresponds to a maximum life span in human beings of 168 years and an average life span of approximately 105. Not only is life extended, but there is a matching extension in the quality of life in animals who have been subjected to this treatment. What is this seemingly magical treatment? In the early part of the 20th century researchers found that by markedly underfeeding animals they survived longer. By the mid 1930's this had been carefully studied, and it was clear that a reduction in food intake could produce a 40% increase in life span in rats.

The structure of Methionine

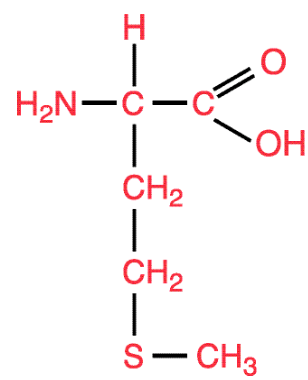

Figure 1.

Since that groundbreaking study scientists have exposed a variety of species to a variety of feeding strategies, and it has become clear that in all species studied the key is to reduce energy (calorie) intake throughout life in order to achieve a marked increase in survival time.

Not surprisingly, most age-related maladies are minimized or delayed by long term energy restriction. For example, in rats fed 60% of their normal caloric intake, all cancers appear approximately 40% later in life, and the animals live, not coincidentally, 40% longer. It is important to note that the range of tumors does not change, only their time of onset.

Why is energy reduction not commonly used to retard aging and delay the appearance of the diseases of advanced age? The answer is that the degree of food restriction necessary to extend life is so intense that animals fed such diets are constantly hungry, and it is unlikely that human beings would subject themselves to such profound lifelong discomfort in order to live longer.

However, scientists have continued over the past 50 years to examine caloric restriction in the hopes of identifying mechanisms through which this remarkable life span extension takes place. If the mechanisms were identified, it might be possible to invoke them through some other intervention, *i.e.,* a caloric restriction mimetic that would be more acceptable to people. The challenge in this approach is that energy is used in so many places and in so many ways that it is extraordinarily difficult to single out key places where reduced energy intake causes life extension.

An Alternative to Energy Restriction Emerges

Imagine, then, the excitement when scientists at OFAS discovered another dietary intervention that extends life but which is characterized by well-known metabolic pathways that are more amenable to analysis. This novel intervention involves lowering the dietary content of the amino acid methionine to a level that reduces growth somewhat but markedly extends life span.

All proteins are composed of chains of building blocks called amino acids. There are a limited number of different amino acids that are used to make proteins, and they can be divided into two broad categories: essential amino acids, those that an organism cannot make itself but must ingest, and non-essential amino acids, which can be made internally and so do not need to be consumed. Of the essential amino acids, methionine ranks as one of the most important since it is used to begin the synthesis of all proteins. The metabolic pathways that use and degrade methionine have been thoroughly studied in many species, including human beings.

The remarkable thing about dietary methionine restriction is that animals consuming this diet are free to eat all they wish and typically consume more calories than usual. This rules out energy restriction as the explanation for the life span extension phenomenon of methionine restriction. Further, since the animals eat all they want, they are not hungry! They behave normally but survive 40-45% longer than animals consuming “normal” levels of methionine. As expected with any age-slowing intervention, age-related diseases appear with the usual frequency for the species, just 40-45% later in life, and markers of important functions such as immunocompetence are preserved further into old age.

In a variety of studies, short term moderate methionine restriction has been shown to produce a variety of beneficial actions in animals. For many years it has been known, for example, that reduced methionine intake sharply retards the growth of solid tumors, most of which are dependent on ample methionine availability for growth and invasion. As you might expect, there is research in progress to convert this observation into a usable clinical approach to cancer. Vegetarians have known for many years that consuming the majority of their protein in the form of soy protein keeps total body fat low. It is now clear that this effect is due to the low level of methionine in soy protein and that enriching soy with methionine increases fat depots. Thus, methionine probably extends life span through a combination of effects—some specific to specific physiological conditions, others acting to retard aging so that most causes of illness and death are delayed.

Daily requirement of essential amino acids (for college-age males). (Other species frequently have other essential amino acid requirements, but methionine is always essential.)

Name	Grams
Arginine	0†
Histidine	Unknown‡
Isoleucine	1.30
Leucine	2.02
Lysine	1.50
Methionine	2.02
Phenylalanine	2.02
Threonine	0.91
Tryptophan	0.46
Valine	1.50

†Required by infants and growing children.
‡Essential, but the precise requirement is not yet established.

Table 1.

Scientists now have two interventions that slow aging: energy and methionine restriction. One of these mechanisms (energy restriction) is characterized by diffuse sites of utilization; the other (methionine restriction) must be occurring through some of the well-known pathways of methionine metabolism. Therefore, it is possible to compare these two interventions and, hopefully to identify key metabolic points amenable to direct specific manipulation without the imposition of difficult-to-follow dietary regimens.

Why bother trying to identify the key events involved in life span extension from methionine restriction? Why not just consume a low-methionine diet to achieve longer life? The answer to these important questions is that it is virtually impossible to assemble and consume a low-methionine diet. Nearly all meat, dairy, and vegetable proteins are rich in methionine. Those few that are naturally of low methionine content, *e.g.,* soy, as noted above, are usually processed by the food industry with added methionine to convert them into high-quality proteins. In addition to difficulty in finding and consuming such a diet, there is no assurance that low-methionine ingestion will be without some negative side effects. For example, female rodents receiving this diet are unable to reproduce, and all animals fed this diet from a young age are undersized.

An even more important question about dietary manipulation of life span concerns the validity of results in experimental animals to human beings, *i.e.,* results attained in rodents might not be duplicated in human beings consuming similar diets. There is no certain answer to this problem other than to note that both caloric and methionine restriction have been tested in a wide variety of species (ranging from yeast to primates) with good success. There are currently studies underway of energy restriction in monkeys, but since these animals live longer than rodents, it will take many years to determine whether primates respond to energy restriction with life span extension. Early results indicate that some metabolic changes resemble those seen in rodents fed low-energy diets, so there is some hope that the longer-term studies will be successful.

On the assumption that caloric or methionine restriction is effective in human beings, is there hope for those of us who have already passed through youth and would like to extend whatever remains of our lives with high quality? Drawing from animal experiments, there is some reason for optimism. In animals, caloric restriction has been shown to extend life span even when begun later in life, although the effect is considerably less robust, and the duration of the extension is less than that seen when the restriction is initiated early in life. Similarly, methionine restriction has some life-extending properties when begun in adulthood, but early is much more effective.