Retardation of aging processes by food restriction: an experimental tool[1-3]

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ABSTRACT The importance of food restriction in rats, mice, and hamsters as a tool for the study of aging is discussed. The evidence that food restriction retards the aging processes is summarized and includes its ability to extend the maximum life span, to decrease the rate of increase in age-specific mortality, to retard age changes in physiological processes, and to delay or prevent most age-associated diseases. Food restriction has its antiaging action by reducing the intake of energy rather than a specific nutrient. Research findings on the possible mechanisms by which food restriction retards the aging processes are discussed. The use of food restriction to test theories of aging is described and the controversial issue of its possible use as an intervention of human aging is addressed. *Am J Clin Nutr* 1992;55:1250S–2S.

KEY WORDS Retardation of aging, Life span extension, Aging intervention, Experimental gerontology, Energy intake and aging

It is more than 50 years since McCay and his associates (1) described the increase in maximum life span of rats in response to reducing their food intake. The design of this pioneering study was not the most desirable in that the rats suffered from infectious disease and the composition of the diet was different for the rats on restricted intake compared with those that were on unrestricted intake. Nevertheless, this phenomenon has proven to be very robust having been reproduced in many subsequent studies. Recent research has used semisynthetic diets to assure an adequate and similar diet composition for both the restricted and ad libitum–fed groups and barrier facilities were used to prevent the occurrence of infectious disease (2).

The potential value of this phenomenon as a tool for aging research began to be seriously considered in the 1970s. The initial question addressed was whether the increase in maximum life span in rats, mice, and hamsters is due to a retardation of the aging processes or to other factors. This question is difficult to answer because the basic biological nature of aging is not known. However, there are compelling reasons to conclude that restricting food intake retards the aging processes. The following summarizes these findings:

1) Aging is associated with changes in most physiological processes, many of which appear to be deteriorative in nature. Food restriction delays, blunts, or prevents most of these changes (3), ranging from delaying and blunting increases with age in serum cholesterol, to decreasing the loss with age in dopamine receptors of the corpus striatum, to retarding the age-related decline in the ability to learn a maze.

2) Food restriction retards the occurrence of most age-associated disease processes (4). In the male Fischer 344 rats used in our laboratory, three major age-associated diseases (nephropathy, cardiomyopathy, and neoplasia) are responsible for death. Food restriction almost totally prevents death due to nephropathy (5) and cardiomyopathy (5) and delays the occurrence of neoplasia to older ages (6).

3) Food restriction slows the increase with advancing age in the age-specific mortality rate. Recently, Finch et al (7) concluded that the rate of increase in age-specific mortality from maturity is a better indicator of the rate of aging of a species or population than the widely used maximum life span. Moreover, they pointed out that the time required for the age-specific mortality rate to double (MRD) is an excellent quantitative index of the rate of aging. Holehan and Merry (8) analyzed the data from four studies in regard to the effects of food restriction on the MRD and found it to average 102 d for ad libitum–fed rats and 197 d for food-restricted rats. This finding coupled with the broad spectrum of effects on age-associated physiological and disease processes provides strong evidence in support of the view that food restriction slows the aging processes in rodents.

A manipulation that slows the aging processes should provide a powerful tool for the study of aging. Indeed, it seems likely that determining the mechanisms by which food restriction retards the aging processes should provide insight on the basic biological nature of aging. Based on this assumption, research in our and other laboratories has been aimed at identifying these mechanisms.

The first question addressed was the nature of the restricted nutrient or nutrients responsible for the antiaging action of food restriction. Extensive research in this regard indicates that the antiaging effect is due to the restriction of energy intake rather than that of a specific nutrient (2).

McCay et al (1) postulated that food restriction extends the life span by slowing growth and delaying development. Many still hold this view as is evident from the presentation of Dr.

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Widdowson (9) at this meeting when she expressed concern about applying such a regimen to children. However, the concept has been discredited by research findings from our (10) and Walford's laboratories (11). A summary of our results are shown in **Table 1.** There was not a significant difference in the age of the 10th-percentile survivors between rats in which food restriction (60% of the ad libitum intake) was initiated at 6 wk of age (2 wk postweaning) and those in which it was started at 6 mo of age (young adult life). The maximum life span of these two groups was almost identical and was much greater than that of the ad libitum–fed rats.

Another popular belief is that food restriction influences aging processes by reducing body fat content. It does indeed lower body fat but evidence from two laboratories (12, 13) shows that the reduction in fat content does not play a causal role in life span extension by food restriction.

Sacher (14) proposed that food restriction retards aging by reducing the metabolic rate per unit of body mass. This concept was appealing for two reasons. First, it is the reduction in energy intake and not of other nutrients that is responsible for the effects of food restriction on the aging processes. Second, reactive oxygen molecules, such as superoxide, hydrogen peroxide, and hydroxyl radicals, generated during fuel use have been proposed to play a major role in aging (15). However, two lines of evidence indicate that Sacher's hypothesis is not correct. First, for most of the life span the intake of energy per unit of body mass is not lower for food-restricted rats than for the ad libitum–fed animals (16). Second, for most of the life span, the daily energy expenditure expressed as kcal/kg lean body mass is not reduced in food-restricted rats below that of ad libitum–fed rats (17). The reason for this, which at first seems to be an unlikely finding, is the rapid fall in lean body mass in response to food restriction. Within a few weeks the lean body mass readjusts, resulting in an energy intake and expenditure per unit lean body mass similar to that before the initiation of food restriction.

Thus, it appears that it is the reduction in energy intake per animal and not per unit of lean body mass that is responsible for the antiaging actions of food restriction. The challenge now is to learn how the reduction in energy intake per animal is coupled to the aging processes. The involvement of the nervous and/or endocrine systems is likely and it is further postulated that this results in metabolic changes that modulate the aging processes in the tissues of the body. Research is ongoing in several laboratories exploring these possibilities.

In regard to neural and endocrine involvement, the glucocorticoid system appeared to be a prime candidate. In 1986, Sapolsky and colleagues (18) proposed the Glucocorticoid Cascade Hypothesis of Aging. This hypothesis proposes that a major factor in the aging of rats (and possibly other mammals) is a loss of feedback regulation of plasma glucocorticoid concentrations because of age changes in hippocampal neurons. As a result, at advanced ages it is postulated that a sustained hyperadrenocorticism occurs, resulting in many of the characteristics of the aging phenotype, such as immunosuppression, osteoporosis, and impaired cognition. The possibility that food restriction retards the aging processes by preventing the occurrence of this hyperadrenocorticism at advanced ages was tested in our laboratory. Our findings (19) show that food restriction does not retard aging by preventing the development of hyperadrenocorticism. Moreover, our results indicate that Glucocorticoid Cascade Hypothesis does not describe a major aspect of aging but rather suggests the possibility that daily periods of moderate hyperadrenocorticism may well have an antiaging action. This study illustrates the power of the food restriction model as a tool for testing theories of aging and as a source of new insights.

TABLE 1
Age of the 10th-percentile survivors and the maximum life span of ad libitum–fed and food-restricted rats*

Dietary program	Age of 10th-percentile survivors	Maximum length of life
	d	
Ad libitum fed	822 (775–941)	941
Food restricted from 6 wk of age	1226 (1183–1296)	1296
Food restricted from 6 mo of age	1177 (1075–1299)	1299

* Data from Yu et al. (10). 95% confidence intervals are in parentheses.

The concept that food restriction may retard aging by reducing glycemia and glycation was also explored (20) and the results to date support this possibility. Food-restricted rats were found to maintain mean 24 h plasma glucose concentrations $\approx$15 mg/dL below those of ad libitum–fed rats throughout the life span. As pointed out by Cerami (21), plasma glucose concentrations are a major factor influencing the glycation of proteins, which he postulates to have damaging consequences and to possibly underlie the aging processes. It is also interesting to note that food-restricted rats maintain plasma insulin at much lower concentrations than do ad libitum–fed rats. Reaven (22) points out that hyperinsulinemia may have long-term detrimental consequences; eg, there is evidence that it promotes atherogenesis.

Although the rate of fuel utilization per unit lean body mass is not decreased, it is still possible that food restriction may protect animals from the damaging actions of reactive oxygen molecules. This protection may involve a reduced rate of production of those molecules, an increased ability to scavenge them by the action of enzymes such as superoxide dismutase and catalase, an increased ability to repair the damage, or a combination thereof. There is evidence that food restriction reduces the generation of reactive oxygen molecules and also enhances mechanisms protecting the cell from their damaging action (3). Thus, this may be another mechanism underlying the antiaging action of food restriction.

There is no question that food restriction is an important tool for the experimental gerontologist. Unfortunately, this fact is often obscured by the debate regarding its use as an intervention in regard to human aging. Walford (23) has been a strong advocate for such use. Others, as is evident from the lecture of Dr. Widdowson (9) at this meeting, are less than enthusiastic about such use because of concerns for potentially harmful effects. As stated above, her concern about its potentially harmful effects in children may be moot because for the antiaging effect to be expressed in rodents does not require the initiation of food restriction before adult life. The concern expressed by Dr. Widdowson in regard to food restriction decreasing the ability to cope with stress, including compromised immune function, requires further comment. It is true that food restriction delays the development of the immune system but it is also true that

it preserves that function into advanced ages during which ad libitum–fed rodents have compromised immune function (24). Dr. Widdowson points out that food restriction reduces the ability of rodents to cope with cold stress, which is true, but it also should be noted that food-restricted rodents cope more effectively with many other forms of stress. In 1988, Weindruch and Walford (25) published a scholarly, encyclopedic book on food restriction. In this book, the authors clearly state that they feel this dietary regimen would be effective in humans but they also discuss potential dangers and disadvantages. It is indeed clear that at this time the value and risks of this dietary regimen for human use have not been fully defined. This author pleads for an open mind in this regard and above all not to allow this controversy to obscure the power of this tool for aging research.

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