Introduction

Chronic Dietary Restriction and Longevity

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Life-span is a genetically controlled (1) characteristic of a species or strain. Longevity is, however, a result of delaying onset of the diseases to which the aged are especially prone. Almost all biomedical research has been aimed at enabling individuals to reach their species life-span by disease prevention or cure. The one method, however, that has been established for increasing longevity toward a maximum life-span is drastic food intake restriction (2). This has been demonstrated for all species studied. It has been found that disease-prone strains (e.g., of mice) show the most dramatic effect of food restriction on longevity (doubling or tripling and occasionally even quadrupling survival time). Animal strains which conform to established "normal" life-spans do, however, also show impressive increases in longevity when subjected to similar drastic reduction in food intake, undernutrition without malnutrition, and it seems likely that the basic mechanism for the increased longevity in mice of short- and long-lived strains are the same.

The original observations of the effect of restricted food intake on longevity (delayed onset of aging diseases) were those of Moreschi in 1909 (3) and Rouse in 1914 (4), both dealing with mice carrying sarcomas. The results were dramatic. The work, however, which has stimulated the progressively increasing activity in this area is based on the reports of McCay *et al.* (5) from at Cornell University. Harper (1) points out the most serious problem of the original Cornell work. Half of the food intake-restricted rats died before 300 days of age, while all of the full-fed animals were alive and well. Thus, it was only the small and immature rats that showed extended longevity as a result of the food intake restriction. This problem can, however, be avoided by using 40% rather than 50% restriction of food intake.

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The experiments of Barrows (6) and Barrows and Kokkonen (7) and those of Nolen (8) indicated that new information must be transmitted from the genes at different ages to account for the continual changes throughout life. On this basis Nolen (8) found that even a restricted intake period of only 12 weeks in adult rats increased survival time almost as remarkably as lifetime restriction, while Barrows and Kokkonen (7) reported that restricted intake begun at midlife (e.g., 12–15 months in rats) increased longevity and delayed onset of diseases of aging. In short-lived mouse strains in which the animals are prone to develop early in life autoimmune diseases, hyalinizing renal diseases, and lymphoid malignancies, the imposition of chronic energy intake restriction very much prolonged life and health and inhibited progression of disease (9). Weindruch and Walford (10) and Weindruch *et al.* (11) have more recently shown that dietary restriction can be imposed as late as midlife. Dietary restriction only during growth does not have this effect. These and many subsequent data appear to suggest that a primary effect of restricted food intake is its effect on gene expression.

Since food contains probably more than 30 different required nutrients, an early search was made as to which of these were involved. For years the belief was held that a toxic build-up of certain minerals was the cause of aging. Too high levels of intake of vitamin D or of protein (or an amino acid) or sucrose, and so forth, have all been suggested as causes of aging. Most workers, however, felt that the increased longevity following restricted food intake was just due to too high levels of food under *ad libitum* conditions. Davis *et al.* (12) showed that only restriction of calorie intake was effective in increasing longevity in rats.

If calorie intake restriction in the adult is the immediate nutritional cause of increased longevity, which calorie source is the cause of "early" death in full-fed animals? Is the food intake restriction benefit due to restriction of any specific one of the three calorie sources, carbohydrate, fat, or protein?

Several strains of mice, (NZB × NZW)F_1 hybrids, an autoimmune strain which develops a fatal immune

complex glomerulonephritis, and two other autoimmune-prone strains, MRL/MpJ-*lpr/lpr* and BXSB/MpJ, were used to study this question (13, 14).

The answer was clear and unmistakable. Using diets fed so that vitamin, mineral, and required protein intakes were identical between full-fed and food intake-restricted mice and only calories were limited in the restricted mice, the very large differences in survival depended solely on the calorie intake and not on the source of calories. The diets fed to the mice consuming a restricted calorie intake contained either 62% of their calories as carbohydrate (sucrose + glycerol) or 69% of their calories as fat (lard), or in the case of protein as much as 86% of the calorie intake (the higher level in this case is of course to allow adequate essential protein for the full-fed group and yet keep protein as the primary energy source in the restricted group).

The groups consuming the restricted intakes were restricted to 60% of the calorie intake of the full-fed groups. In all cases, regardless of calorie source, the mice fed the 60% calorie intake lived from two to three times longer than their paired full-fed mice. There was, however, a secondary effect of fat so that the mice which consumed a restricted calorie intake of a diet proportionate in fat almost uniformly died at approximately twice the age of the full-fed mice. On the other hand, those mice placed on chronic energy intake restriction of a high carbohydrate diet that was also low in fat lived two to four times longer than full-fed mice. They lived on average three times as long as full-fed mice consuming diets relatively high in fat or carbohydrate, and the longest survivors lived more than 44 months. These results suggest a separate additional harmful effect of fat, as has been repeatedly reported.

The conclusion from almost the total of the publications in this field is that the hope for extension of lifetime must come from understanding the continuous control of gene expression. For this understanding chronic energy intake restriction represents a critically important tool.

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