



Starving for Life: What Animal Studies Can and Cannot Tell Us about the Use of Caloric Restriction to Prolong Human Lifespan^{1,2}

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Abstract

Caloric restriction (CR) is the only experimental nongenetic paradigm known to increase lifespan. It has broad applicability and extends the life of most species through a retardation of aging. There is considerable interest in the use of CR in humans, and animal studies can potentially tell us about the impacts. In this article we highlight some of the things that animal studies can tell us about CR in humans. Rodent studies indicate that the benefits of CR on lifespan extension are related to the extent of restriction. The benefits of CR, however, decline as the age of onset of treatment is delayed. Modeling these impacts suggests that if a 48-y-old man engaged in 30% CR until his normal life expectancy of 78, he might increase his life expectancy by 2.8 y. Exercise and cold exposure induce similar energy deficits, but animals respond to these energy deficits in different ways that have a minor impact on lifespan. Measurements of animal responses when they cease restriction indicate that prolonged CR does not diminish hunger, even though the animals may have been in long-term energy balance. Neuroendocrine profiles support the idea that animals under CR are continuously hungry. The feasibility of restricting intake in humans for many decades without long-term support is questionable. However, what is unclear from animal studies is whether taking drugs that suppress appetite will generate the same impact on longevity or whether the neuroendocrine correlates of hunger play an integral role in mediating CRs effects. J. Nutr. 137: 1078–1086, 2007.

The effect of restricting the intake of food on longevity was discovered over 70 y ago in rats (1). Since this seminal study, the effect of food restriction has been shown to extend lifespan in many species including rats, mice, yeast, *Drosophila*, rotifers, bowl and doily spiders, and nematodes (*C. elegans*). However, its effects are not universal, as it does not appear effective in houseflies [*Musca domestica* (2)], and its effects vary with genotype in the mouse (3). In some cases the impact can be dramatic, with increases in mean and maximum longevity of 50% (4). The impact of chronically reduced food intake has been shown to depend solely on the reduction of caloric intake,

rather than intake of specific dietary nutrients (5–7). Hence, the phenomenon has become known as caloric restriction (CR),³ although more recent studies have pointed to an additional role that may be generated by restriction of particular dietary components such as certain amino acids, e.g., methionine (8). An important series of studies has established that the impact on lifespan occurs because CR attenuates the onset of many age-related diseases, particularly cancer (5,9–17), and generally reduces the expression of markers of age-related decline in function. Hence, the effect on lifespan is a consequence of a reduction in the rate of aging. At present CR is the only experimental manipulation of the environmental circumstances known to extend maximum lifespan through a reduction in the rate of aging.

Nonhuman primate studies initiated in the late 1980s (18–20) have verified that the same attenuation of age-related disease, and markers of aging-related decline, occurs in these animals (20–24). The almost universal nature of CR's impact on aging, particularly the success with nonhuman primates, has made it an attractive approach to potentially manipulate aging in humans. The attractive nature of this manipulation is obvious. If the figure of 50% increase in lifespan that is observed in some

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³ Abbreviations used: BAT, brown adipose tissue; CR, caloric restriction; CRON, calorie restriction with optimum nutrition; DEE, daily energy expenditure; RMR, resting metabolic rate; UCP, uncoupling protein.

rodent models is replicated in humans, then simply by eating less food one might be looking at an extension of healthy life from the current mean expectancy of 78 y to 117 y in men and from 83 y to 124.5 y in women. Perhaps unsurprisingly, groups of individuals have already started to voluntarily restrict themselves in the hope this will slow their aging rate and extend their lives (see <http://www.cron-web.org>) (25). Moreover scientific appropriately randomized controlled trials of the impacts of CR have also been started (e.g., the CALERIE trial in the United States; see <http://calerie.dcri.duke.edu/>).

Because the prospect of CR in humans is already a reality, it is important to evaluate more closely what the likely impacts of CR will be. Because many animal studies have been performed, and replicated in multiple laboratories, these studies provide us with a good platform on which to judge the effects of CR in humans. This article therefore has 2 aims. The first is to detail some of the things that animal studies can tell us about CR when it is used in humans. The second is to highlight some of the things that these animal studies cannot tell us. We will restrict discussion of “animal” studies as far as possible to studies in other mammals.

What animal studies can tell us

How much restriction is needed? Studies in rodents have been done at various levels of restriction below that of “control” fed animals. Such results show that there is a strong linear relation between the degree of restriction and the longevity benefit (Fig. 1). The maximum benefit derived from CR is an increase in the lifespan of 50% above that observed in control animals. To achieve this extension in lifespan required a reduction in caloric intake by 60% relative to controls. It is worth pointing out here that in many CR protocols in rodents, the control group is actually also restricted by ~10% relative to true ad libitum intake to avoid the effects of obesity. The effects of CR on survival are therefore not simply related to the avoidance of obesity-related problems. Consequently, animals fed at 60% reduction relative to control animals were actually feeding at ~65% reduction relative to completely ad libitum fed animals; that is, the animals were given only 35% of what their ad libitum counterparts ate. Reducing intake by 30% gives a lifespan (mean and maximum) extension of on average 20% (Fig. 1).

When should restriction start? Hypotheses concerning the mechanism by which CR works have included 3 major ideas: 1) that it is involved in retardation of growth; 2) that the primary

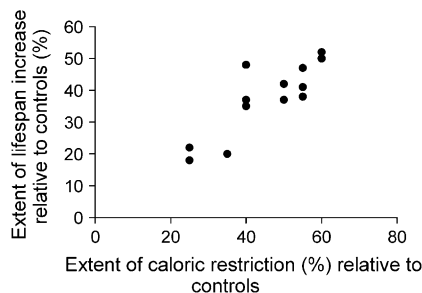


Figure 1 The benefits of CR (percentage increase in life over controls) in relation to the extent of restriction (percentage decrease in intake relative to controls), summarized across studies of both rats and mice. Note that in some rodent protocols control animals are also slightly restricted relative to true ad libitum intakes (references in Table 1).

mechanism is to restrict the accumulation of excess body fat and hence prevent the associated comorbidities of fat accumulation [but see the note above about protocols designed to eliminate this factor and studies of Dubey et al. (26)]; and 3) that the restriction initiates a number of pathways that are involved in the prevention of somatic damage (or enhancement of somatic repair). These latter ideas have emphasized the potential importance of such pathways in reducing oxidative stress during CR (27–30), but other effects including reduction of glycation (31–33) and modulation of protein metabolism (34–38) are also potentially important. Recent gene expression studies are highlighting the very wide range of processes that are affected during CR (15,16,39).

Almost all studies of CR in rodents and other animals have been initiated very early (often immediately postweaning) and maintained throughout life. As a model for human interventions these studies tell us little because it is completely unfeasible for humans to engage in CR for their entire lives. Such a protocol would raise clear ethical concerns because, if it were attempted, it would need to be involuntary for at least the first decade of life. A key question therefore is what impacts on lifespan are there when CR is initiated much later in adult life. This is important because 1 hypothesis for the major mechanism by which CR might work is to restrict normal growth and development. If this is correct, the impact of late-onset CR may be negligible. Relatively few studies are available in animals to answer this question.

Several studies have recently shown that gene expression profiles alter rapidly when animals are placed under restriction (within ~8 wk in mice) and are similarly rapidly reversed when restriction ends (16,39). Because the effects of restriction depend on its accumulated benefits under all the model mechanisms of action, the fact that gene expression changes may be rapidly invoked by restriction does not mean their complete consequences are similarly rapidly acquired (or their benefits completely lost). Nevertheless, these physiological changes do translate almost immediately into alterations in the mortality profile (16). This has led some to suggest that it is never too late to start a restriction protocol (40). It also raises an obvious conundrum: if it is never too late to start, then why would one ever start early? The results of late-onset restriction studies in

TABLE 1 Studies of late-onset CR in rodents and the relative benefits in terms of observed life extension relative to the effects observed in the same strain and under the same level of restriction when initiated at weaning¹

Reference	Species	Strain	Percentage life at onset	Percentage increase relative to control
70	Mouse	B103Hf1	41	33
71	Rat	F344	19	67
72	Rat	Long Evans	57	0
73, 74	Rat	F344xBN f1	52	0
73, 74	Rat	F344xBN f1	76	0
16	Mouse	B6C3f1	62	38
17	Mouse	C57BL6	41	55
15	Mouse	C57BL6	48	52

¹ Percentage life at onset is the percentage of expected lifespan that had been completed before restriction started. Percentage increase relative to control is the percentage increase in lifespan of the late-onset animals relative to the increase in lifespan that was observed in animals under the same protocol but under restriction from weaning.

rodents are summarized in **Table 1** and clarify why delaying the start of CR is not advisable. These data show that the later the restriction starts, the lower the benefit relative to the same restriction in the same strain and conditions started at weaning. The pattern of declining benefits of CR as the age of onset increases is entirely consistent with an accumulated damage model for the mechanism of CR action.

Although mice and rats are close in phylogeny and physiology to humans (relative to other model species such as yeast and nematodes), there is very little information to gauge whether this declining benefit effect has any relevance to humans or not. Studies of energy intake in humans indicate that there is a natural decline in intake in late life, which leads to a natural reduction in body mass. This late-life anorexia is linked to the onset of many terminal illnesses and generally heralds the beginning of a terminal decline. It is unclear to what extent this decline in intake precipitates terminal illness or is caused by it (41). Nutritionists interested in the nutrition of the elderly repeatedly emphasize the benefits of maintaining intake and body mass in late life. It is possible that late-life restriction might serve to bring forward this terminal weight loss, thereby shortening lifespan, consistent with the rodent studies that indicate that very-late-onset CR brings no benefits.

If the reduction in benefit of CR is plotted as a function of the age at onset, expressed as a proportion of the unmanipulated mean lifespan, then the function shows a steady decline, which is almost linear (**Fig. 2**). Because there is also an effect of the extent of restriction on lifespan, we can use these 2 relations (**Figs. 1** and **2**) to hypothesize the likely benefits that would accrue under different "adult onset" scenarios, making the very large assumption that humans will respond to CR in the same manner as small rodents (**Table 2**).

These data show that if an individual male aged 48 (assuming a normal BMI of 20–25) were to decide to start a regimen of CR to 70% of ad libitum intake (i.e., intake would be reduced by 30% from ~10 MJ each day to 7 MJ each day, approximately from 2500 to 1750 kcal/d), and the person were to sustain this level of restriction for the next 30 y (to the current life expectancy of 78 y), such a person might expect to derive a benefit of an extension in life of ~2.8 y. This is slightly less attractive than the scenario highlighted above of living to be 117. However, if the person waited another 7 y before starting the restriction (initiating it at age 55 and then engaged in it for 23 y) the prediction would be that the payback for over 2 decades of restricting intake would actually only be an extra 6

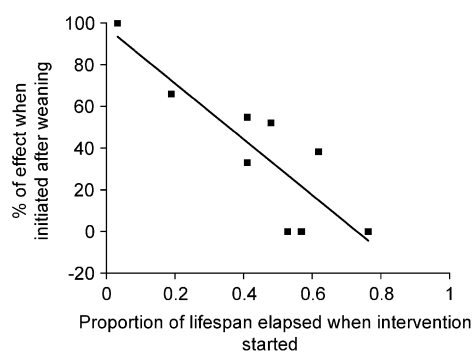


Figure 2 The effect of CR expressed relative to the same effect when initiated at weaning as a function of the proportion of expected lifespan that had elapsed when restriction was initiated. Data are summarized across several studies of rodents (mice and rats) [references in (4)].

TABLE 2 Modeled benefits (years of life extension) of CR in humans at 2 different levels (15% and 30% CR below control) in relation to the age at which restriction is initiated¹

Percentage of life at onset	Age at onset, y	Time on restriction, y	Benefit, y	
			15%	30%
20	15.6	62.4	5.6	11.2
30	23.4	54.6	4.7	9.4
40	31.2	46.8	3.3	6.5
50	39	39	2.4	4.8
60	46.8	31.2	1.4	2.8
70	54.6	23.4	0.25	0.3
80	62.4	15.6	0	0

¹ Percentage of life at onset and years on restriction are calculated to expected lifespan without restriction of 78 y. The model is based on rodent studies and assumes that caloric restriction in humans will be as effective as it is in rodents.

wk! In contrast, if someone decided to start restriction at age 23, then by age 78 (after 55 y of restriction) he or she would enjoy just over an additional 9 y 5 mo of life expectancy.

The argument here that late-onset CR (from age 39 in men and 41 in women, i.e., 50% of expected lifespan without manipulation) is unlikely to provide significant benefits in terms of increased lifespan, is separate from arguments provided elsewhere about the likely small benefits of CR in humans (42–44). Phelan and Rose (42) suggested that the major benefits accrue in CR because of the diversion of resource destined for reproduction into somatic protection. Because the investment in reproduction in small mammals such as mice is massive compared with that in humans, the argument was developed that the benefits of CR in humans would be far lower than that observed in mice and rats. Recent experimental evidence, however, indicates that the assumption of an axiomatic trade-off between CR and reproductive performance may be incorrect (45). Grey (43), on the other hand, suggests that CR is a response to seasonal shortage of resources, and because the time scale of this seasonal effect is constant independent of the animals involved, the evolution of CR would tend to give all animals the same absolute protection (i.e., relatively less as they get larger). In contrast to these arguments we have assumed in deriving the estimates in **Table 1** that CR will work and, moreover, that it will be as effective as it is in rodents. Using the known impacts of extent of restriction and duration of restriction on lifespan in rodents, we then modeled its likely effects, under various realistic scenarios of age at onset and level of restriction in humans (**Table 2**).

Unbiased statistics on the characteristics of humans populations engaged in voluntary CR are hard to come by. However, respondents to a web-based questionnaire on a CR dedicated web site (www.cron-web.org) revealed that the average age of respondents was 42 and that of these 86% were male, and they had been engaged in restriction for on average 32 mo. Average intake was 1750 kcal per day, which is ~25% below the intake of the general population. Similar data were compiled by Fontana et al. (25) for a sample of 30 individuals of the voluntary CR population. The analysis presented here suggests that this population (if the web-based survey is representative) is unlikely to derive very large benefits for their future decades of restriction, even assuming CR in humans is as effective as it is in rodents. The model in **Table 2** suggests the caloric restriction

with optimum nutrition (CRON) individuals may extend their lives by ~2.5–3.5 y on average. If the arguments of Phelan and Rose (42), Grey (43), and Demetrius (44) are correct, even these short lifespan extensions may be unrealistically optimistic. Unfortunately, the web-based questionnaire on the CRON site did not ask respondents what extent of lifespan extension they were expecting to achieve. It would, however, be instructive to know if people are engaged in voluntary CR under unrealistic scenarios for the likely life extension benefits. Unrealistic expectations may be fostered by exaggerated claims in popular books (e.g., 46–48) and analyses that suggest CR may be as effective if started late in life as restriction started early (40). This latter conclusion stems from using relatively few studies in the comparison ($n = 4$) and expressing the achieved extension in lifespan not in absolute terms but relative to the expected amount of life remaining at the age of onset. Our analysis suggests that when more studies are included in the analysis even this expectation is unrealistic (Table 2 and Fig. 3).

After long-term restriction does the system adapt and hunger diminish? Restricting food intake for several decades to obtain a life extension of 2.8 y would be more acceptable if these decades of restriction were not characterized by perpetual hunger. An interesting question therefore is whether the hunger eventually dissipates on long-term CR. When mice are placed on restriction, they come into energy balance, but at a lower level of intake after a period of ~20–30 d (equivalent to ~2.5 y in humans) (49). Once mice reach this balance, perhaps their hunger attenuates. To explore this effect we took mice that had been on restriction for 50 d at 20% below ad libitum levels. We either took them off restriction immediately at the end of 50 d, or we maintained them on restriction for an additional 10, 30, or 50 d, clamped in energy balance. When mice were brought off restriction after 50 d and given ad libitum food, they went hyperphagic for a period, reflecting their hunger. The extent of this hyperphagia is a measure of their hunger drive. Our study indicated that even after 50 d of being in energy balance, the hunger had not diminished (Fig. 4; our unpublished data). Neuroendocrine profiles strongly support this notion that animals physiologically are hungry after prolonged periods of CR (C. Hambly, and J. G. Mercer (The Rowett Research Institute) and J. R. Speakman (The Rowett Research Institute, and Aberdeen University), unpublished data).

Are the effects mediated by energy imbalance or by something special about eating less? When laboratory rodents are fed ad libitum, it is reasonable to assume that they



Figure 3 Modeled benefits of CR (*percentage extension of remaining life*) in relation to the proportion of expected life remaining when restriction was initiated using the human data in Table 2 and those in Fig. 2, which was based on rodent studies. The pattern indicates that even when expressed relative to the remaining lifespan, the benefits decline as age of onset increases.

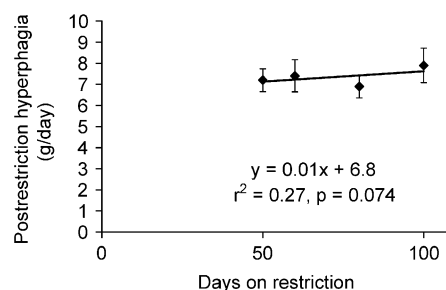


Figure 4 The extent of postrestriction hyperphagia observed when mice were taken off restriction after increasing periods. The hyperphagia is a measure of hunger, and the lack of a trend suggests that even after 100 d of CR, 50 d of which involved feeding in energy balance, the animals were just as hungry as after 50 d of CR. (From our unpublished data.)

are in slight energy surplus because they gradually accumulate body fat. However, this accumulation is so slow that for all intents and purposes the budget is effectively in balance. Under CR this balance is perturbed, and the animals experience a period of energy deficit before regaining balance. For the majority of their lives, therefore, animals under restriction are in energy balance, but at a different level from that when they are fed ad libitum. It is possible to perturb the energy budget to the same extent but in a different way, by elevating expenditure rather than decreasing intake. For example, animals may be forced to engage in exercise or may have their thermoregulatory demands increased. The way animals respond to these increases may mimic the effects of CR; hence, similar benefits in terms of lifespan extension may accrue without the need to constrain intake.

How do animals respond to these different impositions of energy deficits? Responses are summarized in Table 3. When mice are restricted in their intake early in life, they achieve energy balance within ~20 d. This is attained in 4 main ways. First, enhanced absorption efficiency may offset the lowered intake. Second, the animals reduce their allocation of energy into growth, and hence their body tissues are reduced in size (49). The energy saving realized by not investing in growth accounts for ~6% of the energy deficit in restricted mice. Animals also respond by reducing their resting rate of metabolism (Fig. 5). The extent of reduction in metabolism has been an issue of debate. Some studies suggest that it is not greater than that anticipated from the gross reduction in body size and changed body composition (Fig. 5) (49–51). Other studies, however, have indicated that the reduction in metabolism exceeds that anticipated from the lowered body size and that, consequently, some

TABLE 3 Comparison of responses of rodents under CR to elevated expenditure evoked by voluntary exercise or cold exposure

Response	Treatment		
	CR	Cold	Voluntary exercise
Food intake	Down	Up	Up in females Down in males
Energy expenditure (whole body)	Down	Up	Up in females Unchanged in males
Energy expenditure (per gram tissue)	?Uncertain	Up	Up
Body mass	Down	Unchanged	Unchanged in females Down in males
Lifespan	Extended	Unchanged	Slight extension

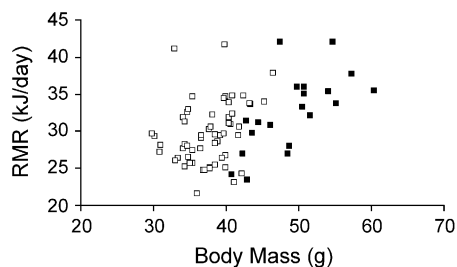


Figure 5 RMR of MF1 mice either fed ad libitum (solid squares, $n = 20$) and mice that had been under 25 d of 40% CR (open squares, $n = 58$). The mice on restriction had absolutely lower RMRs ($P = 0.015$) but were also lighter. Once corrected for the body mass difference using ANCOVA, the difference in RMR was not significant ($P = 0.14$). (From our unpublished data.)

additional metabolic adaptation must be occurring. Studies of the individuals in biosphere II who were involuntarily energy restricted for 2 y show similar reductions in resting metabolic rate (RMR) relative to fat-free mass (52). Lowered resting body temperature may be part of this effect and is observed in CR rodents as well as nonhuman primates (53). The reduced RMR in mice accounts for ~25% of the energy deficit.

By far the largest contribution to the total balancing of the budget is a reduction in the remainder of the budget. In small rodents this comprises 2 main components: the thermoregulatory component and energy expended on exercise. Rikke and Johnson (54) examined the responses of many strains of mice to 30% CR for a period of a month. They found that the responses to CR were highly variable between strains; some strains entered daily torpor to conserve energy, but others remained at high body temperature. The total thermoregulatory demand at 20°C is about twice the resting rate of metabolism (55). In rats we have shown that the major site of thermogenesis brown adipose tissue (BAT) actually increases during CR, suggesting that thermoregulatory demands may also increase. These changes in BAT were not replicated in mice under CR (S. Johnston (The Rowett Research Institute) and J. R. Speakman (The Rowett Research Institute, and Aberdeen University), unpublished data), but the duration of the CR in this case was much shorter.

Many studies have investigated the changes that occur when small rodents are acutely exposed to cold conditions. In the face of this energy restriction there is an immediate up-regulation of energy expenditure, driving the animal into energy deficit. This increased expenditure is initially mediated via shivering. Small rodents then up-regulate uncoupling protein 1 (UCP1) in BAT, mediated via β -adrenergic stimulation. The up-regulation of UCP1 gene expression takes <1 h, and by 24 h all the cold-induced thermogenesis is supplied via nonshivering mechanisms (56). Over more extended exposure, there is hypertrophy of the BAT to maintain the nonshivering thermogenesis. Within 2 h there is an up-regulation of food intake to meet this elevated demand. The animals come to a new steady-state balance of intake and expenditure, generally within a short time period. The elevated demand for energy in the cold is sustained in the long term by continued elevation of heat production mediated via nonshivering thermogenesis and supported by high levels of UCP1 gene expression. Animals deficient in UCP1 can survive in the cold (56), but only by continuous shivering. There is no evidence that UCP2 or UCP3 is involved in mice. Cold exposure therefore involves fundamental differences in response to CR.

McCarter et al. (57) examined the running wheel response of rats to CR and found that rats on CR maintained running wheel activity well into late life, substantially higher than rats fed ad

libitum. The significance of these effects, however, may depend on the method used to measure activity. Running wheels may actually stimulate activity, particularly under restriction conditions where it is often interpreted that the animals are food seeking. Such behavioral effects may be less profound or absent if spontaneous activity is monitored instead. Without a running wheel, male mice reduce their activity as the main mechanism of accounting for the reduced energy intake (49).

During elevated long-term voluntary exercise without CR, there appears to be a difference in the response of male and female rats. In female rats forced to run, their primary response is to increase food intake to cover the elevated demands. Male rats, on the other hand, appear not to increase intake but rather to lose weight, with attendant compensations in other parts of their energy budgets. There have been few studies that have examined the long-term impact of prolonged voluntary exercise and cold exposure on longevity. However, what little evidence we have in rodents points to both of these manipulations having no or relatively minor impact when compared with CR.

Most of the impact on total MR therefore appears to come about by a combination of reductions in thermogenesis and reductions in activity. By measuring DEE in rats using DLW and comparing the levels of DEE between ad libitum fed and CR rats in relation to their body composition changes, we have shown that the total reduction in DEE is less than anticipated from the reduced body composition (58). Per gram of tissue, therefore, animals under CR are probably expending more energy than their ad libitum counterparts. This is consistent with other observations that individual mice with high rates of metabolism live longer than those with low rates (59), that lifespan of different dog breeds is inversely linked to their metabolism (60), and that Tau mutant Hamsters also combine higher metabolic rates with longer lives (61).

Responses of normal-weight humans to CR following long-term restriction from early life have not been performed. Anecdotally, 1 of the major comments by people who voluntarily restrict caloric intake is that they feel cold, consistent with reductions in thermoregulatory performance, but systematic studies are lacking. Effects on activity have not been measured, but it seems likely that a complete balance of the energy budget could not be attained without some reduction in activity, and a common comment also is that individuals engaged in long-term CR feel lethargic and tired.

The data at present therefore indicate that the effect of CR is mediated via the restriction of intake and the unique manner in which the animal responds to this energy deficit when compared with the responses to energy deficits imposed by elevations of expenditure. Obviously there is a large body of epidemiological evidence regarding the impacts of exercise in humans that contradicts the suggestion that exercise in rodents generates only minor benefits (62,63). The differences between rodents and humans in this respect may primarily reflect the different reasons why rodents and humans die. In mice the major cause of death is cancer (15,16), and heart disease is a very small contributor. In humans circulatory disorders (heart disease and stroke) account for the majority of deaths. Data from the Centers for Disease Control (2004) indicate 656,000 deaths from heart disease, 555,000 from cancer, and 231,000 from stroke in the United States during 2002. These data show that although cancer is important (35% of deaths), it is not quite so significant as it is in mice or rats. In humans, therefore, there is a large exercise benefit that acts primarily via heart health (63), but such benefits, although apparent (64), are less important for mortality in rodents.

This may expose an important problem with extrapolating the results of CR protocols between rodents and humans. The benefit of CR appears to be primarily a result of its effects in stalling and reducing cancer prevalence (15,16,65). If CR leads to a reduction in physical activity, this might expose humans to elevated risks of cardiovascular problems that would offset the CR benefits. Such a trade-off would not be apparent in rodents because the reduction in exercise would not expose them to elevated atherogenicity. (Clearly such a trade-off is also not going to be evident in flies or nematodes, as they have no hearts.)

Such a perspective might be overcautious because the nonhuman primate trials have indicated that markers of cardiovascular health are significantly improved (66). Moreover, Fontana et al. (25), studying the voluntary restriction population, have emphasized the enormous differences in measures of risks of heart disease relative to the general U.S. population. In fact, this population has levels of blood pressure typically observed only in children. There are, however, some difficulties with this comparison. If survey responses on the CRON website are representative, 98% of the CRON population is also regularly exercising, and the reference group were overweight. The heart health benefits may therefore derive more from lowered body fat and exercise than from CR per se. These problems emphasize the importance of the randomized controlled trials of CR that are currently under way. Nevertheless, this analysis does indicate that when CR is applied in humans, particular attention should be paid to its impact on physical activity levels and markers of cardiovascular health.

What animal studies cannot tell us

Is the required extent and duration of restriction feasible in humans? The analysis performed above concerning the extent and duration of CR that will be necessary to attain even a very modest degree of extension in life expectancy suggests that to have a reasonable impact of 4–5 y, humans of normal weight would need to restrict their intake to at least 20% below ad libitum for periods in excess of 40 y. In rodents such restriction is easily performed. The animals are simply given the required amount of food and kept in an environment where there are no opportunities to acquire additional intake. Unless humans on CR are incarcerated, they will have to voluntarily restrict their intake in the face of large quantities of highly palatable and cheaply available food and survive socially in a society where food intake has functions far beyond the ingestion of sufficient energy and nutrients to survive. The question arises, therefore, over whether it is feasible for humans to perform such extensive and long-duration restrictions. Animal studies are unable to shed any light on this question.

Although controlled trials of CR have not been applied for extended periods in humans in the context of attempting to reduce aging, there have been many large interventions that have restricted energy in the context of attempting to reverse obesity. The context of these 2 types of intervention are not exactly identical. In 1 case we are talking about imposing a restriction in energy on people who have body mass indices in the “normal” range of 20–25. Over this range there is no evidence that differences in body mass index have any linkage to differences in mortality, and the curve relating mortality to BMI has its nadir in this range. In most of the restriction studies performed so far, subjects have been in the overweight (BMI > 25 and < 30) or obese (BMI > 30) categories. In this range of BMI, there is already a detectable increase in the mortality risk that gets greater as BMI increases. Subjects with BMIs in this range are already expected to have a reduced life expectancy, and

imposing CR on them to bring them into the “normal” range will likely only bring their life expectancies back to normal. The motivations of subjects in these 2 situations and the abilities of these groups to control caloric intake may be very different. Extrapolating between the 2 conditions should therefore be done with caution. Nevertheless, it is clear that CR as strategy for weight reduction in the obese is largely ineffective in the long term. Most studies have found that CR can be adhered to and weight reduction occurs as long as there is a substantial degree of support for the subjects. That is, when subjects are enrolled in studies and receive guidance and help with the CR intervention, which may extend to having all their meals prepared for them, then adherence to a CR protocol is possible. If subjects are subsequently set free, without support, their body weights and adiposity generally relapse, often to their original weight before the intervention. Several points are worth making here.

First, our knowledge of the control of food intake systems is insufficient for us to know if a 500-kcal deficit protocol in a person with a BMI of 35 generates the same degree of hunger and hence propensity to relapse compared with a person starting with a BMI of 23. Potentially the neuroendocrine drivers for intake may be more expressed in the obese subject, and that may have precipitated their obesity in the first place. Consequently under restriction, such subjects may find it far more difficult to avoid relapsing. However, an obese person on a 500-kcal diet is still eating 2000 kcal each day, compared with only 1500 kcal for a normal weight person entered into a CR protocol. This much lower level of intake on the CR protocol may severely restrict social functioning in a manner that a dieting obese person does not experience. This might indicate that the prospects of unsupported adherence to the protocol would be less likely to be successful in a normal-weight person.

On the other hand the motivations of the 2 groups are very different, and it is this motivation that may make the difference. On balance it seems that unsupported restriction for periods spanning decades would not be feasible, and the resources necessary for such support to be provided by clinics would be prohibitive. However, groups of people with similar objectives might be able to provide mutual support systems and social contexts that do not include food, enabling long-term adherence to the protocol. Indeed, such voluntary CR communities already exist and have been studied (25), but data on adherence and dropout rates are not available.

Will using drugs to restrict intake have the same impact?

If long-term adherence is difficult, particularly without support structures in place, then perhaps normal-weight individuals could achieve long-term CR by engaging in drug-based control of their caloric intake. There are 2 drugs currently in use for CR in the obese. These are a lipase inhibitor that reduces the absorption of fat (orlistat) and a 5-HT reuptake inhibitor that suppresses appetite (sibutramine). Several other drugs are in late-phase clinical trials, and 1, an endogenous cannabinoid receptor antagonist, is close to market. The latter 2 products act via mechanisms that are not entirely clear but appear to suppress appetite. In normal clinical use, for patients who are being treated for extreme obesity, these drugs are normally not prescribed for longer than 12–24 mo. We do not therefore know what the long-term effects might be of continuing treatment with these drugs for several decades or whether they continue to be effective. However, there is an additional problem if the mode of action of the drug-based treatment is to reduce appetite. We have mentioned above that mice on CR appear to be continuously hungry (Fig. 4) and that there are neuroendocrine

changes that accompany CR (C. Hambly, J. G. Mercer, and J. R. Speakman, unpublished data). Apart from mediating the continued hunger, however, these neuroendocrine modulations may also be an integral part of the CR effect on lifespan. Although most diets fail, there is 1 procedure for the treatment of obesity that enjoys great success and that is surgical intervention. This should not be ignored as a potential method for ensuring lifetime adherence to CR protocols.

What about life in the real world? In addition to being held in an environment where only limited energy is supplied, CR rodents live in a very different world from humans in several other respects. Although their food supplies are limited, the animals do not have to do very much at all to obtain this food. In fact they live their entire lives in a cage equivalent in relative size to a medium-sized lounge. Scope for activity even if the animals wished to perform it is consequently limited. By contrast, humans need to perform at least some level of activity to function effectively in society. Measurements of body condition in rodents under CR suggest large reductions in fat-free body mass (skeletal muscle) and also bone mass. This may not be a problem given the lifestyle of the captive mouse, but for humans these problems may elevate the risk of falls and of osteoporotic fractures. Rodent colonies are also generally maintained as specific pathogen-free environments, so the animals do not need to fight off diseases. Obviously this does not extend to free-living humans; so if immune function of CR subjects were to be compromised, they might also suffer elevated disease (and mortality) risks. Surprisingly, indicators of immune function of CR rodents (67–69) and nonhuman primates actually indicate improved immune status, so this may not be a serious issue. One thing that is completely incompatible with a CR lifestyle, however, is reproduction. Indeed, at the body mass indices sustained by most voluntary CR practitioners, we would expect females to become amenorrhagic. Interestingly, a recent study of mice temporarily brought off CR at age 6 mo and bred revealed that their reproductive performance was actually greater than that of control mice of the same age fed ad libitum. The rejuvenating benefits of CR therefore seem to extend to the reproductive system as well because the performance of the CR individuals matched that when they were 6 wk old (45).

Apart from the fact that we would know nothing about the existence of the effects of CR on lifespan if it had not first been discovered in animals, investigations of CR effects in animals provide some valuable insights into the likely impacts that using CR in humans may possibly have. Studies of late-onset CR in rodents can allow us to model the impact of CR protocols initiated in the middle or later in adult life, as will need to be the case if CR is used in humans. Such modeling reveals that realistic scenarios of restricting intake by 15–30% and initiating such restriction in one's 40s will only bring rather small benefits in extended lifespan despite the CR being extended over multiple decades. Commencing CR even later, in one's 60s, may have no positive effect on life expectancy.

Comparisons of the impacts of reducing energy intake with increasing energy expenditure, either through exercise or cold exposure, reveal that these are far from equivalent states, and in rodents the only manipulation to significantly extend life is CR. In contrast to studies of humans, exercise appears to have only minor benefits in terms of lifespan in rodents. This may expose a potential problem extrapolating between rodents and humans because 1 compensatory consequence of CR may be reduced physical activity. Because rodents are not unduly troubled by heart disease, they derive little benefit from elevated exercise but

may also be less affected by reduced exercise. In humans reduced activity in response to CR may lead to problems with heart health that offset the benefits of CR.

Two major things that animal studies cannot currently tell us are, first, whether enduring a CR protocol without sustained support structures for many decades is feasible. This raises the important issue of whether drug-assisted CR will have the same benefits or whether the neuroendocrine correlates of hunger are an essential part of the mechanism of CR. In other words, if there is no hunger pain, can there still be a longevity gain? A second issue not yet addressed by CR studies in animals is whether the same effects will be apparent in humans who have to exist in an environment where it is necessary to fight off pathogens and perform various activities beyond sitting in a small room isolated from the external environment simply to function effectively.

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