Food Restriction and the Aging Process

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Almost 50 years have passed since McCay and colleagues[1] first demonstrated that restricting the amount of food consumed increases the length of life of laboratory rats. This finding proved to be highly reproducible and to also be true of other laboratory rodent species, e.g., mice. As a result, this phenomenon has become a cornerstone of experimental biologic gerontology. In fact, many investigators believe that it provides a basis for experimental explorations aimed at the understanding of the fundamental nature of the aging process.

Indeed, the results of the many studies conducted during these 50 years almost unequivocally establish that food restriction slows the aging process.[2] The findings establishing this can be summarized as follows: 1) lifespan is extended; 2) age-related physiologic deterioration is retarded; and 3) age-related disease processes are retarded. Any one of these effects alone is indicative of a slowing of the aging process, and in combination they provide strong evidence that such is the case. Although the many studies strongly indicate that food restriction acts on the basic aging process, they provide little insight into the mechanism of this action. In this paper, data evidencing each of these effects are presented and possible mechanisms of action of food restriction on the aging process are discussed.

Since many of the data utilized in this presentation are from studies carried out in our laboratory during the last eight years, the design of our research is briefly described: Our first study involved two groups of male Fischer 344 rats. One group (Group A) was fed ad libitum a diet with a caloric composition of 21 per cent protein, 57 per cent carbohydrate, and 22 per cent fat, and the other group (Group R) was restricted to 60 per cent of the food intake of Group A from 6 weeks of age on. The second experiment involved five dietary groups. Groups 1 and 2 were the same as Groups A and R, respectively, of the first study. Group 3 was restricted to 60 per cent of the food intake of Group 1 from 6 weeks to 6 months of age and then fed ad libitum for the rest of life. Group 4 was fed ad libitum until 6 months of age, then restricted to 60 per cent of the food intake of Group 1. Group 5 was fed ad libitum a diet with a caloric composition of 12.6 per cent protein, 65.4 per cent carbohydrate and 22 per cent fat from 6 weeks of age on.

LONGEVITY

The results of the longevity component of the first study[3] are shown by the survival curves in Figure 1. Both Group A and Group R were composed of 115 rats. It is clear that not only did food restriction increase the median length of life, it also markedly increased the maximum length. Indeed, approximately 70 per cent of the Group R rats were still living when the last of the 115 Group A rats died. The longevity component of the second study involved only 40 rats in each group. The survival curve of Group 1 almost perfectly replicated that of Group A and that of Group 2 replicated Group R; this is particularly striking when it is realized that the first study took place between 1975 and 1979 and the second study between 1979 and 1983. The median length of life of Group 1 was 701 days and the maximum length of life 941 days, compared with a median length of life of Group 2 of 1,046 days and a maximum length of life of 1,296 days. Group 3, which was food restricted only during early life (until young adulthood) had a median length of life 808 days and a maximum length of life of 1,040 days, i.e., food restriction limited to early life caused small but significant extensions of both the median and the maximum lengths of life. Group 4, which was restricted starting in adult life, had a median length of life of 941 days and a maximum length of life of 1,299 days, i.e., food restriction started in adult life, although less effective in extending median length of life than near-lifelong

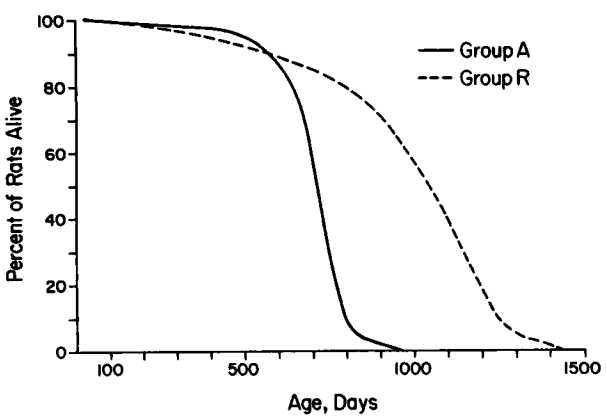

Figure 1. Survival curves of Group A (fed ad libitum) and Group R (food restricted) rats. Reproduced with permission from Yu et al.[3]

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restriction, was just as effective in extending the maximum length of life.

The median length of life of the rats in Group 5 was 810 days and the maximum length of life was 969 days. The Group 5 rats had a similar caloric intake and grew as rapidly as Group 1 rats. Thus, protein restriction without caloric restriction caused a small increase in median length of life but did not significantly increase maximum length of life.

AGE-RELATED PHYSIOLOGIC DETERIORATION

Food restriction retards age-related deterioration of the physiologic system. The changes in serum cholesterol concentration with age[4] are a typical example of this (Fig. 2). At 6 months of age (young adults), the serum cholesterol concentration of Group A rats was the same as that of Group R rats. However, in the case of Group A rats, there was a marked rise in serum cholesterol concentration with increasing age, and this rise was both delayed and less marked in Group R rats. Similar results were obtained in our laboratory[2] in regard to age-related changes in the responsiveness to hormones, changes in the serum concentrations of hormones, changes in adipose tissue function, and changes in skeletal muscle structure and function. In addition, Levin and colleagues[5] have shown that the age-related loss of dopamine receptors is delayed and less marked in food-restricted rats. There is also a large body of work that shows that age-related deterioration of the immune system is delayed by food restriction.[6]

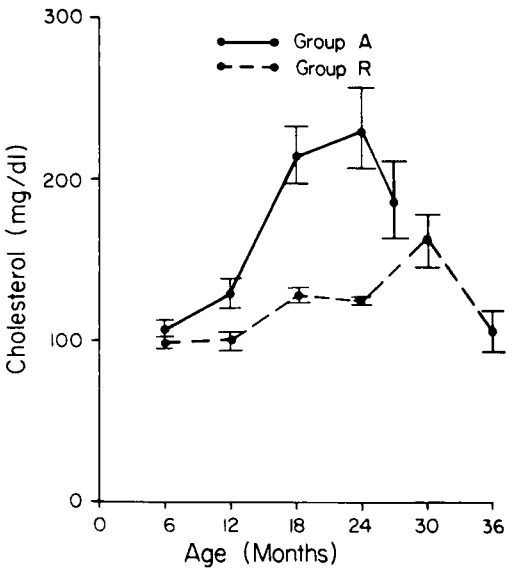

Figure 2. Changes in serum cholesterol concentrations with age in Group A and Group R rats. Reproduced with permission from Liepa et al.[4]

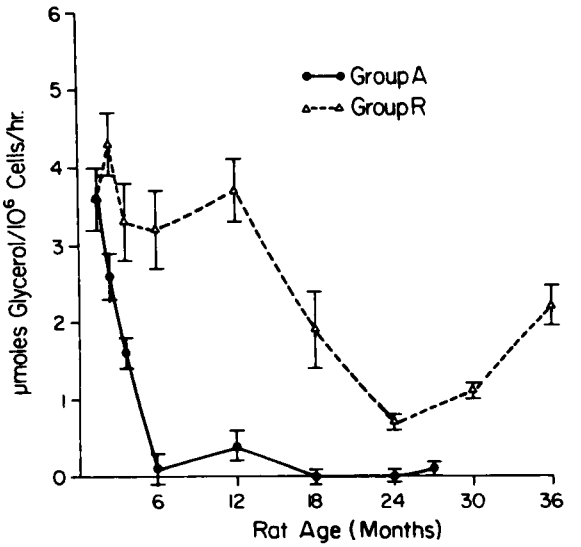

Figure 3. Changes in the lipolytic responses of fat cells to glucagon in Group A and Group R rats. Reproduced with permission from Masoro et al.[2]

The findings with regard to the lipolytic responses of fat cells to glucagon[2] are somewhat unique in that in this case the rats fed ad libitum had lost all responsiveness by young adulthood, i.e., by 6 months of age (see Fig. 3). Food restriction prevented this loss from occurring during the first year of life, and at no age was there a total loss of responsiveness of the fat cells of Group R rats to glucagon. It was further shown that this was not related to the size of the fat cell or to acute effects of food restriction.

AGE-RELATED DISEASE

The major age-related disease in Fischer 344 male rats is chronic nephropathy.[8] The lesions are graded histopathologically as Grades 1, 2, 3, 4, and E in order of increasing severity. Rats with Grade 1, 2 or 3 lesions have normal BUN values and serum creatinine concentrations (indeed, they present no clinical evidence of renal dysfunction). Rats with Grade 4 lesions have moderately elevated BUN and serum creatinine concentrations but no other clinical evidence of renal dysfunction. However, those with Grade E lesions have markedly elevated BUN and serum creatinine concentrations and, in many cases, parathyroid hyperplasia, osteodystrophy, and metastatic calicification. There was a progressive increase in severity of chronic nephropathy in Group 1 rats starting at 6 months of age; by 27 months of age most of the Group 1 rats had Grade 4 or Grade E lesions. In contrast, the progression of these lesions was markedly retarded in Group 2 and 4 rats, with few rats having more than Grade 2 lesions at 30 months of age, i.e., near-lifelong or adult-life food restriction markedly reduces the rate of progression of chronic nephrop-

TABLE 1
Correlation between Adiposity and Lifespan in Rats

	Group A (n = 14)		Group R (n = 16)	
	r*	*P*†	r	*P*
Fat content at 8 months of age	−0.12	*NS*	+0.12	*NS*
Maximum measured fat content	−0.04	*NS*	+0.63	<0.001
Maximum measured % body fat	−0.10	*NS*	+0.63	<0.001

* r refers to correlation coefficient.

† *P* of less than 0.05 is taken as significant; *NS* denotes not significant.

Data from Bertrand et al.[10]

athy. The rats in Group 3 and 5 showed less rapid progression of chronic nephropathy than did Group 1 rats but more rapid progression than did rats of Groups 2 and 4. Of the rats that died spontaneously, 51 per cent of the Group 1 rats, 32 per cent of the Group 3 rats, 10 per cent of the Group 5 rats, 4 per cent of the Group 4 rats and 2 per cent of the Group 2 rats had Grade E lesions. It is surprising that restricting protein (Group 5) had such a great ability to retard clinically relevant renal lesions without markedly affecting median or maximum length of life.

Another age-related lesion that commonly occurs in male Fischer 344 rats is cardiomyopathy.[8] These lesions are graded as Grades 1, 2, and 3 in order of increasing severity. Grade 3 lesions almost certainly indicate cardiac dysfunction because massive degeneration of myocardial cells and fibrosis are involved. There was a rapid progression of cardiomyopathy in Group 1 rats, with 21 per cent of the rats that died spontaneously having Grade 3 lesions. In contrast, none of the rats in Group 2 and only 2 per cent of the rats in Group 4 had Grade 3 lesions at death. Groups 3 and 5 had a less rapid progression of cardiomyopathy than did Group 1 rats and a more rapid progression than did rats of Groups 2 and 4. Near-lifelong food restriction (Group 2) and adult-life food restriction (Group 4) were the most effective dietary regimens in slowing this disease process.

From the data obtained with rats sacrificed at various ages, it is clear that the appearance of neoplastic disease was delayed in the rats in Groups 2 and 4 compared with the rats in Groups 1, 3, and 5. However, the percentages of the rats in Groups 2 and 4 that died spontaneously that had tumors were higher than those of rats that died spontaneously in Groups 1, 3, and 5; but, of course, the rats in Groups 2 and 4 were much older when they died than the rats in Groups 1, 3, and 5. Thus, near-lifelong or adult-life food restriction delays the occurrence of neoplastic disease but does not prevent it from becoming the major clinical problem in relation to death.

HYPOTHESES

The following four major hypotheses have dominated thought about the mechanism by which food restriction slows the aging process: 1) it acts by delaying maturation; 2) it acts by slowing the rate of growth and prolonging its duration; 3) it acts by reducing body fat; and 4) it acts by reducing the metabolic rate per unit body mass.

The first of these hypotheses was the basis for McCay's first experiments.[1] He postulated that aging was a postmaturational process and that if maturation could be prevented, aging would not occur. He used food restriction to prevent maturation and interpreted his findings in this light, i.e., food restriction did not prevent maturation, but slowed it, thereby delaying the onset of aging and prolonging life. However, our findings show that food restriction started in rats at 6 months of age (Group 4) was as effective in the extending lifespan as food restriction started early in life (Group 2). Since maturation should be complete long before 6 months of age, these data are strong evidence against this hypothesis.

The second hypothesis was proposed because of the considerable body of data showing an inverse relationship between rate of growth and length of life in a variety of rodent species. In addition, it had been reported that there is a direct correlation between duration of growth and length of life. Indeed, it has been stated that aging does not begin until growth is completed. Our findings that restricting food intake of rats after rapid growth is completed (Group 4) is as effective as near-lifelong restriction (Group 2) in extending the lifespan and much more effective than food restriction limited to the rapid growth period (Group 3) provide strong evidence against this hypothesis.

The third hypothesis is based on the widely held belief that even mild obesity in humans decreases longevity, a view that has recently been challenged.[9] Data on the relationship between fat mass and length of life in the Group A and Group R rats of our first study[10] are presented in Table 1. It is true that Group R rats were leaner than Group A rats (data not shown). However, within rats of Group A, there was not a significant correlation between length of life and amount of body fat,

TABLE 2
Lifetime Total Caloric Expenditures in Rats

	Mean Length of Life (Days)	Mean Lifetime Caloric Expenditure Per Gram Body Weight
Group A	701	91.5
Group R	986	133.5

Data from Masoro et al.[14]

while in the case of Group R rats, a positive correlation was observed (i.e., the fatter the rat, the longer the life). These findings do not support the hypothesis that food restriction increases the length of life because it reduces body fat.

The hypothesis that food restriction increases longevity by reducing metabolic rate per unit body mass has as its basis the data reported at the turn of this century by Rubner. His findings indicated that domestic animals of various species and sizes utilized similar amounts of calories per kg body mass per lifetime. On the basis of this and other data, Pearl[11] proposed in the 1920s the "rate of living theory of aging" which can be simply stated as the higher the metabolic rate per unit body mass, the faster the rate of aging and the shorter the length of life. This theory, although popular at the time, was out of favor for many years. However, it was resurrected in 1977 by Sacher,[12] in his review of food restriction and life prolongation. Sacher analyzed data reported by Ross on rats fed five different diets, all resulting in different lengths of life. Sacher found that the Kcal of food ingested per gram body weight per lifetime was the same for the rats in all of these dietary groups. Sacher concluded that food restriction prolonged life by reducing the metabolic rate per unit body mass. However, because he was utilizing published data rather than detailed raw data, Sacher had to base his calculations on assumptions; indeed, a different set of assumptions would have led to quite different conclusions. Calculations[13] based on the raw data of our first study and thus requiring no assumptions indicated that the rate of caloric consumption per gram body mass was greater for Group R rats than for Group A rats over most of the lifespan (Fig. 4).

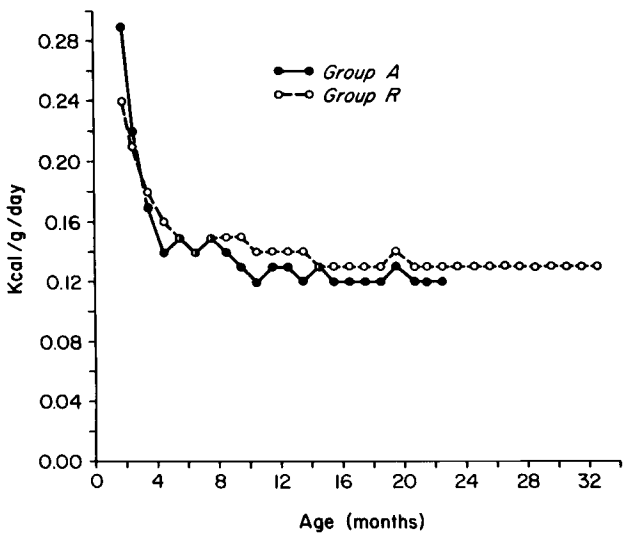

Figure 4. Food intake per unit body mass in Group A and Group R rats. Reproduced with permission from Masoro.[13]

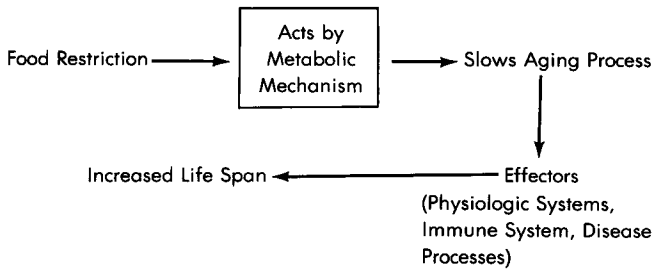

Figure 5. A general metabolic hypothesis.

Based on the lean body mass, the rates of caloric consumption per gram lean body mass were the same for Group A and Group R rats. Moreover, the total caloric intake per gram body mass per lifetime[14] was much greater for Group R than for Group A rats (Table 2). Our data therefore do not support the view that food restriction prolongs life by reducing the metabolic rate per unit body mass.

If the major hypotheses that have been proposed do not provide valid insight into the mechanism of action of food restriction, are there other more productive ways of viewing the interaction of food restriction and the aging process? A general metabolic hypothesis (Fig. 5) developed jointly by Dr. Byung P. Yu and myself provides an orientation consistent with the existing data. In this schema, food restriction is believed to slow the aging process by acting on a specific metabolic process. The slowing of the aging process retards age-related physiologic and immunologic deterioration and age-related disease, which in turn results in an increased lifespan. If this hypothesis is valid, then future research should focus on the nature of the metabolic process or processes coupling food restriction to the slowing of the aging process. Unfortunately, the number of possible metabolic mechanisms that could be involved is vast. That food restriction acts by slowing metabolic rate appears to be ruled out, but there is little information currently available pointing to a specific metabolic mechanism as a particularly likely candidate.

RELEVANCE OF FOOD RESTRICTION IN RODENTS TO HUMAN AGING

The question of the relevance of the findings reported above to human aging cannot be directly tested because of the impossibility of gathering the resources to execute such studies in species longer-lived than rodents. However, it seems likely that the basic aging processes of all mammals are similar and that nutritional manipulations that slow the aging process in rats will do the same in humans. This is not meant to imply that food restriction in humans would lead to a significant increase in lifespan, for the following reason. Laboratory rodents have traditionally been maintained in a nutritionally unique manner: they have been provided food

ad libitum, and the protein content of the diet has usually been in excess of 20 per cent by weight. Both of these procedures have been aimed at attaining rapid growth and a high rate of reproduction, but in addition they have increased the rate of aging and shortened the lifespan. Certainly, many humans also have dietary habits that promote the aging process and shorten the lifespan. However, of the billions of people who have lived and for whom lifespans have been recorded, some must have followed dietary regimens similar to that of the food-restricted rats. A fraction of such people should have reached the maximum lifespan of the human species, thus making it unlikely that nutritional manipulations will lead to a length of life greater than 100 to 110 years.

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