Assessment of Nutritional Components in Prolongation of Life and Health by Diet (42985)

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Abstract. **Restricting the food intake of rodents extends the median length of life and the maximum life-span. It also retards most age-associated physiologic change and age-associated diseases. Our research indicates that the ability to retard disease processes is not the major reason for the extension of life-span or for the retardation of age change in most physiologic systems. Rather, it appears that most of the actions of food restriction are due to its ability to slow the primary aging processes. We found this action to relate to the restriction of calories rather than specific nutrients (e.g., protein or fat or minerals). Our findings point to the reduction in caloric intake per rat rather than per gram lean body mass as the basis of the retardation of aging processes by food restriction. The challenge is to learn how caloric intake per rat is coupled to the aging processes. We are currently focusing on the possibility that neural and endocrine mechanisms are involved. Our preliminary findings point to the likelihood of an involvement of the insulin-glucose system.** [P.S.E.B.M. 1990, Vol 193]

The most striking effect of partial restriction of the food intake of rodents is the marked increase in life-span. The data in Table I were obtained in a study carried out in our laboratory (1) comparing *ad libitum*-fed male Fischer 344 rats with rats receiving 60% of the mean food intake of the *ad libitum*-fed rats. It should be noted that not only was the median length of life markedly increased but the maximum life-span was similarly increased. These findings are typical of those of others with various strains of rats and with hamsters and mice of both sexes (2).

In addition to its effects on longevity, food restriction also retards a broad spectrum of age changes in physiologic processes (Table II). Although the number of age changes in physiologic processes influenced by food restriction is extensive (in no way is Table II a comprehensive coverage of such findings), it should not be concluded that all systems are so affected. For example, the age-associated increase in systolic blood pressure in male Fischer 344 rats is not influenced by food restriction (9). Indeed, it is difficult to know the extent to which food restriction fails to modulate age-associated changes in physiologic processes because of the tendency of investigators and journals not to publish negative findings.

Food restriction retards most of the disease processes that occur with advancing age. In the male Fischer 344 rats studied in our laboratory, all age-associated disease processes were either delayed or the progression in severity markedly attenuated (14). The most striking example is the progression of nephropathy with age. These kidney lesions are scored as Grades 0, 1, 2, 3, 4, and E in order of increasing severity, with Grade 0 indicating no lesions and Grade E end stage lesions. Rats with Grades 4 and E lesions have elevated serum creatinine and urea levels and those with Grade E lesions also have parathyroid hyperplasia, osteodystrophy and metastatic calcification. Clearly, rats with Grades 4 and E lesions are on the verge of or are in kidney failure. Data on the progression of nephropathy with advancing age are presented in Figure 1 (15). The *ad libitum*-fed rats showed a marked progression in severity of lesions with age whereas in the food-restricted rats there was little increase in severity with age. At the time of spontaneous death 72% of the *ad libitum*-fed rats had severe lesions (Grades 4 or E) and 2% of food-restricted rats had lesions of this severity (14); this is particularly remarkable in light of the much greater length of life of the food-restricted rats.

Similar findings were obtained for the progression of cardiomyopathy (14); at the time of spontaneous death, 21% of the *ad libitum*-fed male Fischer 344 rats had severe (Grade 3) cardiomyopathy whereas none of the food-restricted rats had lesions of this severity (14). The other major age-associated disease in male Fischer 344 rats was neoplastic disease. Food restriction delayed the appearance of neoplastic disease to older ages but did not reduce the eventual occurrence of this disease process.

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Table I. Influence of Food Restriction[a] on Longevity of Male Fischer 344 Rats[b]

	Ad libitum-fed rats (n = 115)	Food-restricted rats (n = 115)
Median length of life (days)	711	1046
Age of 10th percentile survivors (days)	797	1236
Maximum length of life (days)	963	1435

[a] Food-restricted rats received approximately 60% of the mean food intake of the *ad libitum*-fed rats.
[b] Data are from Yu *et al.* (1).

Table II. Age Changes in the Physiologic Systems Retarded by Food Restriction

Increases in plasma lipid levels (3)
Increase in plasma parathyroid hormone concentration (4)
Increase in plasma calcitonin concentration (5)
Loss in response of adipocytes to lipolytic hormones (6)
Loss in central nervous system neurotransmitter receptors (7)
Loss in ability to learn a maze (8)
Loss of locomotor activity (9)
Decreased vascular smooth muscle tension development (10)
Loss of bone mass (4)
Loss of γ crystallins of lens (11)
Loss of female reproduction function (12)
Alterations in immune function (13)

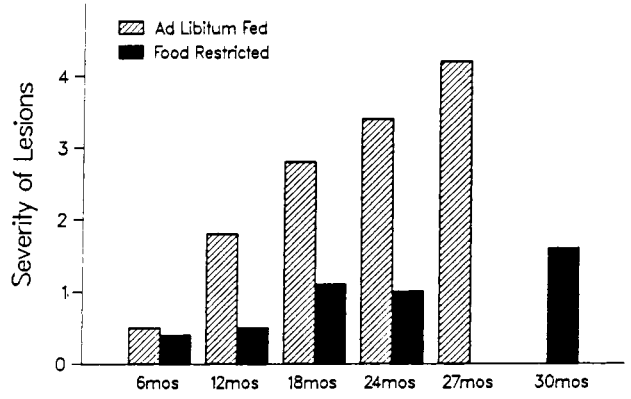

Figure 1. Age and the severity of chronic nephropathy in *ad libitum*-fed and food-restricted male Fischer 344 rats. Data are from Maeda *et al.* (14) and figure is reproduced with permission from Masoro (15).

The very breadth of the actions of food restriction on physiologic and disease processes indicates that it probably acts by retarding the primary aging processes. A caveat in drawing this conclusion, however, is the possibility that this breadth of effects is secondary to retarding a particular disease process, specifically in the case of male Fischer 344 rats the nephropathy. To evaluate this possibility, attempts were made to retard nephropathy by means other than food restriction.

Two other dietary procedures were found to retard the progression of nephropathy: (i) reducing the protein (casein) content of the diet from 21% to 12.6% and (ii) replacing the dietary casein with soy protein. In the former, 37% of the rats has severe renal lesions at the time of spontaneous death (14) and in the latter 27% had such lesions (16). In spite of this marked reduction

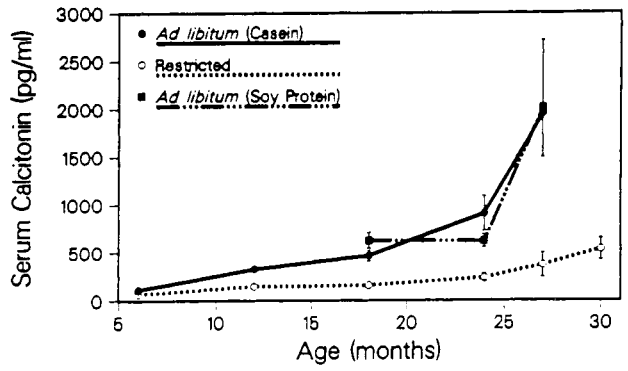

Figure 2. Age changes in serum calcitonin concentration. Rats were fed either a 21% casein diet *ad libitum* or restricted to 60% of the mean *ad libitum* intake or fed a 21% soy protein diet *ad libitum*. Figure is reproduced with permission from Kalu *et al.* (17).

in the prevalence of severe renal lesions, these dietary manipulations resulted in only small increases in longevity (9, 16). In addition, unlike food restriction, these manipulations of quantity or quality of dietary protein did not influence age changes in most physiologic processes (3, 17). Age changes in serum calcitonin concentration (Fig. 2) is a typical example. A marked increase in serum calcitonin concentration occurs with advancing age in *ad libitum*-fed rats whether the source of dietary protein is casein or soy protein while food restriction almost totally prevents this increase (17). This provides strong evidence that food restriction does not prevent a rise in serum calcitonin concentration by retarding kidney disease. A similar conclusion can be drawn in regard to most other actions of food restriction. However, a few of the actions of food restriction are secondary to its effect on nephropathy. For example, serum parathyroid hormone levels increase markedly with age in rats fed the casein-containing diet *ad libitum* but not in rats fed the soy protein diet *ad libitum* or in food-restricted rats (Fig. 3). Indeed, the evidence indicates that the retardation of kidney disease is the major factor underlying the prevention of age-associated increases in serum parathyroid hormone concentration (17). The prevention of the age-associated loss of bone density by food restriction also seems to be secondary to its action on kidney disease. Therefore, although some of the actions of food restriction are related to its ability to retard nephropathy, most are not so explained and rather appear to be due to its ability to retard the primary aging processes.

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Our research on the effects of dietary protein on kidney disease also yielded as a by-product evidence that restricting protein was not a major factor in the antiaging of food restriction. This conclusion was further supported by our recent work which shows that food restriction not involving protein restriction was as effective in increasing maximum life-span as food restriction involving protein restriction (18). In another study, we showed that the restriction of the fat component or the mineral component of the diet was not responsible for the antiaging actions of food restriction (19). Since vitamins were not restricted in our food restriction studies and since restriction of individual dietary components such as fat or protein involved reciprocal changes in dietary carbohydrate content, all evidence points to restriction of calories as the responsible factor in the antiaging action of food restriction.

A major unresolved issue is the mechanism by which restriction of calories retards the aging processes. McCay *et al.* (20), who were the pioneers in food restriction research, suggested that food restriction increased the life-span by retarding growth and development. Research carried out in our laboratory makes this hypothesis unlikely since food restriction of male Fischer 344 rats started at 6 months of age (adult initiation) was as effective as restriction started at 6 weeks of age (initiation soon after weaning) in increasing life-span, retarding age-associated physiologic changes, and retarding age-associated disease processes (9).

Another view (21) which has had many proponents is that food restriction extends the life-span by decreasing body fat content. This concept has been explored in our laboratory (22). Food restriction was found to decrease body fat content but it was further shown that this decrease in body fat is not causally related to the extension of life-span.

The concept that food restriction retards the aging processes by decreasing the metabolic rate (23) has been widely embraced and continues to have many proponents in spite of the fact that research in our laboratory provides strong evidence against it. In our study (24) oxygen consumption was measured for 24-hr periods under usual living conditions. The metabolic rate expressed as k calorie per kilogram lean body mass or per kilogram body mass to the two-thirds or three-quarter power was found to be the same for food restricted as for *ad libitum*-fed rats. Moreover, measurements of food intake (25) are in agreement with the metabolic rate findings, i.e., food intake expressed as k calorie per day per gram lean body mass is the same for food-restricted and *ad libitum*-fed rats.

The conclusion to be drawn from our studies is that it is the caloric intake per rat rather than per gram lean body mass which retards the aging processes. The challenge is to determine how caloric intake per rat is coupled to the aging processes. Our attention has focused on a possible role of the endocrine and nervous systems in this coupling. Our initial work was on the adrenal glucocorticoid system because of the evidence of Sapolsky *et al.* (26) of an involvement of that system in the aging processes. Our current work does not yet permit a definite conclusion on the role of the adrenal glucocorticoid system in the action of food restriction.

However, related research has yielded data which indicate that, in part, food restriction may retard aging by maintaining low plasma glucose levels. Cerami (27) proposed that glucose may serve as a mediator of aging by its ability to cause the nonenzymatic glycation of proteins. The chemical events involved are the formation of Schiff bases, Amadori products, and ultimately what Cerami calls advanced glycosylation end products. Glycation of proteins promotes protein cross-linking as well as other functional changes which Cerami feels may underlie aging. Moreover, the extent to which proteins are glycated increases as the sustained level of glucose in their environment increases. In our study (28), the diurnal pattern of plasma glucose concentration was determined (Fig. 4) and it was found that throughout most of the day plasma glucose levels were

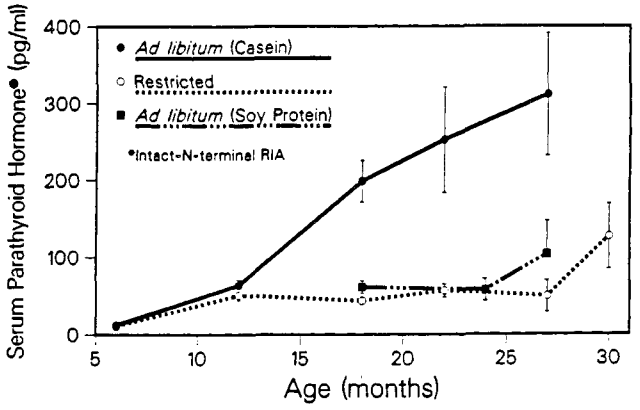

Figure 3. Age changes in serum parathyroid hormone concentration. Rats were fed either a 21% casein diet *ad libitum* or restricted to 60% of the *ad libitum* intake or fed a 21% soy protein diet *ad libitum*. Figure is reproduced with permission from Kalu *et al.* (17).

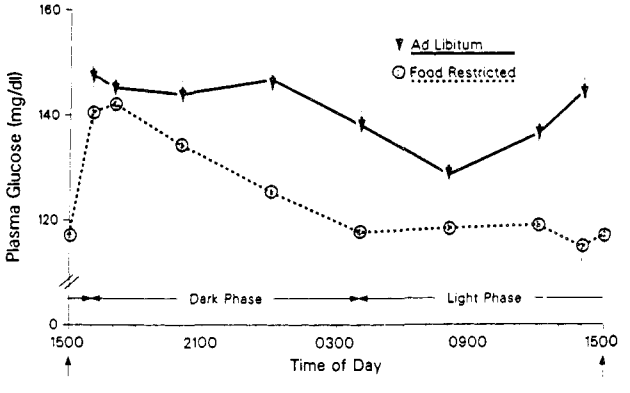

Figure 4. Diurnal pattern of plasma glucose concentrations in 4- to 6-month-old rats *ad libitum* fed or restricted to 60% of the *ad libitum* food intake. The vertical arrow indicates the time of feeding the food-restricted rats. Figure is reproduced with permission from Masoro *et al.* (28).

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lower in food-restricted than in *ad libitum*-fed rats. The extent of glycation of hemoglobin was also lower in food-restricted rats. Moreover, unpublished data indicate that food-restricted rats can utilize glucose at the same rate per unit of lean body mass as *ad libitum*-fed rats while maintaining lower plasma glucose and insulin concentrations. This metabolic characteristic may well underlie much of the antiaging action of food restriction.

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