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Review

Why dietary restriction substantially increases longevity in animal models but won't in humans

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Abstract

Caloric restriction (CR) extends maximum longevity and slows aging in mice, rats, and numerous non-mammalian taxa. The apparent generality of the longevity-increasing effects of CR has prompted speculation that similar results could be obtained in humans. Longevity, however, is not a trait that exists in a vacuum; it evolves as part of a life history and the physiological mechanisms that determine longevity are undoubtedly complex. Longevity is intertwined with reproduction and there is a cost to reproduction. The impact of this cost on longevity can be age-independent or age-dependent. Given the complexity of the physiology underlying reproductive costs and other mechanisms affecting life history, it is difficult to construct a simple model for the relationship between the particulars of the physiology involved and patterns of mortality. Consequently, we develop a hypothesis-neutral model describing the relationship between diet and longevity. Applying this general model to the special case of human longevity and diet indicates that the benefits of caloric restriction in humans would be quantitatively small.

Keywords: Aging; Caloric restriction; Primate life extension; Reproductive effort; Life history trade-offs; Evolution of senescence; Maximum longevity

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1. Introduction

Caloric restriction (CR) extends maximum longevity and slows the aging process in mice and rats (Masoro, 2000). It also has been effective in extending longevity in a wide range of non-mammalian taxa, including fish, protozoa, rotifers, water fleas, spiders, molluscs, ticks, and cockroaches (Comfort, 1979; Weindruch and Walford, 1988). Occam's razor would suggest that, all things being equal, similar results should be obtainable with caloric restriction in long-lived primates. This logic has led to speculation on the implications of dietary variation for human aging (Weindruch and Walford, 1988).

All things, however, are *not* equal. Longevity is not a trait that exists in isolation; it evolves as part of a complex life history, with a wide range of underpinning physiological mechanisms involving, among other things, chronic disease processes. In particular, longevity is well-known to be affected by reproduction, an effect that is often mediated by the utilization of calories from reserves (Finch, 1990; Rose, 1991). We propose that such utilization is central to the effect of diet on longevity, both producing the beneficial effect of dietary restriction and limiting it. We develop the evidential basis for this point of view and then quantitatively model it using human and other mammalian data. Our conclusion is that dietary restriction is unlikely to have a large quantitative impact on human longevity, though it is likely to have a small quantitative impact.

2. Longevity is intertwined with reproduction

Life histories vary dramatically across animal taxa. Even among small mammals, there is large variation. The little brown bat (*Myotis lucifugus*), for example, is mouse-sized, yet does not reach maturity until 1 year of age and can live more than 33 years in its natural habitat (Humphrey and Cope, 1976; Davis and Hitchcock, 1994). The house mouse, on the other hand, reaches maturity in about 1 month and none have ever been reported to reach even 5 years of age, in captivity or in the wild (Brown, 1953; Sacher and Hart, 1978). Whereas the little brown bat typically produces a single offspring per year (Humphrey and Cope, 1976), mice can produce more than a dozen litters of 6–10 offspring in their first year of life (Berry, 1970; Bronson, 1989).

What is responsible for this contrast of life history strategies? Williams (1966) noted that if reproduction carries with it some cost for future survival, an organism's *lifetime* reproductive success may be increased by decreasing its present reproduction as long as the probability of surviving to produce future offspring is sufficiently increased. An organism's life history can thus be thought of as a result of trade-offs between growth, reproduction, and longevity. Rodents, for example, are products of strong natural selection for early, heavy reproductive investment, with little longevity. Primates, on the other hand, are not simply big rodents; they grow slowly, reproduce at a greatly reduced pace, and die at a much lower rate than rodents or even similarly sized non-primates (Millar and Zammuto, 1983; Harvey and Clutton-Brock, 1985; Promislow and Harvey, 1990).

Negative correlations between reproduction and either growth or longevity seem to imply that reproduction simply redirects energy that might be invested in growth or

longevity. If this were true, however, survival could be increased simply by investing more *energy* in that life history component. In other words, all that would be necessary to extend rodent longevity in the laboratory would be to provide more food. Yet, experimentally this does not occur. Rather, the opposite is true. At essentially any level of caloric intake much above the point of starvation, providing more food increases mortality and decreases longevity (Weindruch and Walford, 1988). It is interesting to point out, though, that while food supplementation of natural populations may actually decrease mortality (e.g. Fordham, 1971; Ford and Pitelka, 1984), it invariably leads to increased reproductive effort (Boutin, 1990). This suggests that caloric restriction under natural conditions may carry with it some important costs not manifest under laboratory conditions, possibly including increased vulnerability to predation and parasitism, and thus reduced longevity.

3. The demographic impact of caloric restriction

Longevity can be increased in two distinct ways. First, by reducing the rate at which the mortality rate increases with advancing age. And second, by reducing mortality in a manner unrelated to age such as a constant reduction in mortality rate across all ages. Since age-related accelerations of mortality rate are a useful phenomenological measure of the rate of senescence of a population (e.g. Gompertz, 1825; Finch et al., 1990), the first type of longevity increase is usually seen as a result of a manipulation of the organisms' aging rate. Among long-lived strains of rodents, caloric restriction increases longevity by decreasing the age-specific mortality rate as a function of age (Finch, 1990, Table 10.1, p. 508; based on MRDTs calculated from 14 caloric restriction studies on rats). This pattern of longevity increase is represented in Fig. 1a as a reduction in the slope of the line relating mortality rate and age. The biochemical and physiological basis for this pattern is not known and is not necessarily always the same.

In some cases, dietary change only has effects on the background, or age-independent, mortality level. For example, in *Drosophila melanogaster*, dietary restriction reduces the age-independent mortality rate (sometimes referred to as the initial mortality rate, or IMR) without a detectable impact on the dependence of mortality rate on age (Nusbaum et al., 1996; Mair et al., 2003). This gives rise to the parallel pattern of Fig. 1b, in which the mortality-rate curve shifts position but does not change in slope.

The mechanistic basis of this second pattern is reasonably well-understood. Reduction in food level reduces reproductive output in fruit flies within a few days (Chippindale et al., 1993). Changing in a mirror-image fashion relative to reproduction, starvation resistance substantially *increases* (Chippindale et al., 1993). On the same time-scale as these changes, mortality rates fall almost immediately, an effect that supersedes the effect of prior nutrition (Mair et al., 2003). One interpretation of these results is that reduced nutrition reduces reproductive investment which in turn enhances starvation resistance and survival propensity generally (Rauser et al., 2004). These events all take place in 2–4 days and are completely reversible. Interestingly, fertility in human females responds similarly instantaneously to abrupt increases or decreases in caloric intake (Ellison and Lager, 1986; Lager and Ellison, 1990). Fertility in males shows a similar pattern of response to short-term fluctuations in nutrition as well (Graves, 1993, and citations therein). Additionally, in

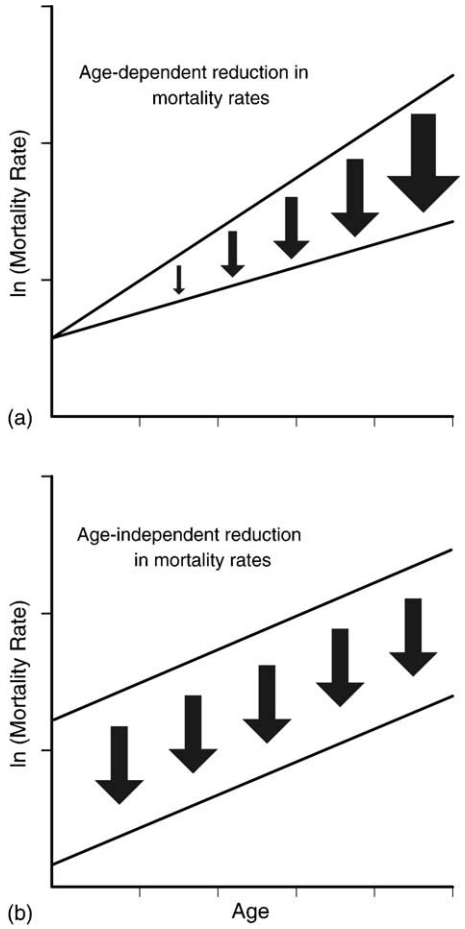

Fig. 1. (a and b) Effect of diet on mortality rates: (a) with age-dependent reduction in mortality rates, the rate of aging is reduced and (b) with age-independent reduction in mortality rates, the *rate* of aging is not changed although the mortality rate at every age is reduced.

studies across a wide range of animals, including fish (Robertson, 1961), marsupial mice (Woolley, 1966, 1971), and cats (Hamilton et al., 1969; Bronson, 1981), males also show a strong negative relationship between fertility and longevity. This relationship is seen in human males, too. In a case-controlled study of eunuchs (Hamilton and Mestler, 1969), the longevity of institutionalized, mentally retarded, castrated men was significantly greater (69.3 years versus 55.7 years) than intact men from the same institution and matched for age and intelligence.

Our intent here is not to argue for the likely occurrence of either of these two kinds of demographic impact, which are not in any case mutually exclusive, but instead to point out the pervasive impact of dietary change on demography, and thus life history. In every case with sufficient data, which certainly excludes the human case, caloric restriction has a broad impact on life history.

4. A simple unified model for diet and longevity

There are a variety of mediating factors that will impinge on longevity as a result of variation in total caloric intake. (Here, we neglect all qualitative variation in diet.) Calories support a variety of metabolic activities that sustain life, a positive effect. The processing of calories imposes metabolic costs and, in some species, additional costs associated with gastro-intestinal infection. Caloric intake tunes reproduction, with increased reproduction usually reducing longevity.

For these reasons, we write the relationship between longevity and diet as $L(K)$, where L is longevity and K is the caloric intake. $L(K)$ is in general a non-linear function of K. We know that there is some lower value for K at which $L(K_{min}) = 0$, with L at zero for all lower values of K. Similarly, there will be some value for K at which $L(K_{max}) = 0$, with L at zero for all higher values. This may arise from acute distension, bacterial proliferation in the gastrointestinal tract, suffocation, or some other acute mechanism. Fig. 2a shows the simplest possible shape for $L(K)$: a triangular pattern defined by two straight lines. We are not arguing that actual L functions will have this shape. It is just the simplest form for a function that has at least one maximum and at least two minima with intermediate positive values. $L(K)$ might in fact be non-linear, with multiple peaks, but that will not change our argument qualitatively. Overall, $L(K)$ must have a hump shape, falling to zero at K_{min} and K_{max}, with one or multiple peaks in between. The value of K at which L is at its global maximum, say L^*, will be labeled K^*. The ''normal'' value of K is given by K_n, with a corresponding longevity of L_n. If K_n is not equal to K^*, then dietary changes can increase longevity. In particular, if K_n is greater than K^*, caloric restriction can increase longevity. To this point, all we are doing is formally representing the phenomenon of caloric restriction.

An interesting feature of the patterns shown in Fig. 2a is that, when starting from K_n, with $K_n > K^*$, a situation in which caloric restriction might increase longevity, we can linearize the function $L(K)$ about K_n, using a Taylor series expansion. This will give us a linear function that will provide a fairly crude estimator for the effects of caloric restriction on longevity, in that extrapolation to lower and lower values of K predicts greater and greater increases in L. With some $L(K)$ functions, this analysis will yield an upper bound on the effectiveness of caloric restriction.

We can apply this analysis to studies of caloric restriction in rodents. Using 27.4 months as the mean mouse lifespan on a normal laboratory diet and 45.1 months as the mean lifespan with a 64% reduction in calories relative to the ''normal'' diet (Weindruch et al., 1986), then the slope for the linearized CR effect is −27.6 (in months/proportionate reduction in calories), calculated as $b = (L_{max} - L_n)/(K_{max} - K_n) = (45.1 \text{ months} - 27.4 \text{ months})/(0.36 - 1.00) = -27.6$ (see Fig. 2b).

If we assume that the maximum caloric reduction is 67% reduction from the amount consumed by mice with free access to food (for a total of 33% of the normal caloric intake), and the effect is linear, then we can estimate the upper limit on lifespan with caloric restriction. This upper limit, $L(K_d)$, is equal to $L_n + (\Delta K \times b)$. In the case of mice, $L(K_d) = 27.4 + (-0.67 \times -27.6) = 45.9$ months. This is shown in Fig. 2b. This is a reasonable upper limit, because it is larger than, but approximately equal to, the 45.1 months which is the highest observed average longevity in a mouse caloric restriction experiment (Weindruch et al., 1986).

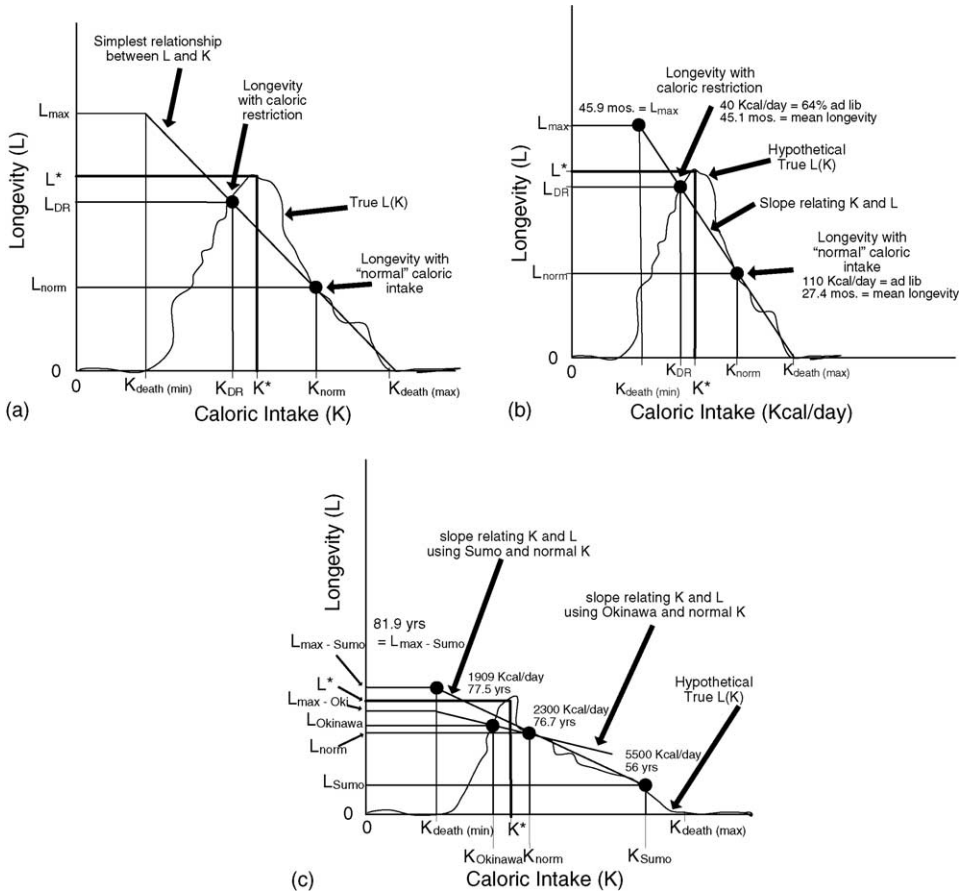

Fig. 2. (a) Quantitative model for the relationship between average longevity (L) and caloric intake (K). We assume a maximum (K_{max}) above which individuals die from too much food and a minimum (K_{min}) below which individuals die from too little food. Between these values, we assume a positive valued non-linear relationship between K and L. This function necessarily has a maximum, which we call for L, which we call L^*, with an associated caloric intake, K^*. In well-studied organisms, like rodents, there will be a calorically restricted food regime (K_{dr}) which is near K^*, giving a longevity (L_{dr}) which is near L^*. If we fit a line from "normal longevity," at ad libitum caloric intake (K_{norm}), L_{dr}, we can continue this line upward to the value of L at K_{min}. This gives an ad hoc maximum bound for the likely impact of caloric restriction on longevity. (b) A fitting of rodent data to our quantitative model. The upper limit for average longevity with caloric restriction is 45.9 months, close to the best-known result of 45.1 months. The overall magnitude of the CR effect is about 67.5%. This result shows that this model can supply a reasonable bound for the effects of caloric restriction. (c) A fitting of human data to our quantitative model. The upper limit for average male longevity in Japan with caloric restriction is 81.9 years, using the Sumo wrestler data, close to the best average longevity records for Japanese prefectures. This effect, relative to Japanese male longevity on a normal diet, is about 6.8%.

We can apply this method of quantitative analysis to human longevity as well (see Fig. 2c). In Japanese populations, for example, the normal male diet is approximately 2300 kcal per day (K_n) (Nishizawa et al., 1976) with male $L(K_n)$ equal to 76.7 years (Japan Ministry of Health, 1995, cited in Willcox and Willcox, 2004). Sumo wrestlers, however, consume an

average of approximately 5500 kcal per day (Nishizawa et al., 1976) and have a life expectancy of 56 years (based on records of Sumo champions from the Sumo Museum in Japan). So, we can say that $L(5500) = 56$ and that the increase in K is 2200 kcal per day. The slope of the regression of Japanese male longevity on caloric change therefore is $b = (L_{norm} - L_{Sumo})/(K_{norm} - K_{Sumo}) = (76.7 \text{ years} - 56 \text{ years})/(2300 - 5500) = -0.0065$.

We can also estimate the slope of this regression using caloric restriction data. If we estimate a 17% reduction in the caloric intake of male Okinawans compared to the rest of Japan (Weindruch and Sohal, 1997) and an average male longevity of 77.5 years in Okinawa (Japan Ministry of Health, 1995, cited in Willcox and Willcox, 2004), the slope of the dietary effect is −0.0020. If we assume that the response of longevity is linear all the way down to the minimum sustainable male caloric intake at about 1500 cal, the best possible case, then we can calculate upper bounds based on these two slopes of longevity's relationship to caloric intake. Using the slopes based on the Sumo data and the Okinawan data and extrapolating to a caloric intake of 1500 kcal per day, the best possible mean human lifespans obtainable from caloric restriction are 81.9 and 78.3 years, respectively. Note that this upper limit requires a linear response to diet over a vast range of caloric intakes, from 1500 to 5000 kcal per day, close to the whole range of sustainable human caloric intake levels. A more reasonable non-linear model would predict a *lower* maximum human lifespan arising from caloric restriction than we do here.

To compare rodent and human results, we need comparable scaling, using percentage lifespan effects and percentage changes in caloric intake. On this scale, the maximum beneficial effect of caloric restriction in humans, based on Sumo wrestlers, is (5.2 years/76.7 years) = 0.068, or a benefit of about 7%. In mice, the comparable effect is a benefit of (45.9 months − 27.4 months) versus a normal lifespan of 27.4 months. This is a benefit of (18.5 months/27.4 months) = 0.675, or a benefit of 67.5%. Thus, this analysis predicts a vastly greater effect—approximately 10 times greater—of caloric restriction on rodent longevity than on human longevity.

Our next task is to explain why this pattern should exist.

5. Explaining the human pattern

Roughly speaking, the response of longevity to diet will scale with the fraction of the organism's energy budget that is allocated to reproduction, in animals that do not grow as adults. This makes the scientific question one of determining this fraction. The fractional investment in reproduction varies widely in nature, ranging from species that make a small reproductive effort per unit time to those that make a relatively large reproductive effort. Humans and other long-lived primates (including the Rhesus monkeys, *Macaca mulatta*, and squirrel monkeys, *Saimiri sciureus*, used in ongoing caloric restriction studies) invest little. Compared to other mammals, mice and rats invest a great deal. Extrapolation of results obtained in rodent models to primates represents extrapolation from one extreme of the mammalian life history continuum to the other. In Fig. 3a, we show the relative investment in gestation made by rodents and by primates. In Fig. 3b, we present the same contrast for lactation. These data show dramatically the greater investment in rodent reproduction, compared with primate reproduction.

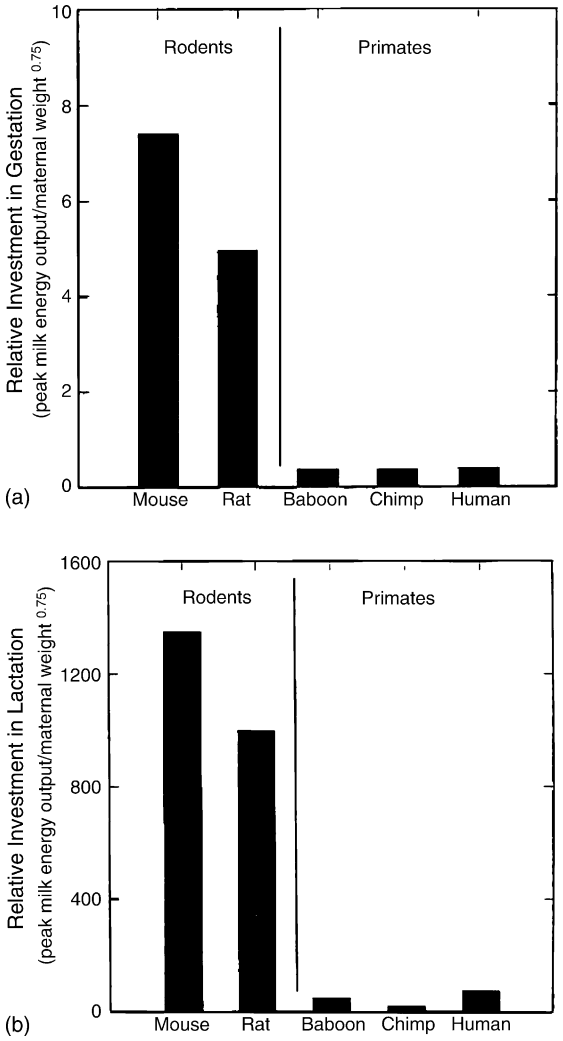

Fig. 3. (a) Comparison of the relative energetic investment in gestation among mice, rats, and three species of primates. Figure follows Prentice and Whitehead (1987), adapted from data presented by Payne and Wheeler (1967, 1968). The stress of reproduction is estimated by computing gestational growth rate as a proportion of maternal weight, where gestational growth rate is estimated as birth weight (summed over the litter) divided by gestation length. (b) Comparison of the relative energetic investment in lactation among mice, rats, and three species of primates. Figure follows Prentice and Whitehead (1987), adapted from data presented by Payne and Wheeler (1967, 1968).

The observation that caloric restriction extends longevity in rodents substantially is not surprising, given the reduction in fertility that occurs with rodent CR. The increased longevity that results from rodent caloric restriction is invariably accompanied by a dramatic decrease in reproductive capacity. More than 50 years ago, Ball et al. (1947) found that female mice maintained on a restricted diet had a fertility index (number of litters per mouse

per month) only one-tenth of that found in ad libitum fed controls. When these mice were subsequently allowed food ad libitum, their fertility promptly increased to that of ad libitum fed controls. In a study of non-mating rats, Holehan and Merry (1985) found that peak values of serum luteinizing hormone and serum estradiol-17β as well as overall serum progesterone values were significantly reduced among calorically restricted females compared with ad libitum fed controls. Among calorically restricted males, they found that peak testosterone values dropped to less than one-third of that found among ad libitum fed males (2 ng/ml versus 6.5 ng/ml; Merry and Holehan, 1981). Additionally, Nelson et al. (1985) reported that most calorically restricted laboratory mice cease ovulatory cycling.

Since primates have such a small relative investment in reproductive effort, less benefit is likely to result from their caloric restriction. The data of Fig. 3a and b show that the rodent investment is approximately 10 times as great as the primates'. An important factor in this difference lies in the exceptionally long gestation period—two to four times as long as a non-primate of similar body size—which is common in primates. This longer gestation period lessens the daily cost of fetal growth by stretching the investment out over a longer period of time.

Reproductive effort does not end with gestation. Energetically, lactation in mammals represents a far greater investment than gestation. Nonetheless, analyses of the stress of lactation paint a similar picture as the gestational stress: primate effort is dramatically less than that of rodents. In Fig. 3b, we present an index of lactational stress, measured as peak energy yield as a proportion of maternal weight, where peak energy yield is a combination of milk volume and composition (data are from Contaldo et al., 1981; Roberts et al., 1985; Prentice et al., 1986; summarized in Prentice and Whitehead, 1987). Again, the primate investment is approximately an order of magnitude smaller than the rodent investment. It should be noted that Fig. 3a illustrates the *peak* cost of lactation and demonstrates the relatively small amount by which primate metabolism is taxed by lactation at its peak. This is only one possible measure of lactational stress. Using a more generalized analysis, Charnov and Berrigan (1993) estimated primate reproductive investment at 40% that of other mammals.

By any accounting, rodent life histories clearly are characterized by greater reproductive effort. Laboratory caloric restriction studies, however, are comparisons of non-reproducing animals and yet the restricted animals still live longer than the controls. This suggests the complexity of the physiology involved and may be due to the fact that an important component of the cost of sustaining reproductive *readiness* in mammals is increased carcinogenesis associated with circulating reproductive hormones, particularly estrogen (see, e.g. Key and Pike, 1988), progesterone (see, e.g. Pike et al., 1993), and testosterone (see, e.g. Guy and Auslander, 1973).

6. Should humans chronically restrict their caloric intake?

Caloric restriction is likely to be almost universal in its beneficial effects on longevity. This does not, however, warrant an expectation that there will be a quantitative equivalence between DR in humans and DR in rodents. Instead, if our quantitative analysis is to be taken at face value, the quantitative benefit to humans from caloric restriction is going to be

small, even if human subjects restrict their caloric intake substantially and over long periods of time.

An important qualification to this argument is that we have formulated our model in terms of lifelong adult CR. In practice, CR might be imposed intermittently, only during early adulthood, or only during late adulthood. The general pattern is that more CR gives greater mean longevity in rodent studies (citations—see Comfort's, 1979 book and Weindruch and Walford, 1988). However, this may mask a predominantly short-term effect on age-specific mortality (cf. Mair et al., 2003). If that is the case, CR may increase longevity more when it is practiced more, simply because of short-term reductions to mortality rate at whatever adult ages it is imposed. This suggests that a more accurate formulation of our model would treat short-term mortality rates as functions of caloric intake, rather than longevity. Unfortunately, the data required to calibrate such a mortality-rate model are not available in any mammals, humans included. This would, however, be an interesting project for further research.

To undergo decades of CR, suffering chronically reduced fertility and increased hunger, for the sake of a much smaller proportionate increase in longevity than is seen in rodents seems unappealing and ill-advised. Our conclusion is that it is reasonably prudent assuming that caloric restriction is unlikely to be a panacea for human aging.

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