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CALORIE RESTRICTION AND AGING: A LIFE-HISTORY ANALYSIS

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Abstract.—The disposable soma theory suggests that aging occurs because natural selection favors a strategy in which fewer resources are invested in somatic maintenance than are necessary for indefinite survival. However, laboratory rodents on calorie-restricted diets have extended life spans and retarded aging. One hypothesis is that this is an adaptive response involving a shift of resources during short periods of famine away from reproduction and toward increased somatic maintenance. The potential benefit is that the animal gains an increased chance of survival with a reduced intrinsic rate of senescence, thereby permitting reproductive value to be preserved for when the famine is over.

We describe a mathematical life-history model of dynamic resource allocation that tests this idea. Senescence is modeled as a change in state that depends on the resources allocated to maintenance. Individuals are assumed to allocate the available resources to maximize the total number of descendants. The model shows that the evolutionary hypothesis is plausible and identifies two factors, both likely to exist, that favor this conclusion. These factors are that survival of juveniles is reduced during periods of famine and that the organism needs to pay an energetic ''overhead'' before any litter of offspring can be produced. If neither of these conditions holds, there is no evolutionary advantage to be gained from switching extra resources to maintenance. The model provides a basis to evaluate whether the life-extending effects of calorie-restriction might apply in other species, including humans.

Key words.—Dietary restriction, fluctuating environments, longevity, maintenance, mice, model, resource allocation.

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In 1935, it was found that life span in laboratory rats is extended by restricting their food intake relative to ad libitum feeding (McCay et al. 1935). Many studies have confirmed this result and extended it to mice, with typical increases of 20–30% in both mean and maximum life span (Weindruch and Walford 1988; Sprott 1997). Long-term calorie restriction results in a small, lean animal, with impaired fertility, but which is otherwise healthy and active. Recent interest has focused on identifying the physiological mechanisms that maintain the animal in what appears to be a youthful state. Almost without exception, somatic maintenance functions are up-regulated (Holehan and Merry 1986; Masoro 1993; Yu 1994; Merry 1995). Life span extension through calorie restriction is not confined to rodents and is observed in other species (e.g., water flea, spider, and fish; Weindruch and Walford 1988). Studies on nonhuman primates have begun and, although it will take several more years to obtain evidence of life span alterations, some changes in physiological profiles similar to those seen in rodents have been reported (Roth et al. 1995; Lane et al. 1996).

Identifying whether there might be an adaptive basis for the response to calorie restriction in rodents will help not only to understand this phenomenon, with its complex effects on the aging process, but also to assess whether it might also work in long-lived species, like humans. The hypothesis examined here is that animals have evolved a response to temporary fluctuations in resource availability, in which energy is diverted from reproduction to maintenance functions in periods of food shortage, thereby enhancing survival and retaining reproductive potential for when conditions improve (Holliday 1989). This hypothesis is examined using the approach of optimizing the allocation of resources to competing physiological demands. This forms one basis of life-history theory (Fisher 1930; Townsend and Calow 1981; Roff 1992; Stearns 1992) and also of the disposable soma theory of aging (Kirkwood 1977, 1981, 1997; Kirkwood and Holliday 1979).

Previous theoretical work has shown that a fluctuating environment can produce delays (e.g., longer life, lower reproductive rate) in optimal life histories even without physiological trade-offs (Tuljapurkar 1989, 1997; McNamara 1997). However, there are many examples providing evidence for the central role of physiologically based trade-offs (Sibly and Calow 1986; Roff 1992; Stearns 1992) and their hormonal control (Ketterson and Nolan 1992, 1999; Finch and Rose 1995) in life histories. For example, high reproductive effort is associated with poor moult (Hemborg and Lundberg 1998), reduced immunological status (Ots and Hõrak 1996), and reduced investment in sexual ornamentation in birds (Gustafsson et al. 1995); reduced growth in guppies (Reznick 1996); flight capability in crickets (Zera et al. 1998); and longevity in insects (Møller et al. 1989; Chipendale et al. 1993) and birds (McCleery et al. 1996). Our present aim is specifically to incorporate physiological trade-offs into a life-history model, based on empirical data for the house mouse, *Mus musculus*, to determine whether the phenomenon of life extension through calorie restriction can be satisfactorily explained as an evolutionary adaptation and what preconditions might be required. To this end, we adopt a state-dependent approach that permits resource allocation strategies and their physiological consequences in terms of individual rates of aging to be investigated.

Basic Observations and Mechanisms

The method of reducing calorie intake has varied between studies. Some have restricted food to a fixed proportion of the ad libitum levels; others have established a level of food intake that maintains a fixed (reduced) body weight (Merry

1995). The essential requirement is that total energy intake is decreased. There is little effect of varying the proportions of specific dietary components, such as protein or carbohydrate, provided the diet does not lack any essential nutrient (Kristal and Yu 1994). Typically, animals that have a 40% reduction in calorie intake, or that are maintained at 50% of the body weight of animals fed ad libitum, show extension of life span by 20–40% (Weindruch and Walford 1988; Merry 1995). The longer the period of calorie restriction in adults, the greater the effect on longevity (Kristal and Yu 1994). However, even a brief (4.5 months) calorie restriction started at 6 weeks of age in rats produced a 15% increase in life span (Yu et al. 1985). Not surprisingly, calorie restriction in juveniles has a detrimental effect on growth and development (Merry 1995).

Rodents kept on restricted diets are smaller, with less body fat and smaller major organs (Weindruch and Sohal 1997). Adult body size also depends on the age at which calorie restriction is begun. If restriction is initiated soon after weaning, growth is impeded, resulting in a stunted but healthy animal (Weindruch and Walford 1988). If initiated at some time after weaning, the main effect is a reduction in body fat (Means et al. 1993). Animals with little body fat on a restricted diet are vulnerable to cold (Johnson et al. 1982), which will have a detrimental effect on their survival in environments where cold is a common hazard. The calorie-restricted rodents are generally more active, which may relate to the need to search for food (Duffy et al. 1997; Hart and Turturro 1998). The normal age-related decrease in physical activity, as measured by voluntary wheel running and hanging strength, is markedly reduced in calorie-restricted animals (Means et al. 1993).

Calorie-restricted rodents appear to have a general up-regulation of mechanisms that protect against accumulation of somatic damage. Protein turnover (Lewis et al. 1985; Ward and Shibatani 1994), serum corticosteroids (Masoro 1995), DNA repair activity (Haley-Zitlin and Richardson 1993), cystolic antioxidants (Yu 1994), and the expression of heat-shock proteins (Heydari et al. 1996) all remain at youthful levels for longer. This enhanced somatic protection and repair is associated with a delay in many aspects of age-related pathology. Incidence rates of spontaneous and chemically induced tumors are greatly reduced (Weindruch and Walford 1982; Klurfeld et al. 1987; Schwarz and Pashko 1994). The age-related decline in the efficiency of wound healing is delayed (Reed et al. 1996). Also, calorie restriction virtually eliminates the development of autoimmune diseases in several susceptible strains of mice (Weindruch and Sohal 1997).

At first sight, it seems paradoxical that an organism with less energy available can up-regulate physiological processes, which must have an associated metabolic cost. This requires that metabolic savings be made elsewhere. The most obvious saving is in reproductive effort. Not only is reproduction costly in direct physiological terms, but behaviors associated with reproduction can also be expensive. Rodents typically invest a large fraction of their energy budget in reproduction. Calorie restriction results in animals that are mostly infertile, although there is some variation depending on the sex, the degree of restriction, and the age at which restriction is first applied (Weindruch and Walford 1988). For example, in mice, calorie restriction by 40% arrests follicular cycles in females (Nelson et al. 1985), whereas in female rats subjected to the same level of restriction, some reproductive activity continues (McShane and Wise 1996). Puberty in female rodents is delayed and reproductive senescence occurs later (Merry and Holehan 1979; Nelson et al. 1985). On refeeding, female rodents previously kept on restricted diets are able to reproduce at much later ages than fully fed controls (see Holehan and Merry 1986). Spermatogenesis in male rats is shut down if moderate calorie restriction is experienced early in life but, interestingly, this does not happen if calorie restriction is experienced in late life (Graves 1993).

Evolutionary Hypothesis

The evolutionary question of why a calorie-restricted organism should retard aging may help shed light on the physiological basis of this phenomenon. Harrison and Archer (1988) suggested that the primary role of calorie restriction is to postpone reproductive senescence. If a famine lasts longer than the normal reproductive life span of the animal, any female that delays reproductive senescence and is able to breed after the famine has passed will experience a selective advantage. Harrison and Archer (1988) predicted that calorie restriction should have greater effect on species with shorter reproductive life spans and suggested a comparison between the house mouse, *Mus musculus*, and the longer-lived white-footed mouse, *Peromyscus leucopus.* They also predicted that calorie restriction should have little effect on long-lived species such as humans. However, Phelan and Austad (1989) argued that, in the wild, very few individuals live long enough to experience reproductive senescence and proposed that natural selection simply postpones reproduction in times of famine, extending life as a secondary consequence of less reproductive effort. This hypothesis suggests that calorie restriction should have greater effect on species with early and copious reproduction than on species with late sexual maturity and smaller reproductive effort. Because age of maturation and reproductive effort are comparable in *M. musculus* and *P. leucopus*, Phelan and Austad (1989) predicted a similar response to calorie restriction in these two species. The direct comparison between these two species has yet to be made.

A more explicit hypothesis was proposed by Holliday (1989), based on the disposable soma theory of aging. The idea is illustrated in Figure 1, where the diagonal line represents, for levels of food availability ranging from starvation through famine (corresponding to calorie-restricted levels) to plenty (corresponding to ad libitum feeding), the energy available for allocation between reproduction and somatic maintenance. The continuous curve represents the partitioning of this energy, the fraction for maintenance being below the line and the fraction for reproduction above the line. Under conditions of plentiful food supply, a constant amount of energy is allocated to maintenance. This follows from the disposable soma theory, which asserts that no advantage is gained by investing more in maintenance than is necessary to ensure that the soma remains in sound condition through the natural expectation of life in the wild environment (determined mainly by the level of extrinsic mortality). As food supply diminishes, reproduction is reduced and eventually

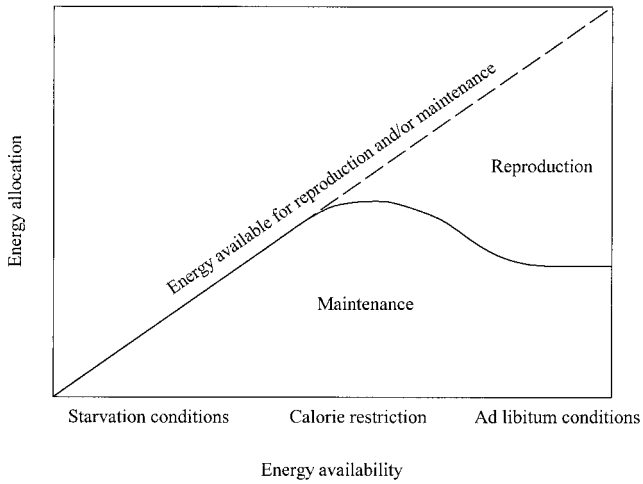

FIG. 1. Variation of the optimal allocation of energy to maintenance and reproduction with the total energy available in the environment.

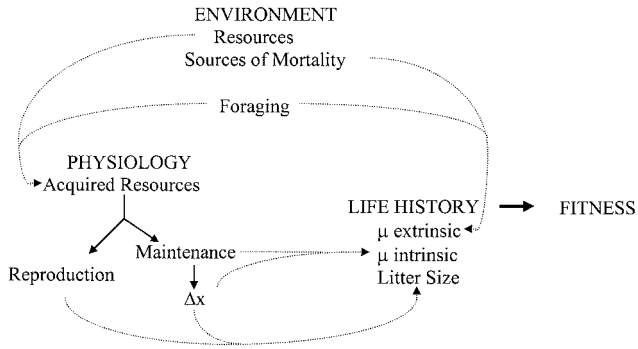

FIG. 2. Overall structure of a model for dynamic optimization of resource allocation between maintenance and reproduction.

curtailed. Holliday (1989) suggested that at famine levels where, in principle, a small amount of energy could be allocated to reproduction, it may in fact be better temporarily to increase the investment in somatic maintenance. The potential benefit is that the animal gains an increased chance of survival with a reduced intrinsic rate of senescence, thereby permitting reproductive value to be preserved for when the famine is over. It should be emphasized that although the greatest effects of calorie restriction are seen when restriction is applied *throughout* the adult life span, the adaptive response, if it is indeed adaptive, is most likely to have arisen as a strategy to cope with a food supply that shows short-term unpredictable fluctuations.

Dynamic Optimization of Resource Allocation

The central prediction of the disposable soma theory (Kirkwood 1977, 1981; Kirkwood and Holliday 1979) is that for any species with a distinction between germ-line and soma, the optimum allocation of metabolic resources to somatic maintenance will be less than required for indefinite somatic survival. In environments with varying food supplies, the level of the optimum may vary. To investigate how the optimum allocation might change at different resource levels requires a dynamic optimization approach. An appropriate methodology, widely adopted in general life-history analysis, is stochastic dynamic programming (Bellman 1957; Houston et al. 1988; McNamara 1991). The age of the organism can be described by a state variable that changes through time depending on the allocation of resources to maintenance. This state variable can be seen as an irreversible accumulation of intrinsic damage. The resource allocation strategy of an individual can be followed through time and optimized to maximize individual fitness. By common convention, the analysis is restricted to females, because female demographic dominance is assumed (Charlesworth 1994, p. 4), and fitness can be defined by the number of descendants derived from an individual founder female at some future time (McNamara 1991).

In this paper, we describe a dynamic programming model to examine whether the physiological responses to calorie restriction observed in the laboratory might reflect an adaptive resource allocation strategy that has evolved to maximize fitness under conditions of intermittent food stress in the wild. The model is developed for *M. musculus,* for which extensive physiological and life-history data have been recorded both in the wild and in the laboratory (Berry and Bronson 1992).

THE MODEL

Model Components

The model is based on a physiological resource allocation rule governing the partition of energy between maintenance functions and reproduction to maximize fitness in the prevailing environment. Resources allocated to reproduction are used to produce progeny, whereas resources allocated to maintenance are used to conserve state. At any age, the change in state is determined by the amount of energy invested in maintenance. With a large investment in maintenance, the state remains relatively unchanged, corresponding to a slow rate of aging. Conversely, with a small investment in maintenance, the state change is large, corresponding to a rapid rate of aging. Sources of mortality are separated into those determined largely by extrinsic factors, such as predation and climate, and intrinsic factors, such as disease and senescence-associated frailty (Promislow and Harvey 1990; Calow 1998). Intrinsic mortality is directly related to the state of the individual; the level of intrinsic damage. The overall structure of the model is shown in Figure 2 and the individual components are as follows.

Environment.—In the simplest scenario examined here, a normally constant level of resources available in the environment undergoes a temporary depression. The environment also sets the level of extrinsic mortality. The greatest source of extrinsic mortality is cold. However, house mice are also a common prey species, and because these principal sources of extrinsic mortality act mainly when the animal is outside the protection of the nest, they are combined in a single term for extrinsic mortality (Berry and Bronson 1992).

Foraging.—Foraging is not explicitly modeled, but foraging efficiency in the wild is assumed to decrease with state (age) corresponding to effects on ad libitum intake recorded

in the laboratory. The result is an age-related decline in the food acquired.

Physiology.—The resources acquired are partitioned between reproduction and maintenance functions. Allocation to developmental growth is omitted because only the resource allocation strategy in adult animals is considered. Storage is also omitted because storage serves only as a short-term buffer in the energetics of small mammals (Bronson 1989). Energy allocated to maintenance is used for anti-aging cellular functions such as DNA repair and free radical scavenging (Blaxter 1989, p. 140). Because the energetics of these functions is still poorly understood, the relationship relating the rate of aging, modeled as a change in state, to the allocated energy is left free to manipulate in the model. Reproductive effort is enormous for a small mammal like the mouse, the most costly period being during lactation when food intake must be substantially increased (Millar 1987; Bronson 1989, pp. 47–53). Litters of newborn pups are often reduced by the mother to match the availability of food during early lactation. For this reason, the energy cost is based on the size of the litter successfully weaned. In addition, the model allows for the possible cost of a reproductive ''overhead'' that must be paid to initiate reproductive activity (Gittleman and Thompson 1988). This includes the energy costs of producing reproductive hormones, mating, and changes that prepare for pregnancy (e.g., lining of the uterus).

State.—The state variable uses the concept of biological, as distinct from chronological, age. An individual is defined as being in state x if its physical condition (biological age) matches that of an average ad libitum fed mouse that has a chronological age of x time units, measured from the end of the juvenile period. Increasing the resources allocated to maintenance results in a state variable that advances at a slower rate than chronological age.

Life history.—The following parameters are used to define the life history: t_j, the time taken for offspring to develop to maturity; S_j, the survival of offspring to maturity given the survival of the mother; S_a, adult survival deduced from extrinsic and intrinsic mortality, μ_{ext} and μ_{int}; t_a, minimum interbirth interval; and n, number of offspring successfully weaned (the number of female offspring, b, is assumed to be $n/2$). The time unit in the model has been set to 1.5 months, which equals both the developmental time, t_j, and the minimum interbirth period, t_a (Berry and Bronson 1992). Both t_j and t_a are assumed to be unchanged by environmental conditions. It is observed that juveniles are excluded from preferred food sources at both high population density and at low food availability, which inevitably gives rise to increased mortality (Dickman 1992). The parameter for juvenile survival, S_j, is left free to manipulate in the model and used to set population growth rate in the normal (nonfamine) conditions to zero, that is, stable population size. Because juvenile survival is likely to be adversely affected by famine, it is also assumed that juvenile survival may be reduced by an amount proportional to the reduction in food availability. For example, with a proportionality constant of 1.0, a reduction of half in food availability leads to a 50% reduction in juvenile survival. Intrinsic mortality, μ_{int}, is state dependent as given by laboratory data in the absence of extrinsic sources of mortality (Finch 1990, p. 123). The maximum number of offspring that can be weaned, even when food is plentiful, is state dependent to represent reproductive senescence.

Fitness.—Relative fitness for alternative strategies is defined by comparing the numbers of female descendants at a time sufficiently far into the future that the ratios have converged (McNamara 1991). The optimal strategy is that which maximizes fitness relative to the possible alternatives.

Model Structure

For a female in state x at time t allocating a proportion u of available resources to maintenance functions, the dynamic programming equation is given by

$$f_t(x) = \underset{u}{\text{Maximum}}\,[S_a \cdot S_j \cdot b \cdot f_{t+\Delta t}(x_0) + S_a \cdot f_{t+\Delta t}(x + \Delta x)], \tag{1}$$

fitness — contribution of offspring — and — focal female

where x_0 represents the initial state of a newly matured female and Δx the change in state in time interval Δt.

The dynamic program is structured as follows. An adult in state x at time t acquires resources R_t. She allocates a proportion u of these resources to maintenance, the remaining $(1 - u)$ to reproduction. She produces n_t offspring and survives to the next time interval with a probability that depends on both extrinsic and intrinsic mortality and, therefore, on her investment in maintenance. The offspring produced at time t survive to the next time interval with a probability that depends on the survival of their mother and on their own survival probability that is manipulated in the program to regulate population growth rate. All surviving offspring mature and are equivalent at this next time interval.

The model is based on experimentally determined data where possible. In the absence of appropriate data, the model is tested for a range of parameter values considered realistic.

Model Parameters

Although there are differences between laboratory and wild mice in the energetics of metabolism (Richardson et al. 1994) and reproduction (Bronson 1984), these differences are small in relation to the overall variation in experimental results. For this reason, they are pooled. Due to variations in the body sizes of mice from which the data have been obtained, values are expressed in KJg^{-1}.

Mortality.—Adult extrinsic mortality is assumed constant at 15% per month (Pennycuick et al. 1986; Berry and Bronson 1992). Juvenile survival is assumed to regulate population growth rate and is therefore calculated in the program. In the wild, juvenile survival is thought to be in the order of 15%. Intrinsic mortality, μ_{int}, is approximated with a Gompertz relationship

$$\mu_{int} = \mu_0 e^{\beta \cdot x}, \tag{2}$$

where μ_0 and β are constants and x is state. Values of 0.001 and 0.3 were used for μ_0 and β, respectively, which represent average figures for a large number of laboratory strains (Finch 1990, p. 123). However, populations of wild mice may experience generally higher levels of intrinsic mortality (Finch

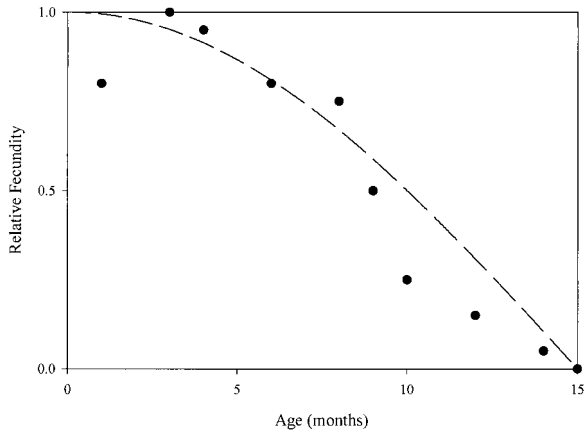

FIG. 3. The relationship between age and relative fecundity for CF-1 mice. Relative fecundity is calculated as the product of the number of pups born and the live delivery rate with respect to maximum fecundity at three months of age (vom Saal et al. 1995, p. 1248).

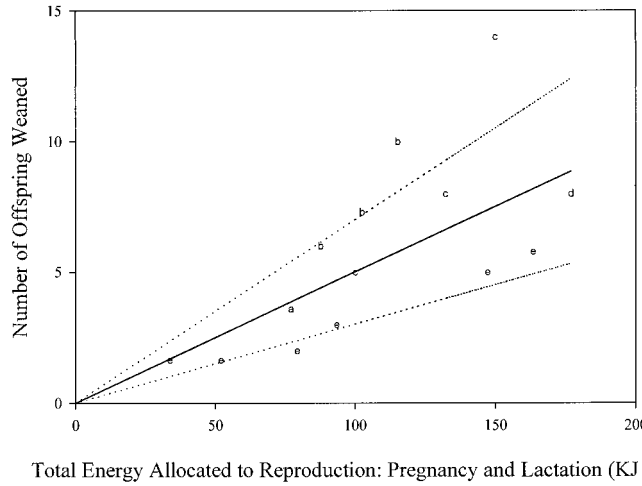

FIG. 4. Relationship between the total energy allocated to reproduction, relative to initial maternal body weight, and the number of offspring successfully weaned. The continuous line indicates a proportional relationship $n = 0.05E_{\text{Reproduction}}$ ($R^2 = 0.4$; also indicated as dotted lines are slopes of 0.03 and 0.07). The datapoints are from the following sources: (a) Polish white laboratory mouse housed at 22–23°C (Mychra et al. 1969; Mychra 1975); (b) BALB/c/Han strain housed at 21°C (König et al. 1988); (c) Swiss-Webster strain housed at 23°C (Hammond et al. 1994; energetic data only for days 32–35 were given, and to overcome this a correlation of energy allocation at this time to total allocation for all other data was obtained and used as follows: $E_{\text{reproduction}} = 20.2\,E_{32-35} + 13.3$, $R^2 = 0.9$); (d) CF-1 strain housed at 22°C (Bronson and Marsteller 1985); (e) fourth to fifth generation wild mice, Calgary, Alberta, housed at 20°C (Perrigo 1987; energetic data includes wheel running; the contribution of wheel running to total energy budget was removed using a regression of the number of revolutions run and prelactating body weight to total intake as follows: $E_{\text{Total}} = 6w^{0.75} + 0.00064Revs$, $R^2 = 0.32$).

et al. 1990) and the model predictions were also tested with higher values of μ_0.

Reproduction.—Reproductive output as a function of age under ad libitum conditions is shown in Figure 3. A cosine relationship (as shown) was used to fit these experimental data for use in the model. To estimate the energy cost of reproduction, data from a number of sources were used to compile Figure 4, which shows the total energy consumed for the number of offspring weaned. The energy expended in one breeding effort is the total of the energy consumed during pregnancy and lactation minus the amount equivalent to basal metabolism at the average of the initial and final (i.e., after body weight has returned approximately to normal) basal metabolic rates.

Maintenance.—A value of 2 $KJg^{-1}day^{-1}$ was chosen to represent the basal metabolic rate of the house mouse, averaged over an extensive dataset (Mychra et al. 1969; Mychra 1975; Studier 1979; Bronson 1984; Stephenson and Malik 1984; König et al. 1988; Manning and Bronson 1990; Mutze et al. 1991; Hayes et al. 1992; Hammond et al. 1994; Richardson et al. 1994). Half of this energy is used in essential service functions and the remaining half is available for cell maintenance functions. A mouse allocating this amount of energy for maintenance is assumed to age at a rate that equates physiological state (biological age) with chronological age. A lower allocation of energy to maintenance results in more rapid aging; a higher allocation results in slower aging. The exact relationship between rate of aging and the resources allocated to maintenance is not known, but a flexible model for the rate of aging dx/dt governed by a parameter, α, was used as follows:

$$\frac{dx}{dt} = \left(\frac{E_{\text{BMR}} - E_{\text{Service}}}{E_{\text{Maintenance}} - E_{\text{Service}}}\right)^{\alpha}, \qquad (3)$$

where E_{BMR}, is the energy used for basal metabolic rate, of which E_{Service} is used for essential physiological tasks and $E_{\text{Maintenance}}$ represents the total energy allocated to maintenance. The effect of altering α is shown in Figure 5. If α is low, the rate of aging is very insensitive to varying the level of maintenance and vice versa. Some trial and error was necessary to identify values of α that predicted aging as observed in the laboratory, and the sensitivity of the results to varying α was assessed.

Energy intake.—The reference values for energy intake are

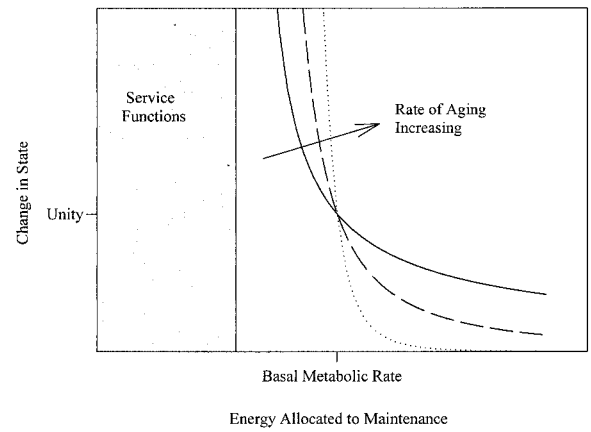

FIG. 5. The rate of change in state (rate of aging) as a function of the energy allocated to maintenance (see text). Curves are shown for three different values of the parameter α. If α is low, the rate of aging is very insensitive to varying the level of maintenance and vice versa.

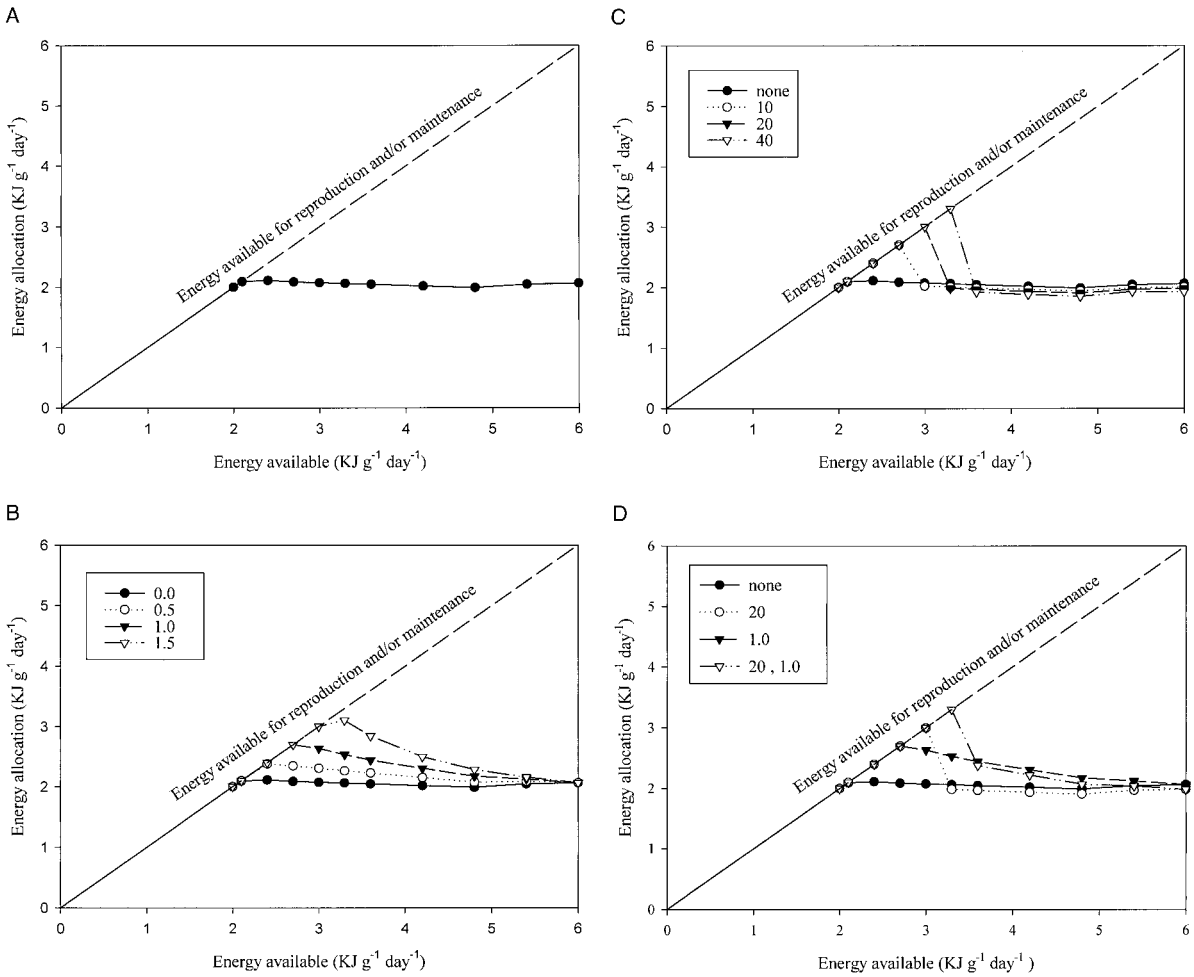

FIG. 6. (A) Variation of the optimal allocation of energy to maintenance and reproduction with total energy available in the environment for a six-month-old mouse during a three-month depression in food level. As in Figure 1, the curve indicates the level of the optimal allocation to maintenance; the difference between this and the diagonal (dashed) line is the allocation to reproduction. (B) As (A), but juvenile survival is reduced by an amount proportional to the level of reduction of energy available. Three cases are shown with different constants of proportionality in addition to the case where food availability has no affect on juvenile survival. (C) As (A), but a reproductive overhead of 0, 10, 20, and 30 KJg^{-1} must be paid to initiate reproduction. (D) As (A), but comparing the effects of a reproductive overhead of 20 KJg^{-1}, a reduction in juvenile survival in direct proportion to the reduction in energy availability, both of these factors, and neither of them.

those available to a wild mouse in an abundant environment. These were estimated as the amount of energy consumed by a fertile laboratory female subject to ad libitum feeding. The energy intake of such a female averages 6 $KJg^{-1}day^{-1}$ when young and declines with aging due to the falling reproductive demand associated with senescence. Calorie restriction was applied by an appropriate percentage reduction on the reference values.

RESULTS

To test the hypothesis that the physiological response to calorie restriction reflects adaptation to periods of famine, a temporary reduction of food level was introduced in an otherwise abundant environment. This was done in two ways. First, we imposed a single episode of famine in a set time period. This allowed us to vary the age at which famine was encountered and its duration. To consider the possible impact of further episodes of famine on the optimum strategy, we also assumed a given probability of experiencing famine in each time period. The results were similar in the two cases and only the former is shown here. Population size was assumed to be stable in the normal (abundant) conditions. In most simulations it was assumed that a young mouse (age four time units, or six months) experienced a famine lasting two time units (three months). Later simulations examined the sensitivity of the results to the duration of famine and the age of the mouse when famine was experienced.

Variation in Optimal Maintenance Level

Two factors have a major influence on the predicted outcome of the model. These factors are the presence or absence of a reproductive overhead and the presence or absence of an adverse effect of famine directly on juvenile survival. Not surprisingly, the presence of either of these factors increases the likelihood that an organism might increase its fitness by suspending fertility in periods of famine. Figure 6 show re-

TABLE 1. Predicted schedules of survival (l) and reproduction (n) for wild and laboratory mice in an abundant environment (ad libitum feeding) contrasted with the wild environment during a temporary period of food shortage and with life-long (postweaning) calorie restriction (CR) in the laboratory. Age is indicated in months; the 1.5-month increments correspond to the time unit of the model.

	Ad libitum feeding				50% CR applied at age * for 3 months				50% CR lifetime	
	Wild		Lab		Wild				Lab	
Age	l	n	l	n	l	n	l	n	l	n
1.5	1	7.7	1	7.7	1	7.7	1	7.7	1	0.0
3	0.797	7.7	0.998	7.7	**0.797***	0.0	0.797	7.7	0.998	0.0
4.5	0.635	7.1	0.996	7.1	**0.635**	0.0	0.635	7.1	0.996	0.0
6	0.506	6.7	0.993	6.7	0.506	6.9	**0.506***	0.0	0.994	0.0
7.5	0.402	6.1	0.989	6.1	0.402	6.4	**0.402**	0.0	0.992	0.0
9	0.319	5.3	0.983	5.3	0.319	6.0	0.320	6.0	0.989	0.0
10.5	0.253	4.6	0.975	4.6	0.253	4.9	0.254	5.5	0.986	0.0
12	0.200	3.3	0.965	3.3	0.200	3.9	0.201	4.3	0.982	0.0
13.5	0.157	2.7	0.951	2.7	0.158	2.9	0.159	2.6	0.978	0.0
15	0.119	0.0	0.900	0.0	0.120	0.0	0.125	2.9	0.972	0.0
16.5	0.086	0.0	0.817	0.0	0.087	0.0	0.095	0.0	0.965	0.0
18	0.062	0.0	0.742	0.0	0.063	0.0	0.069	0.0	0.959	0.0

* Indicates the age at which a food shortage is encountered.

sults for a series of simulations that considered various combinations of presence/absence of these factors. The diagonal line in each panel of Figure 6 corresponds to the energy available for reproduction and maintenance and, as in Figure 1, the curves show how this is partitioned. It is convenient to describe each of these graphs in terms of what happened as food availability was reduced, that is, moving from the right side, where food was abundant, toward the left, where food became progressively more scarce.

In the absence of either a reproductive overhead or an effect on juvenile survival (Fig. 6A), calorie restriction had little effect on the optimal allocation of energy to maintenance. Reproduction declined as food availability diminished, but it continued as long as there was sufficient energy to support any reproduction at all. This prediction was independent of the gradient of reproductive efficiency (see Fig. 4). If the gradient was low, more energy was consumed for a given number of offspring, but these offspring were more likely to survive, due to the constraint of zero population growth. The effects on fitness of producing more offspring with a lower survival probability cancelled out and the predictions were equivalent. For the majority of later results a gradient of 0.05 was chosen, which required a juvenile survival rate of 8% to regulate the population. We used the device of adjusting juvenile survival to regulate population growth so that strategies with different assumed conditions can be readily compared. For any given set of conditions, varying juvenile survival in this way does not affect the conclusions about optimal strategies.

Figure 6B shows how an adverse effect of famine on juvenile survival altered the prediction. Three levels of effect were considered. In all cases, as food availability decreased, the incentive to invest in offspring that had little chance of survival was lost before reproduction became impossible, and there was a window within which extra resources are allocated instead to maintenance. The more severe the effect of famine on juvenile survival, the more readily it was predicted that maintenance was enhanced.

Figure 6C shows the effects of including a reproductive overhead at values for this overhead of 10, 20, and 30 KJg^{-1}. If there was insufficient food to overcome this reproductive barrier, then any available resources were diverted to extra maintenance.

Figure 6D shows the combined effects of a reproductive overhead and an effect on juvenile survival, for the case of a reproductive overhead of 20 KJg^{-1} and a reduction in juvenile survival equal to the percentage reduction in food availability. The combined effect of both these factors was compared with the effects of just one of them or neither. With both factors present, it was readily predicted that calorie restriction resulted in increased somatic maintenance.

To see the effects of increased somatic maintenance on the life history, life tables were constructed for the combined-effects model of Figure 6D (Table 1). Columns 1 and 2 in Table 1 show survival and fecundity schedules for a wild mouse in an abundant environment. Both correspond well with what is known about the wild mouse life history (Berry and Bronson 1992). Columns 3 and 4 show survival and fecundity schedules with the same parameters, but now observed in the laboratory, where extrinsic mortality is removed. Columns 5, 6, 7, and 8 show the predicted survival and fecundity schedules for a wild mouse experiencing a three-month period of famine beginning at three months and at six months of age, respectively. During the period of famine, reproduction ceases but there is only a small effect on survival. This is because the change in intrinsic mortality is swamped by the high extrinsic mortality experienced in the wild. However, it may be seen that reproductive capacity is retained to an advanced age, as is particularly clear in the second set of predictions (columns 7, 8), where reproduction remains possible at 15 months of age. Columns 9 and 10 show the effects projected for a lifetime on a reduced diet in the laboratory, equivalent to the typical calorie-restriction experiment. The predicted enhancement in survival matches the data well. At 18 months of age, 96% of mice remain alive compared to 74% on a normal diet, and the biological age of these mice is only 12 months as deduced from the state. If ad libitum feeding were restored, the model predicts that reproduction would be possible even at this advanced chronological age.

Model Sensitivity

In any model, it is important to know the sensitivity of the results to varying the model parameters and assumptions. We checked this in various ways, described more fully elsewhere (Shanley 1999). The model predictions were relatively insensitive to the age when famine was experienced, although older animals tended to be more reproductively reckless in the face of adverse conditions. As might be expected, this effect was amplified with longer periods of food restriction and by the inclusion of reproductive senescence in the model. An important question was how the predictions were affected by severity of calorie restriction (Fig. 7). At lower food levels, there was a clear advantage in investing all resources in maintenance, resulting in life extension. As food levels increased, the strength of selection for this option was reduced. The sensitivity of model predictions to variation in population growth rate and in the parameter determining the rate of aging were also investigated; the qualitative form of the results was found to be robust.

Discussion

Our model specifically considered the optimal resource allocation between maintenance and reproduction in adult female mice subject to a temporary shortage of food. The advantage was that the relatively little understood allocation to maintenance and the effect on rates of aging could be clearly addressed in an evolutionary analysis that was pegged as closely as possible to the empirical data, with relevance to much current research on rodent calorie restriction. We did not consider other physiological components of life-history strategies (e.g., growth, storage) so the model is not immediately relevant to organisms with more complex life histories, such as insects, but such extensions could, in principle, be made. For the mouse the model showed that natural selection is expected to favor a life-extending response to calorie restriction, provided that there is a reproductive overhead or an adverse effect of famine on juvenile survival, but not otherwise. However, these two factors may have different effects on how the optimal strategy is specified.

A reproductive overhead poses its most serious challenge at very low food levels. In these conditions, one strategy is to reduce the allocation of resources to maintenance, thereby permitting reproduction even with low food availability. The alternative is temporarily to abandon any attempt at reproduction and to direct extra resources to enhancing long-term survival through maintenance. In none of the simulations studied here was maintenance compromised to pay the reproductive overhead. Instead, the strategy of suspending reproduction was always preferred, even when the reproductive overhead was small.

When famine has an adverse effect on juvenile survival, it is less worthwhile to invest energy in progeny that are unlikely to survive to maturity. In these conditions, energy is again predicted to be directed toward extra maintenance and away from reproduction. However, if the famine is not very severe, the strength of selection for this strategy can be weak and becomes even weaker with age.

As the level of food availability is progressively reduced, the two factors, reproductive overhead and adverse effect on juvenile survival, are predicted to have different profiles of effects. If there is only a reproductive overhead, the model predicts a limiting level of energy depletion beyond which further calorie restriction would have no further effect on longevity, as seen in Figure 6C. In contrast, in the case of an adverse effect on juvenile survival, increasing severity of calorie restriction is predicted to cause a continuing increase in life span, as shown in Figure 6B. This presents a possible

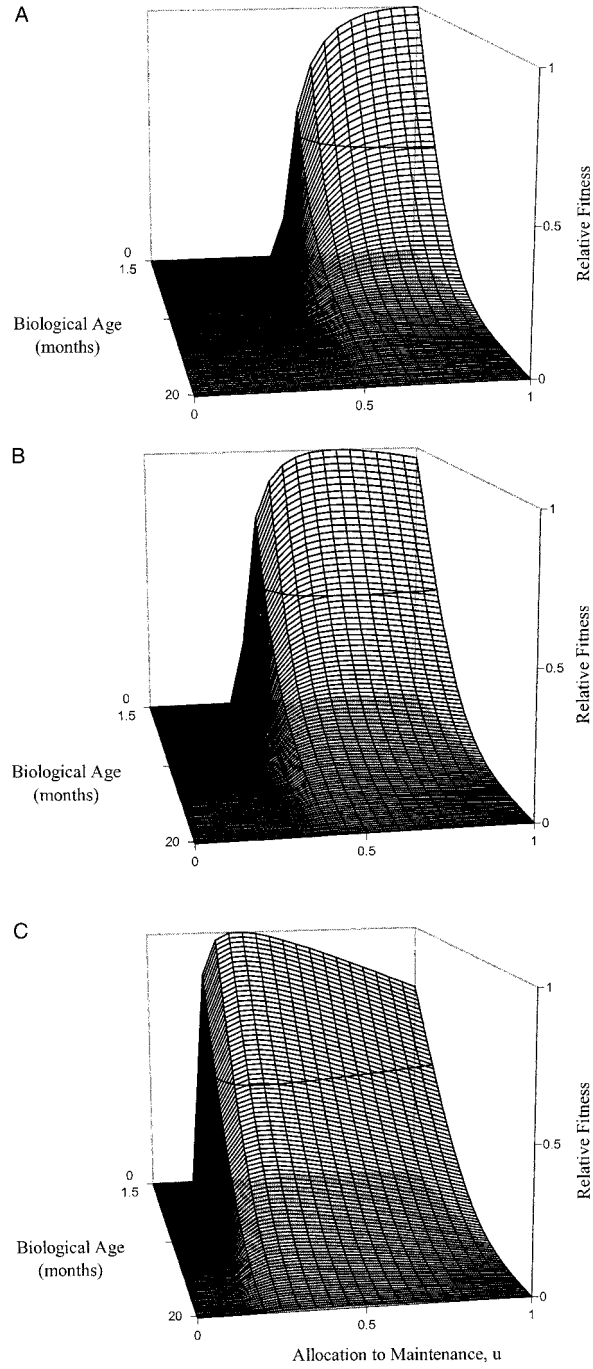

FIG. 7. Relative fitness for each allocation strategy, *u*, corresponding to the proportion of energy allocated to maintenance, for all states at three levels of food availability; (A) 35% of ad libitum level; (B) 50% of ad libitum; and (C) ad libitum level.

means of experimentally testing which factor might be more important. However, in the case that both factors are present, laboratory observations are unlikely to be able to differentiate between them. Some experimental data are available from studies on female C3N10F1 mice fed restricted diets of 30%, 40%, and 65% of ad libitum levels from one month of age. These showed maximum life spans of 55, 52, and 43 months, respectively, compared to 35 months for the ad libitum fed controls (Weindruch et al. 1986). Thus, even a modest restriction in diet resulted in extended life span, which is consistent with the existence of a reproductive overhead. However, unlike the model, the mice in this study were prevented from breeding, which automatically constrained the physiological options available to them. Careful consideration needs to be given to the design of experiments that might clarify these issues.

The predictions of the model do not resolve the debate about whether calorie restriction serves mainly to increase survival or to lengthen reproductive life span (Harrison and Archer 1988; Phelan and Austad 1989). The information in Table 1 suggests that enhanced survival is unlikely to be the major evolutionary force. However, these results assumed a low value for the parameter μ_0 of the Gompertz equation, based on data from laboratory mice. In such a situation, reproductive senescence will be a more important factor than in the case of wild mice, for which μ_0 is likely to be greater. Substituting a higher value for the parameter μ_0 in the model did not qualitatively change the predicted advantage of increasing the allocation of resources to maintenance, and it was even possible in this case to remove reproductive senescence from the model altogether without noticeable effect. Thus, increasing maintenance may be important both in terms of prolonging reproductive capacity and slowing down the age-related increase in mortality.

The model predicts that younger animals should respond to calorie restriction more than older animals. Calorie restriction applied early in life has the greatest effect, providing that it is not applied too early. When applied later in life it is perhaps not surprising that older animals retain some reproductive function, for example, old restricted male rats continue spermatogenesis (Graves 1993). It would be interesting to know the relative response of different age animals fed a restricted diet to breeding opportunities. A related point is the effect of calorie restriction on postreproductive females. An evolutionary perspective is here redundant because no selective forces can be identified once reproduction is terminated. From the energetic perspective, there can be no shift of resources from reproductive to maintenance functions in the model. Unfortunately, there is only a limited amount of data on such a late-life response, and there seems to be conflicting evidence of whether calorie restriction remains beneficial (Weindruch and Walford 1982) or whether it has no effect on life span (Lipman et al. 1995).

In quantifying the possible role of a reproductive overhead, it would be useful to have more data on the energetic demands not only of gestation and lactation, but also of maintaining a fertile condition. For example, the range of values considered as a reproductive overhead correspond to an initial barrier of 200–800 KJ that must be overcome by an average mouse weighing 20 g. Approximately 20% of the costs of gestation correspond to structural investment, such as the lining of the uterus (Blaxter 1989, p. 231), equivalent to approximately 100 KJ. With the additional costs of mating and hormone production, the range investigated in the simulations appears realistic. With increased confidence in the parameter values, the methodology could be applied with greater precision.

Animals subject to calorie restriction rapidly lose body weight and stabilize with little body fat. The gut shrinks, as do major organs such as the liver, heart, and kidneys (Weindruch and Sohal 1997). Because the major organs contribute disproportionately to the overall metabolic rate (Konarzewski and Diamond 1995), it is perhaps not surprising that metabolic rate per unit mass of lean tissue remains little altered (McCarter et al. 1985; McCarter and Palmer 1992). This seems to conflict with a central assumption of the model that maintenance processes are costly and that more energy needs to be allocated to maintenance in periods of famine. As previously noted, this additional energy could be made available without a change in metabolic rate by curtailing investment in reproductive overheads. Other energy savings could be made by adjusting body temperature, by reducing activity, or by altering the characteristics of cellular energetics. An example of the last is a reduction in the energy consumed by ion transport across cellular membranes, which may account for up to 20% of standard metabolic rate (Rolfe and Brown 1997). Mammalian cells are known to be leaky with respect to ion transport across membranes and futile ion pumping is implicated as an important mechanism of maintaining a constant body temperature (Else and Hulbert 1987). Interference in this process, although energetically beneficial, would diminish an animal's ability to withstand temperature fluctuations, which may be particularly significant because cold is a major source of mortality for the house mouse (Berry and Bronson 1992). The issues of foraging, thermoregulation, and body size need additional study.

The model has been quantified with data on house mouse physiology and ecology. The conditions for life extension to be an adaptive response to calorie restriction will not necessarily be the same for other species. Activity levels are affected differently in rodents and primates by short-term fasting (Masoro and Austad 1996), although recent data indicate that primates, like rodents, may up-regulate activity levels when subjected to long-term calorie restriction (Weed et al. 1997). Tropical species may not experience famine as often as species in temperate environments. Masoro and Austad (1996) note that squirrel monkeys, *Saimiri oestedi,* respond differently to calorie restriction than rhesus macaques, *Macaca mulatta* (Weindruch et al. 1995; Masoro and Austad 1996). Species that experience regular periods of food shortage, for example, in winter, often have specific adaptations for energy saving, including the accumulation of food stores, hibernation, and even a dramatic depression of metabolic rate while remaining active, such as the desert-living golden spiny mouse, *Acomys russatus* (Merkt and Taylor 1994).

Modeling is a useful means of examining the optimal strategies for allocating metabolic resources in good times and bad. The model developed here suggests that a life-extension response to calorie restriction may be adaptive and helps to

define the circumstances under which this is likely to be the case.

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