CAN EXPERIMENTS ON CALORIC RESTRICTION BE RECONCILED WITH THE DISPOSABLE SOMA THEORY FOR THE EVOLUTION OF SENESCENCE?

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Abstract.—A publication by Shanley and Kirkwood (2000) attempts to explain data on caloric restriction (CR) and life extension in the context of the Disposable Soma (DS) theory for the evolution of senescence. As the authors concede, this juxtaposition appears at first to offend intuition: According to the DS theory, senescence is the result of a tight budget for caloric energy, such that repair and maintenance functions are shortchanged; yet, in CR experiments, it is found that longevity decreases smoothly as the total caloric budget is increased. In the Shanley-Kirkwood model, an optimized allocation of resources causes energy to be diverted away from somatic maintenance at a greater rate than caloric intake increases, with the net result that more total energy is associated with less energy available for maintenance. In the present critique, the limitations of this model are detailed and its special assumptions reviewed. While the CR experiments find comparable life extension for males and females, measured relative to nonbreeding controls, the Shanley-Kirkwood model draws its energy budget from data on breeding females. In addition, the success in reproducing the observed relationship between feeding and longevity depends crucially on a mathematical relationship between food availability and the probability of reproductive success which may be difficult to justify.

Key words.—Aging, antagonistic pleiotropy, caloric restriction, dietary restriction, disposable soma, senescence.

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The Disposable Soma Theory

According to the Disposable Soma (DS) theory (Kirkwood 1977), every living organism must budget its energy among various priorities, including metabolism, growth, activity, and reproduction. Repair of damaged proteins and error-checking in DNA replication constitute demands on energy resources that must compete with these other functions, and so their allocation is subject to compromise. Failure to do a perfect job in these and other repair and maintenance functions leads to an accumulation of damage over the lifetime of the organism, the outward manifestation of which is the constellation of symptoms we identify as senescence.

The DS theory for the evolution of aging is elegant and economical, with strong common-sense appeal. Perhaps for this reason, it has enjoyed success relative to other theories of senescence, in a field where experimental evidence is subject to diverse interpretation.

Caloric Restriction and Life Extension

One experimental area which is comparatively unequivocal is the data on caloric restriction (CR). Laboratory animals maintained on a diet restricted in calories live longer than ad libitum fed animals, and many of the physiological markers of senescence appear on a delayed schedule. These data pose a particular dilemma for the DS theory, with its foundation in the metabolic energy budget. If senescence is caused by a failure to allocate adequate caloric energy for maintenance of the soma, why is it that the availability of caloric energy in abundance actually leads to more rapid senescence than occurs when energy is in short supply?

Theorists have explained the evolutionary provenance of the CR effect in terms of a shifted balance between the relative value of immediate reproduction and long-term survival: in times of famine, signaled by a meager food supply, the prospects for successful reproduction and for survival of young, vulnerable offspring is diminished; hence, it may be advantageous to delay reproduction, devoting extra metabolic resources to maintenance and survival functions (Holliday 1989; Austad 1995; Masoro and Austad 1996). This theoretical framework creates a context for modeling the effect with optimization of reproductive value; allocation of an unspecified, scarce metabolic resource may be directed either toward the immediate goal of reproduction or toward the long-term benefit of forestalled senescence. In times when the food supply is stressed, the optimum balance may sensibly be assumed to shift.

In the DS theory, the scarce resource is specified to be caloric energy itself; this puts an added burden on the model, which must account for an increasing repair/maintenance budget even as the overall caloric intake is declining steadily. Perhaps for this reason, it was not until just last year that an attempt to reconcile DS with the CR data was first put forward. This is the model of Shanley and Kirkwood (2000).

The Shanley-Kirkwood Model

The Shanley-Kirkwood (S-K) model is based in a detailed accounting of optimized energy rationing in times of famine and times of plenty. Life history optimization is used to determine the allocation of caloric resources, presumably under genetic control, between reproduction and maintenance of the soma. Reproduction is energetically expensive for the females modeled exclusively in the paper, but it offers an immediate payoff; energy expended in maintenance affords no payoff until much later, delaying the effects of accumulated damage which manifest as reduced fertility and increased mortality. Under the model's base assumptions, the authors report that increasing food supply makes more energy available for reproduction, while the maintenance portion

holds constant over a wide range of caloric intake; hence, the essence of the CR response remains unexplained. To engineer an agreement with reality, the model is varied with two additional parameters.

The first is a reproductive overhead, the cost of maintaining fertility independent of whether a litter actually ensues. When reproductive overhead is introduced, Shanley and Kirkwood find, after optimizing energy allocation, that reproduction turns off abruptly at a threshold CR level. The implication for senescence is that there is a narrow range around this threshold in which energy allocation for maintenance decreases sharply with increasing food supply. This result has the right sign to explain the data, but the curve is the wrong shape. In experimental findings, longevity decreases smoothly with increasing food availability over a wide range (Weindruch et al. 1986).

The model is extended with a second parameter, which relates the probability of infant survival to ambient food supply. It is proposed that foraging results for the mouse in the wild are a linear measure of the local availability of food; thus restricted caloric intake is a proxy for ambient famine conditions. The infant's prospects for survival through the nursing period are assumed to increase linearly with ambient food availability; combined with the assumed linear relationship between caloric intake and fertility, this amounts to a quadratic dependence of the effective reproductive rate on caloric intake. Under these assumptions, Shanley and Kirkwood report that optimization can reproduce a smooth relationship between longevity and food intake which agrees qualitatively with the experimental findings.

Shortcomings of the Shanley-Kirkwood Model

Weaknesses of the model fall in three classes: First, there is a mismatch in breeding status between animals in the model and in the laboratory. The model assumes 50% of total metabolic energy allocated to reproduction in the ad libitum controls, and this figure is only credible for pregnant or lactating females. But the laboratory experiments in which the CR effect is observed typically compare nonbreeding animals, male and female, with their CR counterparts. The model applied to males and to nonbreeding females unequivocally predicts declining life span with declining caloric intake—the opposite of what is observed.

Second, there are questionable assumptions in the formulation of the model: Among several variations in the model, the only one that generates the observed qualitative behavior in the curve of life extension versus feeding level relies upon a quadratically increasing relationship between the ambient food availability and the number of offspring successfully weaned. This is justified with a kind of double counting, which will be detailed below.

Third, there are disparities between the model results and the CR data: The model can explain the inverse relationship between food intake and lifespan only over a limited range of feeding levels; in experimental results, the relationship continues a smooth, quasi-linear behavior over more than a factor of two, from the threshold of starvation at the low end to obesity at the high end (Weindruch et. al. 1986; Ross and Bras 1975).

Limitation of the Model to Breeding Females

Half of one sentence justifies limitation of the S-K model to females: ''By common convention, the analysis is restricted to females, female demographic dominance being assumed . . . '' (Charlesworth 1994, p. 4). The reference is to the fact that population genetic analysis may be confined to females with little loss of generality, and predictions concerning growth and steady-state population levels for mixed population levels are little affected by male life histories. But this is no reason to bypass males in the application of theories of senescence or of CR. Life histories of males are separately optimized for fitness in a process analogous to that for females (Charlesworth 1994, p. 231), though, of course, the parameters of the cost/benefit calculus are different. There is no logical basis in the Shanley-Kirkwood model for restricting analyses to females.

The level of caloric restriction in lab settings as conventionally reported is measured relative to the ad libitum intake of nonbreeding animals, male and female. However, the CR variable in the S-K analysis is calibrated with respect to intake for breeding females. Pregnant and lactating females consume up to twice as much food under ad libitum conditions (Bronson 1989). Without this large reservoir to draw down in times of caloric restriction, no adjustment of parameters in the model can reconcile it with the basic finding of life extension due to caloric restriction, and, in fact, the opposite result is predicted. It is an unstated prediction of the S-K model that breeding females should have a lifespan much shortened compared to either males or nonbreeding females, and this is not observed. It is only from this shortened baseline that their model is able to predict life extension.

Fertility is reduced but not completely curtailed in male mice, even under severe calorie restriction (De Paolo 1993). The male control, fed ad libitum, consumed only half as much energy as a pregnant female to begin with. This male mouse on 50% caloric restriction still had most of its fertility (Merry and Holehan 1981), and weighed 60% as much as the control; yet it was more active (McCarter 1993), supported a stronger immune system (Venkatraman and Fernandes 1993), and lived one-third longer than the control (Weindruch and Sohal 1997). Where did the energy come from to fuel its increased budget for somatic maintenance?

Questionable Model of the Relationship Between Food Supply and Weaning Success

As described above, Shanley and Kirkwood report several versions of the model results, only one of which reproduces an allocation of food energy to maintenance which gradually decreases with increasing food supply, supporting results in agreement with observation. The key element in the model that determines this behavior is the assumed relationship between ambient food supply and the probability of weaning success.

In this version of the model, food intake is taken as a proxy variable, predicting the availability of food in the environment ten weeks in the future, when offspring conceived as a result of present fertility impose their greatest caloric demand on the nursing mother. The infants' prospects for survival through the nursing period is modeled as increasing
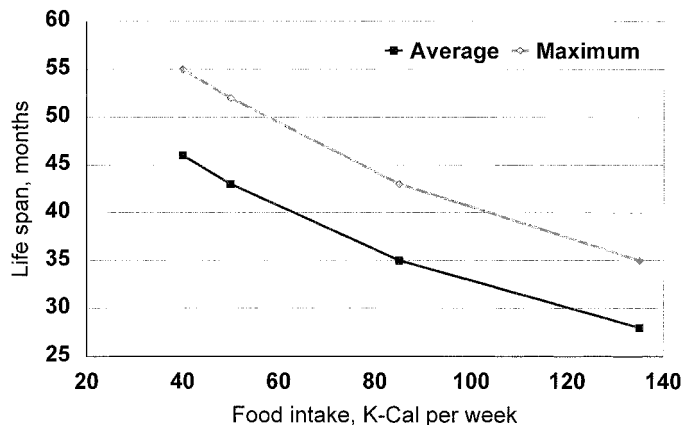
FIG. 1. Life span of nonbreeding female mice increases smoothly over a broad range as calories are reduced. Note that the increase continues substantially below the restriction level (80 K-cal) at which female fertility is zero. This is difficult to reconcile with any model in which life-span extension derives from an energy reservoir which is freed up as the animal diverts resources that had been devoted to reproduction. Graph adapted from Weindruch and Sohal 1997, based on data from Weindruch et al. 1986.
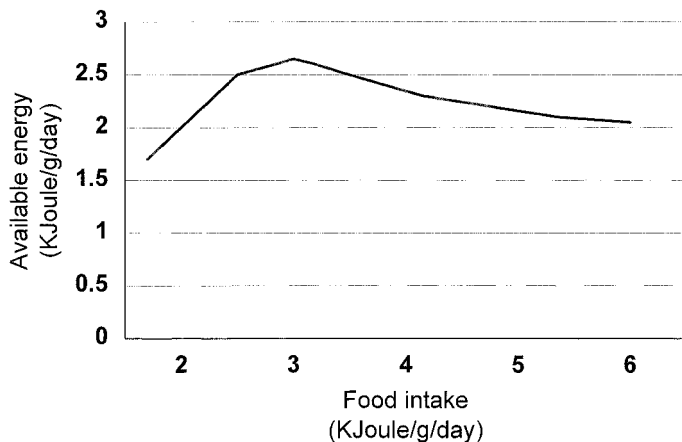
FIG. 2. Results of the best-fitting version of the Shanley and Kirkwood model. Energy that is not allocated to reproduction is considered available for somatic maintenance. Graph is for reproducing females. Note that the plot should not be directly compared to Figure 1 for this reason, and because both axes here have been normalized to body mass, which also varies with food intake. Graph adapted from Shanley and Kirkwood 2000.

linearly with ambient food availability, even as the mother's milk output per offspring is held constant.

In the base model, before this extra parameter is incorporated, there is already a linear per-offspring energy cost of reproduction, based upon published laboratory measurements (Millar 1987; Bronson 1989). But in the variant model, each of these offspring is assigned a probability of survival which is scaled by a second factor of caloric intake/ad libitum. Thus, in this variant, the relationship between surviving offspring and available calories becomes quadratic. Without this quadratic dependence, the model fails to reproduce the qualitative characteristics of life extension via CR.

How the Shanley-Kirkwood Model Arrives at a Counter-Intuitive Result

Many of our intuitions about optimization depend on the "law of diminishing returns": the more of a resource expended in a given effort, the less that each additional increment of allocation is able to accomplish. Very generally, optimization procedures converge because of diminishing returns; in exceptional cases when diminishing returns fails, the extremum is often obtained for variables at one end of their range.

Under conditions characterized by diminishing returns, a reduction in the total amount of any resource always results in a reduction in each of its optimized apportionments. Specifically, we expect that an increasing food supply should result in parallel increases in energy allocations for fertility and for longevity. In two variants of the S-K model, an increase in total caloric budget results in a *decrease* of the optimized portion allocated to somatic maintenance. Hidden in their assumptions is a violation of diminishing returns, in the form of an effective fertility that varies quadratically with available caloric energy. Since the success of the model depends so critically on this relationship, the point becomes crucial: why should each incremental increase in ambient

food supply support a successively larger increment in the number of surviving offspring?

Ends of the Model's Parameter Range

Even the most successful variant of the S-K model corresponds only to a limited range of the data for life extension from CR. The ends of the parameter ranges explored in their paper pose a difficulty, because the model has been optimized to work within these limits, and it falls apart at the boundaries. There is a threshold feeding level at which fertility falls to zero. Below that level, somatic maintenance is predicted to drop sharply with further caloric restriction. But in CR experiments, lifespan continues to increase smoothly even at the lowest feeding levels (Weindruch et al. 1986) (see Figs. 1 and 2).

Three Questions about the Model's Theoretical Foundations

Size: the third variable

The S-K model focuses on differential allocation of energy between reproduction and somatic maintenance; however, as progressive caloric restriction is imposed, the mouse's principal adaptation is in neither of these variables, but rather in body size. As total caloric intake is varied over a factor of three, body weight responds very nearly in proportion, and it is not just adipose tissue that is affected, but muscle mass and most major organs, with notable exceptions of the brain and the gonads (Weindruch and Sohal 1997). The net result is that the range of specific energy consumption (calories per day per gram of lean body mass) varies by only 20%.

Life history analysis can tell us how longevity and fertility are related to fitness; but the relevance of size is much less clear and, presumably, much less direct. The challenge not addressed by the S-K model may be stated: if energy allocation is optimized under genetic control to maximize fitness, then why, as feeding makes more energy available, is such

a large proportion invested neither in fertility nor longevity but in body mass?

Is the measure of fitness appropriate?

Consistent with common usage in the field of life histories, the authors have applied a definition of fitness equivalent to the Malthusian parameter r in the Euler-Lotka equation, as developed by Fisher (1958). It is appropriate to apply r-selection to exponentially expanding populations; it places a premium on early reproduction, because each offspring is weighted by a factor e^{-rt} in its contribution to fitness. The opposite extreme is K-selection, appropriate to steady-state population dynamics.

Despite the ubiquity of Euler-Lotka in the literature, the use of r in steady-state environments (where, by definition, r is identically equal to zero) entails paradoxes that have never been resolved. In fact, K may be very generally a more robust measure of fitness than r, both as a theoretical tool and a model of real-world selection (Benton and Grant 2000). K-selection makes any pleiotropic theory of senescence (including DS) more difficult to support (Mitteldorf, unpubl. ms.).

Thermodynamics of temperature maintenance

One of the competing energy demands invoked by Shanley and Kirkwood is the generation of heat, protecting the animal in winter from hypothermia. They cite evidence (Else and Hulbert 1987) that mammals deploy chemical energy reserves to maintain body temperature in the cold of winter. But low-grade heat should not be reckoned in the same accounting with other metabolic energy demands. In fact, conversion of chemical energy to any other purpose generates low-grade heat as a by-product, and does so with 100% efficiency. The thermodynamic principle is the same as for a 500-watt vacuum cleaner, which delivers to the environment the entire 500 watts as ambient heat, while cleaning the rug ''for free.'' The body's need for temperature homeostasis is not a separate demand on caloric energy, but could be filled, for example, by the waste heat from vigorous efforts in DNA repair, tissue rebuilding, and free radical scavenging. That useless fuel burning has evolved instead is a fact that commands explanation; and on its face, this squandering of free energy casts a shadow on any hypothesis that the caloric metabolism has been optimized for efficiency.

CONCLUSION

The Shanley-Kirkwood model is a serious and careful effort to explain the observed relationship between caloric intake and lifespan in the context of the Disposable Soma theory. Nevertheless, most versions of the model stubbornly predict what our intuition tells us is reasonable: that more food intake corresponds to more calories available for repair and maintenance. Only in the context of the model's least credible variant is the observed sign for the relationship between food intake and longevity correctly reproduced; and even so, the result applies only to lactating females and only within a narrow range of the caloric intake variable. The DS theory remains an appealing and intuitively reasonable hypothesis; however, it may not be easily reconciled with a broad body of experimental data on caloric restriction.

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