

Invited Article

Caloric Restriction for Longevity: I. Paradigm, Protocols and Physiological Findings in Animal Research

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The initial article in this series reviews basic findings in the field of caloric restriction for longevity (CRL). To eating disorder specialists, the data are disconcerting. The chronic dieting and subnormal weight we endeavour to prevent and treat in humans appear highly beneficial when imposed on animals. In the laboratory, organisms from nematodes to monkeys thrive when forced to undereat, as long as they receive sufficient micronutrients. The most remarkable results are obtained through the most extreme measures: mice, for example, do best if limited to a third of expected caloric intake, beginning soon after weaning and continuing throughout adulthood. Deprivation can be achieved through an 'anorexic' protocol of steady underconsumption or a 'bulimic' pattern in which periods of fasting alternate with bouts of binge eating. The benefits of such regimens include delayed senescence, postponement and/or attenuation of age-related disease and dramatic increases in average and maximum lifespan. Although some biological functions are impaired (including growth, reproduction and perhaps resistance to certain stressors), the cost/benefit ratio clearly favours CRL when calculated on the basis of physical outcomes in late age. Advocacy of comparable regimens for people, however, is ill-considered. Enthusiasm for CRL can be sustained only by detaching deprivation from the context of daily life, ignoring psychological effects, and dismissing data on human semi-starvation and eating disorders. The experiences of participants in Biosphere 2 and individuals with anorexia nervosa suggest that the price of CRL is unacceptably high when a wider range of outcome variables is examined. Copyright © 2004 John Wiley & Sons, Ltd and Eating Disorders Association.

Keywords: dietary restriction; ageing; eating disorders; semi-starvation; Biosphere 2

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INTRODUCTION

For more than 60 years, compelling data on the costs and the benefits of caloric restriction (CR) have accumulated in two separate literatures, generated by specialists in the eating disorder (ED) field and the study of caloric restriction for longevity (CRL).¹ To date, there have been few cross-references between them and remarkably little recognition, by either side, of the challenges or the opportunities that each affords the other. Posing different questions, using different methods, studying different populations, the ED and CRL fields have reached sharply disparate conclusions about phenomena of clear common interest. Continued mutual ignorance between these specialty areas is untenable on scientific, clinical and ethical grounds. As outlined in the introduction to the present series (Vitousek, this issue), this article is the first of three written to summarize the CRL literature for readers already knowledgeable about human semi-starvation and disordered eating.

OVERVIEW OF THE CRL PARADIGM

The age-defying potential of CR was first detected within the context of research on veterinary nutrition. McCay, Crowell and Maynard (1935) reported the curious observation that rats supplied with calorie-poor but nutrient-dense diets appeared healthier and lived longer than control animals allowed to consume the same diet on an *ad libitum* (AL) basis. Scores of subsequent studies affirmed the central finding and established its generality across a wide range of species, including yeast, worms, spiders, flies, fish, mice, hamsters and dogs. Experiments with non-human primates were initiated 14–18 years ago (Hansen & Bodkin, 1993; Ingram et al., 1990; Kemnitz et al., 1993). Because the rhesus monkeys studied in these projects can last up to 40 years on standard laboratory fare, complete

data on longevity may not be available for several decades; however, the early returns suggest that prolonged deprivation yields anti-ageing effects in primates similar to those extensively documented in rodents (Bodkin, Alexander, Ortmeier, Johnson, & Hansen, 2003; Lane et al., 2001; Ramsey et al., 2000; Roberts et al., 2001; Roth, Ingram, & Lane, 2001; Weindruch, 1996). The robustness of the CRL paradigm across diverse species increases the confidence with which researchers predict that comparable benefits would obtain for humans as well (Hass et al., 1996; Lane, Mattison, Ingram, & Roth, 2002; Pinel, Assanand, & Lehman, 2000; Weindruch & Walford, 1988).

Superficially, the message of this research seems to reiterate standard public health principles: if we eat 'well' (securing all recommended micronutrients and balancing macronutrients in just the right pyramidal proportion) and we don't eat 'too much', we boost our chances of living to a ripe old age. But in fact the message is radical and counterintuitive: if we eat well enough to avoid deficiencies (without fussing over the optimal details) while scrupulously eating 'too little', we improve the odds of living to an unnaturally great age that flouts our species-specific destiny. It is crucial to understand that the CRL paradigm is not about the avoidance of excess consumption and weight that might interfere with normal physiology. CRL aims for the deliberate sabotage of normal physiology, through undercutting the minimal caloric intake required to sustain it. If 'eating right' is usually assumed to represent an approximate match between an organism's intake and the nutritional parameters under which it evolved to flourish, CRL advocates 'eating wrong', in a particular way, for a specific purpose: the postponement of senescence and death.

When the body detects that too few calories are being consumed, it 'mobilizes well-coordinated, multilevel networks of various defenses to maintain homeostatic mechanisms' (Yu & Chung, 2001, p. 40). The organism reallocates resources through a myriad of complex modifications in the *status quo*, reflecting a 'fundamental shift from a growth and reproductive strategy to a life-maintenance mode' (Roth et al., 2001, p. 306). Insofar as it is possible to ascribe intent to biology, it is clear that Nature designed these conservative measures as temporary expedients to tide the organism over until the caloric drought ended and it could get back to business as usual. But under the exceedingly rare combination of circumstances in which an organism (a) continues to ingest too few calories to support its usual routines, but (b) has regular and relatively easy access

¹Acronyms abound in the field of caloric restriction for longevity. Like other movements with a public relations problem, it seems to be searching for a label that projects a more positive image. A sampler of the terms tried out includes: caloric restriction (CR), dietary restriction (DR), food restriction (FR), energy reduction (ER), caloric restriction with adequate nutrition (CRAN), caloric restriction with optimal nutrition (CRON), hypocaloric diet, high-quality low-calorie diet, and undernutrition without malnutrition. We use 'CR' to denote generic calorie restriction (which can apply to involuntary food deprivation, dieting, anorexic eating patterns, or the regimen advised by researchers in this area); we use 'CRL' to refer more narrowly to the field and the practice of caloric restriction for longevity.

to enough calories to stay alive, and (c) obtains all necessary micronutrients from the bit of food it eats, while (d) remaining protected from predation and competition that it might not be big, strong or energetic enough to resist—some remarkable and almost certainly accidental byproducts of its abnormal physiology will emerge. The chronically underfed animal will appear to age more slowly, show greater resistance to age-related diseases and quite possibly die substantially later than any peers who have had the misfortune to keep eating 'just right'.

Many measures have been demonstrated to increase *average* life expectancy and/or improve the general health of ageing organisms. Weight control, sound nutrition, physical exercise, prevention and treatment of infectious and chronic diseases, avoidance of exposure to environmental toxins—all of these factors contribute to predicting which individuals in a population will age poorly and which well, and whether they will die relatively young or relatively old. None of these factors, however, singly or in combination, can push back the boundaries of ageing and death. In mammals, CR is the one intervention that actually appears to change the *rate* of ageing and increase the *maximum* lifespan attainable by individual members of a species. That is what generates all of the excitement about the CRL paradigm: it seems to break the rules, offering scientists an opportunity to decode the process of ageing and motivated individuals a chance to defy it.

The precise mechanisms responsible for the anti-ageing effects of CR have yet to be identified. Prominent candidates include the reduction of oxidative damage (as a consequence of increased efficiency of oxygen metabolism in the mitochondria), decreases in glycation, neuroendocrine changes such as altered levels and patterns of glucocorticoids, and alterations in gene expression (Arking, 2004; Koubova & Guarente, 2003; Kristal & Yu, 1994; Lin et al., 2002; Masoro, 1988, 2001; Merry, 2002; Mobbs et al., 2001; Patel & Finch, 2002; Sohal & Weindruch, 1996; Wanagat, Allison, & Weindruch, 1999; Weindruch et al., 2001). In view of the multiplicity of defensive reactions to CR, it appears increasingly implausible that any single factor will explain all of its observed effects (Yu & Chung, 2001).

The convergence of conditions outlined previously—not too many calories, just enough calories, sufficient micronutrients, lack of competition—is so very unusual that it is not surprising the CRL miracle went undiscovered

through centuries of vain human search for the elixir of youth. It is plausible to imagine only two circumstances under which more than the odd, isolated (and probably non-replicating) organism would satisfy all criteria: it becomes a laboratory animal that is caged, sheltered, and served up an enriched low-calorie diet by a CRL researcher—or it happens to be a human being in a stable, safe society who harbours a powerful and persistent motive to eat much less than he or she desires and the knowledge and resources to construct his or her frugal menus wisely. In the latter category, two groups of candidates come to mind: the subset of individuals with anorexia nervosa (AN) who carefully manage both the quantity and the quality of their restrictive diets, and a tiny new cohort of recruits who undertake CR for the specific purpose of longevity (Manke & Vitousek, 2002). In recent years, a handful of people—including some of the researchers who study CRL—have been attempting to self-impose the regimen, inspired by the glowing health of thousands of caged-and-sheltered animals who lived out their extra-long lives on half-portions of super-chow in the service of science.

Elsewhere, we outline the case for why the CRL field should be keenly interested in AN and why the ED area should be equally eager to profit from the few individuals who have begun to adopt an essentially AN regimen for apparently non-AN reasons (Vitousek, this issue; Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press). At the same time, both fields of study would also be enhanced through collaboration in the design and interpretation of relevant animal research. ED specialists should begin by familiarizing themselves with existing evidence on the CRL paradigm.

CRL PROTOCOLS IN ANIMAL RESEARCH

As Weindruch and Walford (1988) note, 'there are more ways than one to underfeed a rat' (p. 53). CRL research has established that the specific protocol has scant effect on longevity as long as the diet contains all essential nutrients but sufficiently little actual food so that defensive responses are triggered. Total calorie consumption can be limited by providing animals with a fixed allotment on a daily basis or by allowing intermittent AL access to unrestricted amounts, such as 12 hours of food availability on each of 3 spaced days per week (Weindruch & Walford, 1988). Variations in the

proportion of fat, protein and carbohydrate yield at best minor effects; the key factor is overall reduction in energy intake (Masoro, 1988, 1995; Merry, 1995). Some research suggests that animals respond more favourably when caloric cutbacks are phased in gradually over weeks or months (Walford, 1983).

In much of the rodent research, animals are restricted to 50–60% of the calories they would eat if an unlimited supply were available. The benefits of CR are inversely proportional to the amount consumed. Samples of female mice held to intakes representing 35%, 45% and 75% of AL levels showed maximum lifespans that exceeded the peak survival age of AL controls by 54%, 47% and 19% respectively (Weindruch, Walford, Fligiel, & Guthrie, 1986). Obviously, it is possible to undercut too far. For mice, the lower limit is somewhere around 30% of expected intake, with those supplied with less than that amount dying younger than free-feeding animals. On the mild end of the CR spectrum, modest but discernible benefits are evident for rodents allowed 80–85% of AL consumption.

Unsurprisingly, animals on CR generally end up much lighter and leaner than controls. Within cohorts on equivalent levels of CR, however, body-weight is positively correlated with longevity, so that individuals who manage to remain (relatively) hefty on severe CR outlast their thinner and less metabolically thrifty peers (Bertrand, Lynd, Masoro, & Yu, 1980; Masoro, Yu, & Lynd, 1980; Weindruch et al., 1986). When intermittent schedules are used to achieve CR, most rodents weigh in 30–40% lighter than AL controls because they fail to eat enough on free-feeding days to compensate for fasting days. At least one strain of mouse, however, learns to gorge sufficiently when fed every other day to sustain weight at near-normal levels (Anson et al., 2003). These animals also attain extended lifespans, suggesting that long periods of caloric deprivation can trigger the mechanism(s) of CRL even when overall intake and weight are not significantly reduced.

The only other factors known to influence the magnitude of the CRL effect are the interrelated variables of time of initiation and total duration. In rodents, CR is almost equally effective if started immediately after weaning or not until the end of the juvenile growth phase (Yu, Masoro, & McMahan, 1985). Although some advantages still accrue when restriction commences in middle age, postponement of CR onset yields diminishing returns through the period of adulthood. Some recent studies have found that even older animals profit from underfeeding

(Dhahbi, Kim, Mote, Beaver, & Spindler, 2004; Mair, Goymer, Pletcher, & Partridge, 2003); however, others conclude that CR initiation in late age may be more likely to hasten death than defer it (Forster, Morris, & Sohal, 2003).

Refeeding formerly restricted animals puts them at a survival disadvantage relative to those kept chronically underfed (Merry, 1995). Some residual benefit of time-limited CR, imposed only during rodent adolescence and young adulthood, has been suggested by a 15% increase in median lifespan and 10% increase in maximum lifespan (Yu et al., 1985). (If the same holds true for humans, the typical 4- to 6-year duration of illness for recovered AN patients may pay delayed dividends when they reach retirement age; however, another ironic implication is that through facilitating symptom remission, ED therapists may be cheating patients out of the additional years of vital senior citizenship that they might have earned by staying anorexic.) Few studies, however, have examined this latent effect for reversed restriction. Other research indicates that benefits start disappearing immediately upon return to AL eating (Dhahbi et al., 2004; Mair et al., 2003); more ominously, it has been suggested that ageing may accelerate after previously underfed animals are rehabilitated (Merry, 2002). In any event, it appears that the greatest gains are achieved when CR is initiated relatively early and sustained to late age.

The suppression of weight through physical exercise does not produce benefits comparable to CR. Although regular activity has a modest effect on average life expectancy and a substantial one on mobility in older humans and animals, no current evidence indicates that it can increase maximal lifespan or alter the rate of ageing (Holloszy & Kohrt, 1995; Poehlman et al., 2001). Indeed, it would be unreasonable to anticipate that exercise could change the fundamental rules of ageing; after all, throughout mammalian evolution, regular physical activity was a normal and necessary part of everyday life (Poehlman et al., 2001). Some initial research warned that exercise might even counteract the longevity effects of CR (Holloszy & Schechtman, 1991), causing elevated mortality in young rats that were both physically active and underfed. More recent studies conclude that moderate exercise is neither deleterious nor beneficial in combination with CR (Holloszy, 1997). At least for the purpose of achieving the life-prolongation effect, it appears that the menu of options is severely limited: if we are determined to overlive, we have to undereat.

OTHER BENEFICIAL CHANGES ON CRL

If increased maximum lifespan is the most singular and spectacular pay-off for prolonged CR, the underfed animal can expect to profit from numerous other advantages along the way (some of which help to account for that ultimate reward). Taubes (2000) observes that 'the list of the beneficial effects of calorie restriction in laboratory animals reads like the packaging on a miracle cure' (p. 2). In this instance, the extravagant claims are supported by solid science.

Many of the changes converge on the impression that CR animals 'appear to be "younger" than their chronologic ages indicate' (Walford, Weber, & Panov, 1995, p. 30). Elderly CR rodents seem more alert and frisky, remaining mobile and flexible as tendons and ligaments are slower to stiffen and age-related loss of muscle mass is postponed. They keep their balance better when placed on a rotating rod, and hang on longer when suspended by their paws from an elevated wire. The blood profiles of underfed animals reveal decreased levels of cholesterol, triglycerides, glucose, insulin and white blood cells. Food deprivation forestalls the deterioration of the immune system associated with advancing age and increases survival rates and speed of recovery following surgery. CR strikingly lowers the incidence and/or delays the period of risk for numerous diseases, including diabetes, hypertension, arteriosclerosis, cancer, kidney disease, autoimmune conditions and cataracts. Underfeeding heightens resistance to chemical carcinogens and irradiation, suppresses the expression of genes associated with malignancy and retards the progression of tumours. (For summaries of the substantial literature on physiological changes associated with CRL, see Fishbein, 1991; Hart, Neumann, & Robertson, 1995; Heilbronn & Ravussin, 2003; Hursting, Lavigne, Berrigan, Perkins, & Barrett, 2003; Masoro, 1988, 2001; Merry, 1995; Ramsey et al., 2000; Roberts et al., 2001; Walford, 2000; Weindruch & Walford, 1988; Yu, 1994.)

Among the most important potential benefits of CR are its neuroprotective functions. Evidence from animal research suggests that CR attenuates a variety of age-related brain changes, by reducing protein oxidative damage in at least some regions, increasing microvascular density and cerebral blood flow, slowing the loss of striatal dopamine receptors, decreasing glial activation and eliminating age-related deficits in long-term potentiation. CR may also protect neurons against

damage from toxins and increase neuronal resistance to stroke and degenerative diseases such as Alzheimer's and Parkinson's (for reviews, see Casadesus, Shukitt-Hale, & Joseph, 2002; Mattson, Chan, & Duan, 2002; Mattson, Duan, & Guo, 2003; Patel & Finch, 2002). Some of the rodent research suggests that benefits observed on the molecular, cellular and physiological levels are paralleled by superior performance on learning tasks relative to ageing AL controls. As discussed in the companion article, however, the results are not uniformly reassuring; moreover, there are as yet no data on cognitive function from any of the primate projects currently underway (Vitousek, Manke, Gray, & Vitousek, *European Eating Disorders Review*, in press).

IMPLICATIONS FOR OUR VIEW OF AN

ED specialists who are appalled by the advocacy of CR for humans would be well advised not to enter the fray by contesting its benefits—in debate with either CRL experts or any AN patients who invoke the paradigm to justify their own restriction. We would lose such arguments on the merits. The health-related boons of sustained CR with adequate nutrition are indisputable. For many years, the ED community committed an analogous error in clinical work with AN patients. Struck by the suffering the disorder causes, we dismissed the considerable psychological benefits it also confers on affected individuals, who may rank-order particular advantages and disadvantages quite differently from observers (Vitousek, Watson, & Wilson, 1998). We should not repeat the mistake with reference to the assets of CRL, which are impeccably documented and, by any standard, highly consequential.

In particular, ED specialists should not make the mistake of assuming that the real-world effects of CR on human longevity are already evident in the shortened life expectancy of AN patients. Clinicians are often baffled when they first learn about the death-defying powers attributed to CR, since standardized mortality rates for AN samples are estimated to be between nine and 17 times higher than expected population risk (e.g. Fichter & Quadflieg, 1999; Herzog et al., 2000; Lowe et al., 2001). No one suggests, however, that CR done *wrong* promotes health and longevity. Most AN patients do practise faulty CR, and the data indicate that those who die implement it particularly poorly and/or die from causes related to their ED

but not directly attributable to their CR. For example, in one study, all seven deaths examined (which represented 5.1% crude mortality over an 11-year follow-up period) occurred in patients who were both anorexic and bulimic (Herzog et al., 2000). Six of the seven individuals had abused alcohol; one died from acute alcohol intoxication and three committed suicide. Suicides account for between 17 and 42% of the ED-related deaths in AN samples (Emborg, 1999; Lowe et al., 2001; Nielsen et al., 1998).² Much of the mortality attributable to physical causes results from some combination of rapid weight loss, intakes far below 50% AL and/or purging—none of which is consistent with the principles of sound CRL. The more relevant reference group is the subset of AN patients who sustain their low weights through steady abstemiousness, selecting diets that feature the same 'healthy' food choices (e.g. fruits, vegetables, bran, tofu, yogurt, fish) favoured by CRL practitioners. ED specialists will recognize that pattern as a variant of chronic AN that is associated with minimal risk for medical crises or premature death in the few anorexic individuals who can sustain it.

On the basis of the remarkable data on the benefits of long-term, correctly implemented CR, should ED professionals reconsider their position on the merits of restriction? Maybe we should stop trying to convince anorexic patients that they have got it terribly wrong and concede that in fact they have got it more right than the general public and most healthcare professionals yet appreciate (or could ever manage to achieve, once they did). Perhaps, rather than dispensing well-intentioned advice about the value of normal eating and weight, we should be soliciting our patients' expertise about how to subvert both. Or, less facetiously—and in complete accord with the animal data on CRL—perhaps we should shift our treatment goal from *eliminating* dietary restriction to *refining* dietary restriction.

²CR cannot be absolved from making some contribution to the AN suicide statistics, in view of the association between food deprivation and depression in normal individuals (Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950); in addition, many AN patients link their suicidal ideation to despair over the constricted life required by CR and self-loathing for their inability to sustain it. It is probable, however, that pre-existing psychopathology (quite likely exacerbated by CR) explains most of the variance in deaths by suicide. It is more awkward to contend that the negative effects of bulimia should not count as direct costs of CR. Binge eating is a lawful response to caloric insufficiency, and purging a predictable reaction to its occurrence in people committed to caloric control.

Following the evidence of CRL research, we might urge our anorexic patients to replace their pathological set of motives with a more defensible, empirically supported impetus for the same basic behaviour pattern.³ We might encourage those who are still adolescent to defer CR until they are 18 or 20 (although the animal literature suggests they need not wait if they don't mind sacrificing a bit of adult stature). If the disorder is not yet fully established, we could counsel individuals with incipient AN to work their way gradually into restriction, since some data indicate that maximum CR should be achieved incrementally. If patients have already gone a little too far, we could advise them to fine-tune their CR level to a relatively modest 30–40% reduction in normal intake (although, once again, some animal evidence gives the green light down to 65% below AL level). We should certainly underscore the importance of consuming all requisite vitamins and minerals. We would stress, just as we do at present, the inadvisability of compensatory tactics such as vomiting and laxative abuse, and should discourage excessive exercise. Indeed, as the objective shifts from the 'anorexic' motive of attaining low weight to the approved motive of promoting health and longevity, all compensatory behaviours become antithetical to the goal rather than alternative but risky means of trying to achieve it. To take advantage of the life-extending benefits of the CRL paradigm, our patients need to focus their efforts on the one strategy that makes all the difference: life-long dietary restriction.

Before deciding to redirect our professional efforts, it is appropriate to review the items on the cost side of the decisional balance for CRL. It will not come as a surprise to ED specialists that there is a catch—in fact, there are quite a lot of them.

³If our suggestion that AN patients might be encouraged to replace haphazard CR with proper CRL seems far-fetched, the following post to the CR Society listserve is instructive: '[CR practitioners should] reach out to specific groups who might derive serious benefit from [CR] membership... [including individuals with] anorexia or bulimia [sic]. [We] can take these people in, not telling them that they are ill, but rather informing them that thinness is not only OK, but desirable... They can be taught that both goals [i.e. thinness and health] can be met together, and that they will stay young and beautiful many extra years by [ensuring adequate nutrition on a CRL regimen]. Instead of going to therapy to deal with their mental aberration, they will attend [CR support groups] to encourage their desire in a healthy direction' ('Adzoe', 2002). Our own recommendation for the fine-tuning of anorexic restriction is rhetorical; this correspondent seems disturbingly sincere.

WHERE ARE THE COSTS?

When immersed in the CRL literature, it is easy to overlook the possibility that there is any downside to the intervention. The enthusiasm of CRL researchers for their powerful paradigm is understandable and infectious, and rarely shadowed by qualifications. The calculation of cost–benefit ratios for CRL is not discussed in most review articles. Because no entries are recorded in the minus column, there do not appear to be any liabilities to counterbalance the spectacular gains; therefore, the problem of assessing the relative importance of conflicting considerations simply does not arise. The lone disappointment that is commonly expressed is that humans may lack the fortitude to self-apply extreme restriction (e.g. Mattson et al., 2002; Pinel et al., 2000; Roth et al., 2001; Weindruch & Walford, 1988). The view that perhaps humans should *not* do so, even if they *could*, is seldom entertained.

To the ED specialist who is all too familiar with the detrimental effects of AN and aware of the data on natural and experimental semi-starvation, the CRL silence on the matter of costs is initially disorienting. With increased exposure to this topic area, the pattern becomes easier to understand—while remaining difficult to accept or excuse.

At least in part, CRL researchers take a more benign view of CR because they create and study a more benign form of CR. The devastating picture of caloric deficit suggested by famine victims and many AN patients unquestionably exaggerates the costs of ‘pure’ CR and masks some of its benefits. In the laboratory, investigators can ensure that semi-starvation is carefully calibrated and deficient in nothing but calories. Because researchers retain total control over the restricted organism’s intake, they can also prevent its reactions to CR from disrupting CR itself. Under the pressure of hunger, the underfed animal—unlike the free-ranging human—cannot make poor food choices or break down and overeat. In addition, the research context eliminates not only the extraordinary stresses that generally accompany privation in the natural environment but the ordinary perturbations of daily life at liberty. Laboratory animals are typically isolated in individual cages, protected or exempted from germs, temperature variation, work, fatigue, social interaction, parenting and competition. In effect, their only job is to cope with CR, so that all of the meagre energy supplied by their otherwise optimal diets can be put straight to that purpose.

Another reason that the downside of restriction is less salient in the CRL field is that negative effects do

not interest researchers unless they impact the outcome variables that do: retardation of the ageing process, resistance to disease and extension of the lifespan. Most observers of human CR would be disposed to classify phenomena such as cold intolerance, orthostatic hypotension, elevated stress hormones, decreased sex hormones, hunger, food preoccupation, irritability and social withdrawal as costs of caloric deprivation. None of these variables, however, seems to interfere with the targeted outcomes of CRL—indeed, one or two may actually facilitate them. Accordingly, none of these consequences is consistently recognized as a liability in the context of CRL research. Where others may view the thin, cold, hungry, asexual, subfertile, moody and occasionally dizzy organism with peculiar lab values as unwell, CRL investigators point to their criterion data: if such an animal can remain active, disease-free and alive longer than its normally nourished peers, it is manifestly thriving.

With reference to research focused on the mechanisms of CRL, this indifference to extraneous costs is not as callous as it first appears. Some investigators take the position that the raw ‘just eat less’ protocols used with animals are not intended for direct translation to the human case. Radical restriction is simply a tool for elucidating mechanisms that might be targeted in future through ‘mimetics’—drugs that exploit the underlying processes without requiring self-starvation (e.g. Ingram, 2003; Lane, Ingram, & Roth, 2002; Lane et al., 2002; Roth et al., 2001; Spindler, Dhahbi, Mote, Kim, & Tsuchiya, 2003). Yet even toward this objective, it may be crucial to examine the full range of CR effects, since desired and undesired elements in this ‘well-coordinated multilevel network’ (Yu & Chung, 2001, p. 40) could prove to be interdependent. Moreover, many researchers do advocate the adoption of CR itself by humans—sometimes tentatively and provisionally (e.g. Bucci, 1992; Roberts et al., 2001; Weindruch, 1996) and sometimes with an unsettling messianic fervour (e.g. Mattson et al., 2002; Pinel, 2000; Walford, 1983, 2000). When animal studies are construed as pilot projects for an intended application to people, neglect of potential ill-effects is indefensible on ethical grounds as well as scientific ones.

There are, of course, inevitable costs to caloric deprivation. The reason for their inevitability is tucked away in the verb of a sentence used earlier to introduce the benefits of CR: when an organism is not getting enough calories to eat, it automatically *reallocates* resources, shifting priorities for energy utilization. By definition, the underfed organism has less fuel available for distribution than its

normally-eating fellows; therefore, if some functions are geared up, others must be shifted down. As it turns out, the processes that Nature privileges during times of food shortage are just the sorts of variables that CRL investigators select for close examination, while the functions that Nature opts to shortchange or to disrupt are precisely those that fail to capture their interest. Most of the benefits of the CRL paradigm are manifested on the molecular, cellular and physiological levels; many of its costs show up in the behavioural, 'soft' cognitive, affective and social domains. Because CRL specialists are generally animal physiologists by training and inclination, it is unsurprising that they are more struck by the wonders CR works in the systems they favour than by the damage it does elsewhere.

The scanty but ominous data on behavioural outcomes will be the focus of the second paper in this series (Vitousek, Manke, Gray, & Vitousek, *European Eating Disorders Review*, in press). The remainder of the present paper outlines the subset of physiological adaptations that carry direct costs for the food-restricted animal—at least under some conditions and with reference to the achievement of particular goals. A notable feature of the biological economies of CR is that their impact is context-dependent. With a few exceptions, the physical price paid for restriction must be calculated on a sliding scale according to the organism's circumstances and objectives.

ADVERSE PHYSICAL EFFECTS OF CRL

Growth Retardation

One of the most obvious costs of CR is the suspension or delay of physical development. If an organism has not yet attained full size when rations are reduced, it will get bigger more slowly and end up of slighter stature. If it has not yet reached sexual maturity, it will do so later than expected—or perhaps not at all if restriction is severe and sustained. These consequences are well known to ED specialists. Early onset AN is associated with slower growth, decreased adult height and primary amenorrhoea. Research with animals on CRL confirms that 'pure' caloric deficit can produce all of these effects even when dietary intake is otherwise optimal.

Initially, researchers speculated that the interruption of development might be key to the benefits of CR rather than merely one of its unfortunate side-effects. Perhaps the energy spared from the costly processes of growth and maturation fuelled extension of the lifespan or reset the timetable for progressing through adulthood and senescence. Most

experts concluded that if people could secure extra years only by stunting their growth in childhood, CRL was not an ethical option for human use. A few advocates were not so easily dissuaded. At one point, the most fervent popularizer of CRL ventured right up to the edge of recommending prepubertal restriction (Walford, 1983). In fact, Walford suggested, parents who provide sufficient food to maximize genetic height potential are doing their children a disservice:

'That's fine if you just want big kids who are sexually developed at a younger age so they can breed like rats . . . Settling for a slower growth rate and slightly smaller body size under a regime of caloric undernutrition would secure a longer life with fewer diseases, and very possibly increase intelligence'. (Walford, 1983, p. 107)

The tone of Walford's reference to 'big kids who . . . can breed like rats' is disconcerting—and also revealing, in that it illustrates the surplus meaning often attached to AL and CR consumption by the messianic branch of the CRL field. Like patients with AN, some advocates invest the control of natural appetite and normal weight with moral significance, implying that non-restrictive eating is somehow a sinful and bestial choice as well as an imprudent one (Walford, 1986, 2000; Weindruch & Walford, 1988). Walford's intimation that inches can be exchanged for IQ points is simply baffling. Although CR may help preserve cognitive function to a more advanced age, there is little evidence that it augments intellectual capacity.

As it turns out, there is also no need for a forced choice between inches and longevity. Animal research has established that CR can be deferred until the growth phase is completed, with only slight shrinkage in the margin of added life expectancy. In a recent book, Walford (2000) still noted—perhaps a bit wistfully—that 'calorie restriction beginning in childhood would yield the greatest extension of maximum life span' (p. 77); however, he joined his colleagues in rejecting the option of juvenile CR. Walford identified two reasons for deeming the trade-off unacceptable: the sacrifice of stature, and the fact that CR imposed on very young animals occasionally kills them, 'even though the survivors do go on to enjoy remarkably long lives' (Walford, 2000, p. 77).

Reproductive Function

However long the underfed organism survives, it is less likely to enjoy an active sex life along the way or

to generate its fair share of progeny. Every aspect of reproduction takes a hit on CR, in males and females, to a degree that varies by species, strain, age and severity of restriction. The fertility of mice is obliterated by even modest caloric reductions; rats are knocked back, but eventually get about making more rats if CR is not extreme (McShane & Wise, 1996; Merry & Holehan, 1991; Nelson, Gosden, & Felicio, 1985). Rodent strains that are bred for rapid development and larger size may retain more normal functioning than wild-type and leaner animals on equivalent levels of CR (Leakey et al., 1994).

The reproductive moratorium has clear adaptive advantages for the semi-starved animal. It is not depleting its energies on courtship, mating, pregnancy or lactation at a time when the odds of producing healthy offspring are remote. Because periods on CR extend the reproductive lifespan once the organism is refed (Merry & Holehan, 1991), the animal also buys time to procreate in future if conditions become more favourable. Few evolutionary biologists believe, however, that CR's life-extending properties were selected through the fecundity of elderly famine survivors. In the rough-and-tumble of life in the wild, animals rarely survive long enough to approach reproductive senescence. Most experts conclude that the longevity effects prized by human fans of CRL are incidental—the unselected consequences of conservative shifts in physiology that were favoured because they helped organisms hang on through brief periods of food shortage (see discussions in Allison et al., 2001; Austad, 1997; Graves, 1993; Harrison & Archer, 1991; Hart & Turturro, 1998; Holliday, 1989; Phelan & Austad, 1989; Shanley & Kirkwood, 2000).

As discussed in the companion article on behaviour (Vitousek, Manke, Gray, & Vitousek, *European Eating Disorders Review*, in press), the shutdown of sexuality on CR poses an obvious problem for human applications. Astonishingly, its implications go unmentioned by advocates, apart from the acknowledgement that women would need to take a break from CR in order to conceive, carry and nurse children. Across the CRL literature, there is a conspicuous silence about the loss of libido expected in both males and females on significant dietary restriction.

Cold Intolerance

Organisms on CR become frigid in a literal sense as well. To avoid squandering energy on heat, basal body temperature is turned down. Underfed animals, like individuals with AN, are likely to feel

chilled in environments that the fully fed find comfortable, and will be less able to withstand cold stress. In one of the original CRL experiments in the 1930s, two failures in the laboratory heating system killed 35 of the 73 rats on CR; all subjects in the AL condition survived the cold snaps (McCay, Maynard, Sperling, & Barnes, 1939). In a small footnote to contemporary CRL research, it has been reported that water-maze testing often proves fatal to aged CR mice, presumably as a function of lower body temperature and reduced thermal insulation as well as decreased buoyancy (Means, Higgins, & Fernandez, 1993). Although few humans on CR would be confronted with comparable sink-or-swim situations, both anorexic patients and CRL practitioners describe cold intolerance as an unpleasant side-effect of restriction.

On the positive side, rodents on CR cope better than AL animals when lightly baked in radiant ovens, and show a slower age-related decline in the synthesis of heat shock proteins (Aly et al., 1994a, 1994b; Heydari, Wu, Takahashi, Strong, & Richardson, 1993). In fact, in a mirror-image mishap decades after McCay's CR subjects perished in their unheated laboratory in New York, restricted rats had the edge when the air conditioning failed at a facility in Texas: 84% of AL rodents succumbed to the heatwave, while 75% of those on CR pulled through (Heydari et al., 1993).

Stress Resistance

Little is known about whether CR facilitates or compromises response to most other forms of stress. The paucity of research in this area is surprising—not only to us as ED specialists, but to a prominent CRL researcher as well. Weindruch (1996) has commented that: 'Oddly enough, stress resistance has been little studied in rodents on low-calorie diets, and so they have little to teach about this issue' (p. 52). The matter of resilience to stress is clearly relevant to proposed extensions of the CRL paradigm outside laboratory settings. Except for specimens with the bad luck to be assigned to a water-maze or heat shock study, the only stresses encountered by the average CR rodent are tedium, confinement, the occasional blood draw and (presumably) hunger. The world that humans inhabit is more taxing and intrusive, periodically subjecting them to competing task demands, sensory overload, sleep deprivation, interpersonal pressures and exposure to a wide range of pathogens. It would seem worthwhile to evaluate whether facsimiles of these conditions have differential impact on the health and behaviour of CR

and AL animals. The net effects of life lived alone in a germ-free laboratory may differ from those that come with immersion in a bustling, sometimes hostile milieu (which is also dense with food cues).

On the physiological level, the evidence suggests that CR regimens are chronically stressful in their own right, producing elevated mean corticosterone levels (Armario, Montero, & Jolin, 1987; Han, Evans, Shu, Lee, & Nelson, 2001; Leakey et al., 1994; Patel & Finch, 2002). One complication of assessing stress hormones in CR rodents is that the daily peak shifts from the onset of darkness to the time just before feeding and then plummets during meal consumption (Stewart, Meaney, Ailken, Jensen, & Kalant, 1988). Some investigators speculate that this jolt of preprandial anxiety may actually contribute to the life-prolonging effects of CR (Masoro & Austad, 1996), noting that mice subjected to regular electric shocks or periods of cold exposure enjoy longer lives too (although the verb seems incongruous under the circumstances). Other investigators emphasize the paradox inherent in the data on stress hormones during CR (Mattson et al., 2002; Patel & Finch, 2002). Chronic elevation of glucocorticoids from other causes is associated with a broad range of ill effects, while CR-induced changes are either directly beneficial or counteracted by other protective factors activated by restriction.

Resistance to Injury and Infection

The data on the body's response to injury and infection on CR are mixed. Aged CR mice retain the potential capacity for more rapid wound healing than their AL counterparts; however, this latent advantage is demonstrated only if they are renourished for a month prior to the infliction of a test injury (Reed et al., 1996). (By extrapolation, that seems like good news for elderly CR humans facing elective surgery for which they can be fortified in advance—but unhelpful for any underfed seniors who take an unscheduled tumble down the stairs.)

Consonant with anecdotal and some research evidence from human semi-starvation and AN (e.g. Armstrong-Esther, Lacey, Crisp, & Bryant, 1978; Bowers & Eckert, 1978; Brozek, Wells, & Keys, 1946; Golla et al., 1981; Leyton, 1946; Thygesen, Hermann, & Willanger, 1970), animals on CR show normal or increased resistance to some microorganisms, but may be less capable of fighting off others or combating established infections (Dong et al., 1998; Roecker, Kemnitz, Ershler, & Weindruch, 1996; Sun, Muthukumar, Lawrence, & Fernandes, 2001). As noted earlier, little is known

about how their immune systems would respond to constant bombardment by pathogens in the natural environment (Lipman, Dallal, & Bronson, 1999; Weindruch et al., 2001). Most of the work on immune function has been conducted *in vitro*, rather than by deliberately exposing intact CR and AL animals to disease. In consequence, researchers can better predict how semi-starved cells react to single infectious agents in the Petri dish than anticipate how semi-starved bodies might cope with the array of germs lurking outside the laboratory or handle active illnesses they have failed to fend off.

Bone Density

One specific discrepancy that may surprise ED experts is the omission of decreased bone density from the list of CR liabilities. Osteopenia and osteoporosis are among the most predictable and disabling physical effects of AN (Grinspoon et al., 1999; Katzman & Zipursky, 1994; Lennkh et al., 1999; Pomeroy & Mitchell, 2002; Rigotti, Neer, Skates, Herzog, & Nussbaum, 1991; Serpell & Treasure, 1997; Siemers, Chakmakjian, & Gench, 1996). In CRL research, however, underfeeding has minimal effect on rats' bone mineral content (Sanderson et al., 1997). Equivocal results have been reported to date from the primate studies (Ramsey et al., 2000; Roberts et al., 2001). Slight reductions in bone mineral density and peak bone mass have appeared in both male and female monkeys on CR, but may simply reflect their lower weight status.

The mismatch between the animal and human findings on bone density could be attributable in part to differences in diet composition or the pattern of weight loss. In AN, however, adequate calcium intake may reduce bone degeneration but does not appear to prevent it (Bachrach, Guido, Katzman, Litt, & Marcus, 1990; Biller et al., 1989; Castro, Lazaro, Pons, Halperin, & Toro, 2000). Moreover, decreased density has been recorded in non-anorexic women who lose as little as 10 pounds (Prior, cited in Roberts et al., 2001). No data are yet available on the small cohort of (mostly male) individuals who have adopted high-quality low-calorie regimens for the purpose of longevity. According to an informal scan of self-reported status posted to a CRL interest group, early signs of osteoporosis have been detected in a few cases (Johannes, 2002). Clearly, such anecdotal accounts provide no useful information in the absence of baseline data, control groups and verification of dietary intake; it is reassuring only that freelance CRL practitioners seem aware of the potential risk and that at least some are monitoring this aspect of their health on CR.

Another possible explanation for the apparent inconsistency between the animal and human data is a true species difference in response to underfeeding. Although the age-mitigating and life-extending properties of CRL are robust, the animal literature does include numerous examples of species, strain and sex differences in specific parameters of response (Harrison & Archer, 1988; Masoro & Austad, 1996; Rikke et al., 2003; Weindruch, Kemnitz, & Uno, 1995). On the one hand, such discrepancies provide valuable information that can be used to narrow the field of possible CRL mechanisms. For example, the fact that rats (but not mice) can maintain cyclicity on moderate CR confirms that a complete shutdown of reproduction is not essential for CR-induced life extension (Allison et al., 2001). On the other hand, distinctive patterns of response obviously limit the confidence with which findings can be extrapolated across species or even subgroups. Although the central CRL effect may well obtain for humans, it is difficult to predict its magnitude or to rule out the possibility of untoward effects not observed in other tested species. On the basis of the scanty information currently available, decreased bone density is one prime candidate.

Individual Differences

Another variable that may differ across species and strains is the optimal degree of reduction below AL intake (Weindruch et al., 1995); even when desirable CR levels are established on the group level, it is likely to remain hazardous to generalize across individuals. Although rodents are described as bright-eyed, sleek and glossy-coated on drastic 50–65% cutbacks, several of the rhesus monkeys in the Wisconsin CRL project began to deteriorate on the modest 30% restriction level prescribed, showing hair loss and a 'clinically ill appearance' (Ramsey et al., 2000, p. 1135). Apparently, these primate participants had entered the anorexic zone. A full complement of micronutrients notwithstanding, caloric deprivation was impairing rather than enhancing their physical condition. The protocol was modified to permit intake adjustments on the basis of body composition measured by dual-energy X-ray absorptiometry (DEXA), in order to allow a 'margin of safety' for each animal.

Individual differences in response to CR do not receive comparable attention in rodent studies, for which subjects can be purchased and randomly assigned in large batches. If the occasional rat or mouse languishes on the CR level to which it has been allocated, it is not whisked off for DEXA scan-

ning of its body fat content and issued extra rations based on its personal needs. Even if a few animals die from underfeeding, the consequences are minimal (except, of course, for the animals themselves). Data points from stray casualties of CR barely deflect group results, since, as noted earlier, many of the survivors 'go on to enjoy remarkably long lives' (Walford, 2000, p. 77). Primates are more precious, in part because each has a proportionally greater impact on averaged outcomes. Accordingly, when some monkeys appeared to suffer from CR, investigators intervened, changing the CR itself rather than waiting to see just how adversely the ailing animals would be affected by adherence to the original protocol.

Such concern for individual outcomes anticipates the vigilance that would be required in the monitoring of human CRL. At least for some organisms, the margin between flourishing on CR and foundering on CR appears distressingly narrow. Unfortunately, fine-tuning of optimal-but-safe restriction through regular DEXA scanning is not a realistic possibility for people outside the context of research. Moreover, it is troubling that some CRL experts have not hesitated to recommend levels of human CR equivalent to the 30% reduction that made a number of monkeys look 'clinically ill'. None of these advocates has highlighted the risk that moderate, correctly implemented CRL might jeopardize rather than improve the health of normal humans who adopt it.

Marked variability is already evident in the small group of humans who are attempting to implement the CRL regimen. Just like individuals desperate to control their weight, people determined to extend their longevity seem to differ in the ability to tolerate CR. Some describe their hunger as manageable or even enjoyable, and claim to be energized by restriction. Others find hunger oppressive and sometimes intolerable, and report feeling fatigued, impaired and unwell. In the on-line community of CRL practitioners, these subgroups are termed 'cruisers' and 'strugglers'. The former are strikingly reminiscent of patients with restricting AN; the latter seem to share characteristics with those more likely to develop bulimic behaviour in response to dieting (Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press). Because the phenomenon of human CRL is relatively new and virtually unstudied, it is too soon to know whether individuals will shift category membership from 'cruising' to 'struggling' (or from restricting to bingeing) as a function of duration, matching the temporal pattern associated with AN (e.g. Eddy et al., 2002). As ED specialists routinely observe, even those patients who react

positively to extreme restraint in the early going tend to find it increasingly difficult to sustain over time.

Less commonly, individual CRL practitioners report serious side-effects—again of a type familiar to ED experts but apparently not anticipated by professional advocates of CRL. For example, one man who had practised CR for several years began to experience cardiac irregularities at a BMI of 18, on an ostensibly CRL-consistent regimen of 1500 kcal/day (Best, 1998). Prudently, he decided to retreat to a more moderate CR level and a higher weight. Now more than 10 years into CR, however, he reports that he still has difficulty restraining his ‘incessant compulsion to overeat’ and currently follows a less rigorous regimen ‘in hopes of keeping [the] psychological strain [of CR] to a tolerable comfort level’ (Best, 2002, p. 2).

PUTTING THE CONSEQUENCES IN CONTEXT

For the most part, the present paper has stayed within the boundaries set by CRL experts, narrowing the scope of review to the physical outcomes of nutritionally correct CR administered under controlled conditions. As long as cost–benefit analyses are restricted to that frame of reference, we concur that a lab animal gains far more than it loses through random assignment to a CR regimen. In trade for being a bit smaller, colder and presumably hungrier than fellow subjects condemned to normal eating, the food-deprived organism will defer disease, disability and death. Indeed, CRL researchers suggest, the restricted animal should not be pitied for its plight, but congratulated on its good fortune (Masoro, 1992; Weindruch, 1996). In the breadth and magnitude of benefits bestowed, no other treatment from the most benevolent of caretakers can match the simple act of underfeeding. Cell membranes, blood vessels, muscles, kidneys, heart and brain all profit when substandard amounts of vitamin-enriched chow are dished up each morning (or perhaps on alternate days) over the lengthened lifespan of the lean and lucky recipient.

In contrast, the physical costs of nutritionally sound CR are surprisingly modest—and most of them are negotiable. As noted earlier, the price the body pays must be calculated in context, varying as a function of each organism’s specific circumstances and goals. Accordingly, it is possible to maximize the net gains of CR by engineering environments that minimize its liabilities. Standard

protocols for animal research are well suited to the purpose. Experimental subjects are protected from pathogens, predators and aggressive conspecifics. With no competition for resources, no social position to maintain, no mate to attract and no offspring to nurture or defend, the underfed rodent or primate can delete many potential drawbacks of CR from its personal cost–benefit calculations. Its slighter stature and lower weight carry no disadvantage under the conditions arranged on its behalf; in fact, the downsized specimen is actually better fitted to the cage-bound niche it occupies. In its climate-controlled habitat, even the discomfort associated with cold intolerance can be prevented.

The importance of context is also evident when laboratory routines are disrupted, by accident or design. The paired anecdotes about the failure of heating and cooling systems at facilities in New York and Texas provide a particularly stark example (Heydari et al., 1993; McCay et al., 1939). CR proved fatal to rodents plunged into the harsh reality of winter in the northeast; CR was life-saving for rodents hit by a sudden blast of summer in the southwest. Obviously, the altered capacity to tolerate extreme temperatures on CR cannot be characterized as an asset or a liability in any absolute sense, turning up on opposite sides of the cost–benefit ratio for groups of animals faced with different environmental challenges.

More generally, the disparate fates of these chilled and roasted rats remind us that the success of any adaptation can be judged only with reference to specific circumstances. Underfed animals are brilliantly adapted to the laboratory setting, which exempts them from risks, responsibilities and reproduction so that all available energy can be allocated to the maintenance of basic physical functions. Any time those conditions change, however, cost–benefit ratios must be recalculated. In some cases, the balance will continue to favour CR—indeed, adversity may reveal latent assets (such as resistance to heat shock) not evident in more benign environments. In other instances, however, the costs of restriction will rise so precipitously that the package deal represents a poor bargain for the underfed organism. The moment that a larger and stronger animal is introduced into its domain, CR status becomes a potentially lethal liability; if the wrong germ turns up in the lab or feedings are briefly suspended, its depleted state presents an immediate threat to survival.

There is nothing sinister about studying food deprivation under circumstances that show the CRL effect to particular advantage. Indeed, the

favourable terms arranged in the laboratory are essential to defining the outer limits of CRL and identifying the mechanisms through which it operates. The problem arises when investigators forget that they are assessing the value of a context-dependent phenomenon within a specific context. Advocates emphasize the remarkable robustness of the CRL effect—yet while the paradigm holds across diverse species on a variety of regimens, it is consistently examined within a narrow range of environmental conditions. As researchers move towards the implementation of human CRL, it is especially surprising that they have made few attempts to anticipate potential interactions between CR and other independent variables associated with human life at liberty.

The prospect of human restriction is often discussed as if the only new term that needs to be checked out in a well-established equation is the identity of the underfed species. On the basis of what they have learned through decades of research, specialists are confident of obtaining comparable results: since animals thrive on CR, people will too. But what investigators actually know from decades of study is more qualified than this broad statement implies. When the omitted *context* of that research is reinserted, the syllogism runs into trouble. A more complete version would scan something like this: since animals (*housed separately in stable, protected environments*) thrive (*physically*) on (*correct, sustained, externally controlled*) CR, people will too. If all of the parenthetical conditions could be carried over to the human case, we agree that similar results should be expected (although we would choose a less expansive term than 'thrive' to summarize them). Most of the specified conditions will shift, however, along with the species. Like lab animals, contemporary humans are usually shielded from predation and extreme cold; on other dimensions their circumstances are radically different. People do not live isolated in individual compartments, but in close connection to partners, children, friends and co-workers. Their environments are diverse, fluctuating, demanding and occasionally dangerous. Free-living humans cannot be furnished with (or limited to) a lifetime supply of nutritionally sound rations, but must make dozens of daily decisions about their own intake; under the pressure of deprivation, they are especially disposed to make poor ones.

Moreover, humans will insist on considering a wider range of *outcome variables* relevant to gauging the merits of the intervention. By focusing exclusively on physical consequences, specialists have inflated the net profits of CR by keeping whole

classes of costs off the books. Although varying the set of environmental conditions will not necessarily lower the overall rating of CR, expanding the criteria used to measure its success certainly will. Critical thinking about the adaptive purpose of the CR syndrome supports that conclusion (as does the available evidence from both animals and humans). The system of defensive responses to food shortage evolved to serve *survival*, and furthers that objective with remarkable vigour and efficiency. The system was not designed to facilitate sociability, sexuality, parenting, play or psychological well-being; in fact, as discussed in the companion article, it appears to do a comparably vigorous and efficient job of disrupting them (Vitousek, Manke, Gray, & Vitousek, *European Eating Disorders Review*, in press). As soon as CRL researchers concede the relevance of outcomes unrelated to physical health and survival, the recognized price of restriction will soar.

TRANSLATING THE CRL SYLLOGISM TO THE HUMAN CASE

The importance of attending to all the terms in the CRL syllogism is suggested by two of the most apt human examples currently available. Both provide preliminary support that CRL would improve at least some aspects of physical health in the human case; both also warn that its costs may be prohibitive when CR is attempted in the context of normal daily life and measured by a broader range of outcome criteria. More specifically, both suggest that the experimental conditions set up to support CR in the laboratory are not just useful means of studying the regimen, but prerequisites for its sustained practice.

Biosphere 2

The first example comes from the Biosphere 2 project (Allen, 1991; Alling & Nelson, 1993; Walford, Harris, & Gunion, 1992; Walford et al., 1995). This quirky little quasi-experiment is often cited as the most encouraging evidence to date that the CRL effect would hold for humans; more mysteriously, it is also construed as proof that the regimen is 'reasonable' and 'feasible' for people to adopt. To the extent that any conclusions can be drawn from the Biosphere story, we would extract a different take-home message (Vitousek, Manke, Stumpf, & Gray, in preparation). Rather than demonstrating the feasibility of human CRL, the Biosphere data foreshadow its futility. If we were invested in promoting the regimen, we would be less inclined to put this poster project for CRL on display than to roll it up and hide it in the back of a closet.

The condensed version of the Biosphere story is that between 1991 and 1993, eight scientists and technicians spent 2 years on closely monitored CR while enclosed in a glass-domed complex in the Arizona desert. Unlike the conscientious objectors recruited for the Minnesota Study (Keys et al., 1950), the participants had not signed up to semi-starve for science. They had enlisted as 'crew members' for a highly publicized attempt at self-sustained living within a sealed environment. The CR subplot came about through misadventure, when crop yields proved insufficient to meet the dietary requirements of both human and animal residents. In lawful response to deprivation, the pigs stopped making piglets, the chickens laid few eggs and the goats produced less milk. Shortchanged by all their intended food sources, the four men and four women of Biosphere 2 rapidly lost weight. Intakes averaged 1800–2200 kcal/day during the first 6 months, easing to 2000–2400 kcal/day over the remaining 18 months of enclosure (Silverstone & Nelson, 1996); maximum weight loss approached 20% for males and 13% for females.

One of the crew members was Roy Walford, already a prominent CRL researcher and long-term CRL practitioner (Walford, 1983, 2000; Weindruch & Walford, 1988). While 'an ordinary nutritionist would have freaked out and insisted that food be brought in' (Walford, in Kahn, 1996, p. 48), Walford's background prepared him to recognize the opportunity within the ordeal. Here were eight human subjects caught up in a CR protocol much like those he routinely imposed on rodents back home in his UCLA lab: confinement to a small space on short rations of high quality and equal portion size in the context of a shared, sheltered and virtually germ-free environment. In contrast to other human samples, this committed little cohort was unlikely to drop out of the study and unable to cheat on their diet. Like people stranded on life rafts or ice floes (e.g. Callahan, 1986; Greely, 1886), the enclosed Biospherians could gratify their hunger only through fantasy. Following the classic traditions of the semi-starved, they did so with relish—indulging in animated discussions of food, imagining themselves in supermarkets and restaurants, compiling cookbooks, and making lists of all the delicacies they looked forward to eating in the future. Some took to chewing on peanut shells, fennel stalks and banana skins, and some to hoarding their rations. There were also a few deplorable incidents of banana-stealing, discouraged through the installation of locks on the community storeroom and freezer (Alling & Nelson, 1993). For the duration of

the 2-year mission, however, the only real behavioural choices were to undereat or to abandon the premise of self-sufficiency. With Walford's assurance that their health would be enhanced rather than jeopardized through prolonged CR, all eight Biospherians stuck with semi-starvation.

As Walford predicted, many physiological indices showed dramatic shifts in a desirable direction, paralleling short-term changes seen in lab animals on CR. Blood pressure, cholesterol, fasting blood glucose, insulin and white cell counts were all lowered from 18% to 42% (Verdery & Walford, 1998; Walford, 2000; Walford et al., 1992, 1995); body temperature also decreased, but could not be measured with precision because the available thermometers were not calibrated for values below 96°F (Walford, Mock, McCallum, & Laseter, 1999). The duration of internment was too brief (by some 25–100 years) to ascertain whether crew members would age more slowly or reach a lifespan of 130, but the immediate results seemed to presage such possibilities.

Unfortunately, the moment team members were released from the portion-controlled confines of their complex, they got right down to the business of undoing CRL. Although most had found the regimen arduous during their stint under glass,⁴ at least some had planned to continue moderate restriction after the project ended, in hopes of preserving their positive lab values (Alling & Nelson, 1993; Silverstone, 1993). Yet despite 2 years of direct experience with 'successful' CR (and, presumably, 2 years of earnest advocacy from their expert-in-residence), the Biospherians' food preoccupation predicted their subsequent behaviour more accurately than did their intent. Once back in the world within which all other humans must implement the CR regimen, seven of the eight promptly relapsed into AL eating—and eight of the eight rapidly gained

⁴Consistent with the positive spin placed on every aspect of life on CR, Walford repeatedly maintains that the Biospherians 'were not overly hungry' and 'did not feel undue hunger' while on their restricted regimen (Walford & Walford, 1994, pp. 20, 24, 29). All the accounts we have located from Walford's fellow team members contradict his characterization of their experience. For example, Silverstone (1993) indicated that 'hunger was an almost constant companion', Nelson (in Erickson, 1993) that 'hunger was a nearly constant, nagging presence', Alling and Nelson (1993) that 'hunger [was]... always there to struggle against' and Leigh (Associated Press, 1996) that '[it] made us all a little cranky, always being hungry'. The classic semi-starvation phenomena that emerged in Biosphere 2—including food fantasizing, maximizing, hoarding, stealing, massing, substitution habits and mistrust of others over the distribution of rations—are also inconsistent with the claim that participants 'were not overly hungry'.

weight. The only participant who stayed loyal to CR was, of course, Walford himself—yet he too put on considerable poundage, despite a reported caloric intake (1600 kcal/day) substantially lower than his documented consumption (1800–2400 kcal/day) during confinement.

Six months after leaving the Biosphere, most of the positive physiological changes produced by semi-starvation had disappeared without a trace (Verdery & Walford, 1998; Walford et al., 1999). One adaptive response proved more durable: the depression of metabolic rate (Weyer et al., 2000). Twenty months after the doors were unsealed, the group weighed in at 105% of baseline levels (Walford et al., 1999). Walford concluded that unsustained CR is a bad idea, since fat-stored toxins are released during periods of weight loss, while body fat levels rise and temporary benefits reverse when weight is regained (Walford, 2000; Walford et al., 1999). Therefore, he advised, substantial CR is advantageous only if people keep it up in perpetuity. As Walford's own pilot data memorably illustrate, people won't.

The Biosphere 2 project provided a rare opportunity to demonstrate that humans respond like mice and monkeys when placed on correct CR in a constricted, controlled environment. Ironically, the data also suggest that the benefits may not be available on any other terms. All participants seemed to find the costs of CR unacceptably high when transferred to the context of their natural environments—with the (partial) exception of the one Biospherian who had already organized his personal and professional identity around the virtues of undereating.

Anorexia Nervosa

The second example comes from our own specialty area: the observation of patients with chronic, relatively stable AN. If rodents and primates allocated to a CR condition are the most fortunate of laboratory animals, these individuals hold the winning ticket in the human species. Through their own initiative—albeit for different reasons—they have found their way to a dietary regimen that should be associated with unprecedented health, vigour and longevity.

In some senses, individuals with longstanding AN make even better exemplars of human CRL than the tiny sample of enclosed Biospherians. Their existence affirms that at least a few people can practise radical restriction at liberty; their persistence means that we can trace its effects over much longer periods than the token 2-year stint in Biosphere 2. Of course, only a fraction of AN patients will meet criteria for

correct CR over time, and their compliance cannot be verified with precision. Experts stress, however, that the critical element in the CRL paradigm is simply prolonged caloric deficit in the absence of malnutrition. Some AN patients clearly fulfill those specifications. So what can this subgroup of individuals tell us about serious, sustained CR outside the context of the laboratory?

One ready conclusion is that CR does indeed 'work' for human beings, at least in the same limited sense affirmed by the Biosphere data. CRL advocates were excited (if not surprised) when food restriction was shown to lower the blood pressure, body temperature, glucose levels and white cell counts of the eight Biospherians. Precisely the same results can be read off the medical charts of thousands of AN patients. (Moreover, such benefits are discernible not only in the model cases who adopt nutritionally sound CR, but the considerably larger percentage of patients who practise unsanctioned forms of restriction—although the animal research predicts that only the former will enjoy the full array of long-term benefits.) Two recent datasets also offer tantalizing hints about the potential protective power of prolonged CR. In one records-based study of patients with possible, probable or definite AN seen up to 63 years earlier, the total sample appeared at heightened risk of death from psychiatric causes, including suicide and alcoholism; however, all-cause mortality was not elevated and there was a *decreased* risk of death from cardiovascular disease (Korndorfer et al., 2003; see discussions in Palmer, 2003, and Sullivan, 2003). Because of diagnostic uncertainties and lack of information about diet and duration, these findings are no more than suggestive. But through the noise of methodological limitations, the signal that CRL researchers would most like to discern emits a faint hum. Whatever damage AN may reflect and/or inflict in other areas of patients' lives, it could be working wonders in their circulatory systems—just as imposed CR improves the cardiovascular health of underfed rodents and monkeys. Another retrospective study of 7303 women previously hospitalized for AN found a 53% lower incidence of breast cancer over the follow-up interval (Michels & Ekblom, 2004)—ironically, almost precisely matching the risk reduction for mammary tumours in energy-restricted mice (Dirx, Zeegers, Dagnelie, van den Bogaard, & van den Brandt, 2003).

On the other hand, data from the ED field suggest that CR virtually *never* 'works', in the sense that it is rarely sustained over time and generally done quite badly—even by individuals who are fiercely

committed to keeping it running and doing it right. Dieters regain, 'restrained' eaters limit their intake in theory more than practice, and a majority of restricting anorexics slide inexorably towards bulimia. Quite commonly, AN patients find themselves unable to continue hard-core restraint without ever having made an affirmative decision to let it go. After years—sometimes even decades—of grimly 'successful' CR, they can no longer summon the strength required for the constant battle with their own biology.

We can also learn more about the significance of the silent terms in the CRL syllogism by analysing how some AN patients manage to restrict as valiantly and persistently as they do. At the start of their disorder, the external circumstances of anorexics-in-the-making show little resemblance to those of lab rats or Biospherians. By the time AN is well established, however, most have recreated a strikingly similar environment. In effect, anorexic individuals construct their own virtual cages and move in for the duration of their illness. Each finds her way, individually but lawfully, to the same set of conditions that researchers create for animals on CR: isolation from others; protected, predictable and constricted surroundings; minimal demands or expectations; fixed and monotonous rations; elimination of activities and goals incompatible with the maintenance of CR. It seems probable that those are the only circumstances under which severe restriction can be practised or endured. For psychological reasons, individuals with AN may be willing to pay the astronomical costs of chronic deprivation that less troubled people reject as unacceptable. Advocates of CRL are urging the general public to reconsider, in view of the objective benefits to be gained from an anorexic lifestyle. From our perspective, it is fortunate that their efforts will seldom succeed (Vitousek & Gray, 2002).

Recently, experts have begun to acknowledge that CRL may not gain widespread acceptance (e.g. Mattson et al., 2003; Pintel et al., 2000; Roth et al., 2001)—but they have yet to come to terms with *why* that is so. Many seem to view the human reluctance to semi-starve as a blend of ignorance, short-sightedness, weakness and hedonism. Whatever the merits of these models in explaining the steep rise in obesity rates, they do not provide an adequate account for the rejection of radical CR and subnormal weight. To understand why Biospherians and lab animals refeed the moment they are reprieved from restriction—or why anorexics must retreat from the world in order to pursue it—we need to look to the CR syndrome itself. In addition to the

conservative biological changes that foster health and longevity, the network of defensive reactions to CR includes profound, predictable shifts in behaviour, cognition and affect. These neglected elements of the syndrome clarify why it can be examined only in captive animals, enclosed Biospherians and self-imprisoned individuals with AN—and are the subject of the second paper in this series (Vitousek, Manke, Gray, & Vitousek, *European Eating Disorders Review*, in press).

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