

Invited Article

Caloric Restriction for Longevity: II—The Systematic Neglect of Behavioural and Psychological Outcomes in Animal Research

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Research on caloric restriction for longevity (CRL) has generated hundreds of articles on the physiology of food deprivation, yet almost no data on consequences in other domains. The first paper in this series outlined the generally positive physical effects of CRL; the second analyses the meagre and sometimes disturbing record of research on behaviour, cognition and affect. The available evidence suggests that nutrient-dense CRL in animals—just like nutrient-poor semi-starvation in people—is associated with a number of adverse effects. Changes include abnormal food-related behaviour, heightened aggression and diminished sexual activity. Studies of learning and memory in underfed rodents yield inconsistent findings; no information is available on cognitive effects in primates. To date, the CRL field has ignored other variables that are crucial to the human case and known to be disrupted by chronic hunger, including sociability, curiosity and emotionality. Promotion of CRL for people is irresponsible in the absence of more reassuring data on the full range of expected outcomes. Eating disorder specialists should be contributing to scientific and public discussions of this increasingly prominent paradigm. Copyright © 2004 John Wiley & Sons, Ltd and Eating Disorders Association.

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INTRODUCTION

The initial paper in this series (Vitousek, Gray, & Grubbs, 2004) summarized physiological findings

in the active and upbeat field of caloric restriction for longevity (CRL). For eating disorder (ED) specialists, the data contain some surprises (Vitousek, 2004). Our field equates radical restraint with sickness and suffering, and urges patients towards the 'healthy' choices of normal eating and weight. Yet when caloric restriction (CR) is accompanied by adequate micronutrient intake, animals derive a remarkable range of benefits from regimens supplying only

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35–80% of the energy they would consume on an *ad libitum* (AL) basis. Moreover, the rewards increase in proportion to the severity of the diet, so that health and longevity are maximally enhanced just above the threshold for death by semi-starvation (Weindruch, Walford, Flieguel, & Guthrie, 1986). Certainly, there are physical costs to CR—but under the right conditions, they do not affect targeted outcomes. Virtually all organisms age more slowly and live longer when forced to undereat: yeast, mice and (probably) monkeys; youngsters, adolescents and middle-aged adults; the obese, the average weight and the already lean. On the basis of these robust findings, many experts contend that the time is right for self-imposition of CRL by our own species. Small numbers of people have taken their advice—most adopting the regimen on a freelance basis (Vitousek, Gray, & Talefore, *European Eating Disorders Review*, in press) and a few as participants in exploratory studies of brief analogue CRL (National Institute on Aging, 2000; Velthuis-te Wierik, van den Berg, Schaafsma, Hendriks, & Brouwer, 1994).

Still more surprising to ED experts is that lifelong restriction is being recommended without consideration of its effects on psychology and behaviour. Clinicians who treat anorexia nervosa (AN) worry about the physical risks of severe, sustained CR; far more consistently, they witness its powerful impact on how individuals think, feel and act. Familiarity with other instances of human semi-starvation suggests that many of these derangements are direct effects of CR, rather than signs of ED-specific psychopathology (Garner, 1997; Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950). Critical thinking converges on the same interpretation. From an evolutionary perspective, the behavioural changes accompanying CR do not look like random byproducts of depletion and stress; they are most plausibly viewed as selected mechanisms that serve survival. If the conservative shifts in physiology evolved to sustain life through periods of scarcity, the vigorous behavioural components of the CR syndrome were designed to terminate the CR itself as expeditiously as possible.¹

¹Because of the instrumental quality of some of the behavioural responses to CR, it is difficult to avoid metaphors suggesting that they were ordained by a grand design. We occasionally use such language when referring to the adaptive value of the CR syndrome, implying that Nature 'wants' the semi-starving organism to be food-obsessed, irritable and asocial; however, we do recognize the fallacy of imputed intent. Nature is not invested in how individuals (or, for that matter, whole species) feel, function or fare. Animals that react to famine in these selected ways are simply likely to out-compete animals that do not, surviving to bear and rear similarly disposed progeny.

More than a half-century ago—not long after the discovery of the favourable physical effects of CR in rats—Keys et al. (1950) were struck by the lawfulness and uniformity of the adverse psychological response to CR in humans. If both the physical and the psychological reactions are broadly adaptive, we might expect to see a high degree of cross-species consistency in their expression. The present paper reviews the evidence on behavioural effects in animals. Available data indicate that the active, instrumental elements seen in semi-starving humans do emerge in rodents and primates on CRL—although investigators seem actively, instrumentally invested in ignoring their presence.

In contrast to their keen interest in all things physiological, CRL specialists have so far shown minimal curiosity about the other side of the CR syndrome. Some assume that untoward effects are somehow 'fixed' by the inclusion of vitamins and minerals in the calorically constricted diet. The relevance of the classic Minnesota study of human CR (Keys et al., 1950) is specifically disavowed (e.g. Heilbronn & Ravussin, 2003; Walford, 2000; Weindruch & Walford, 1988), on the grounds that substandard nutrition must have been responsible for the depression, irritability, social withdrawal, asexuality, fatigue and food preoccupation that subjects experienced. The implication is that if only the Minnesota volunteers had received a few more grammes of protein and an extra dash of riboflavin and vitamin A in their 1570 kcal/day ration, they would have been symptom-free on CR (Manke & Vitousek, 2002). Yet the glimpses of animal behaviour on impeccable low-calorie regimens suggest that most of the same phenomena run alongside the salutary physiology of CRL. If these unwelcome effects seem less salient to investigators, it is probably because their attention is focused elsewhere.

CRL experts occasionally note that the behavioural aspects of the CR syndrome are under-researched. Few, however, see the absence of data as an impediment to human applications. For example, one panel of experts acknowledged that 'Little is known in the area of how [CR] affects behavioural or cognitive function' (Poehlman et al., 2001, p. 52). The panel did recommend putting such questions on the research agenda as 'interesting area[s] for further investigation' (p. 52); it did not suggest deferring human CRL until answers are obtained.

The neglect of whole classes of outcomes in CRL research means that the evidence available for review is often unsatisfactory. By default, some

sections of this summary draw on informal comments about behaviour tucked into articles on CR physiology, brief references to unpublished data and studies of underfeeding conducted outside the framework of CRL. The pattern of topics pursued and topics avoided, of research undertaken but not reported, and of adverse effects mysteriously recast as neutral or advantageous becomes informative in its own right.

BEHAVIOUR ON CRL

In the behavioural domain, gross locomotor activity has been investigated most extensively—and the results appear positive, at least at first glance. In contrast, the findings of the few studies that have examined food-related behaviour, aggression, social interaction, sexual behaviour and parenting are ominous when considered as predictors of the human response.

In fairness to the CRL field, it should be noted that some kinds of behavioural research pose practical difficulties. In most protocols, animals are housed individually, so that there are no social interactions available for analysis. Colonies cannot be fed collectively, since it would be impossible for investigators to verify individual CR status (Weindruch, 1991). Moreover, as Nature plays these games by rather nasty rules, some group-housed specimens who were meant to be eating their fair, proportionate share of the rations would end up dominant and amply fed, while others would be forced down to more stringent CR levels than intended. In a rat-eat-rat world, there is also the potential problem of cannibalism, which complicates parenting research in particular. Some projects do house CR animals together, separating them for individual feeding and reuniting them after meals (e.g. Cefalu et al., 1997); however, such arrangements add to the animal husbandry workload and, if fighting gets out of hand, can jeopardize the study of CR effects on health and longevity.

None of these problems presents an insurmountable barrier to research, but few CRL investigators have been sufficiently interested in behavioural effects to find their way around the obstacles. That is especially—and most regrettably—true of the primate research that was initiated 14–18 years ago (Hansen & Bodkin, 1993; Ingram et al., 1990; Kemnitz et al., 1993). In spite of the fact that these expensive, long-running projects are characterized as invaluable opportunities to learn how our closer

relatives respond to CR, they have so far yielded little information about the effects of food deprivation on complex behaviour or, as discussed subsequently, on cognitive function.

Activity Level

Nature faces a dilemma in setting the behavioural default value for free-ranging animals during periods of famine. Staying on the move increases the chance of successful foraging; remaining sedentary conserves energy. There is scattered evidence about how this cost–benefit equation is solved by different individuals and species under various environmental conditions. Laboratory rodents on CR tend to opt for heightened activity, especially when provided with exercise equipment (Routtenberg & Kuznesof, 1967). This response attracted the attention of some in the ED field because it seemed to offer an analogue for AN (e.g. Davis, 1997; Epling & Pierce, 1996; Pierce & Epling, 1997; Smith, 1989), particularly since the effect is bidirectional: hungry rats run more, and running rats eat less. With more background information, unfortunately, much of the aptness goes out of the analogy (Fichter & Pirke, 1995; Watanabe, Hara, & Ogawa, 1992).

The claim that increased activity should be classed as a *benefit* of CR may be tenuous as well. In fact, activity levels in CR rodents rise selectively at feeding time—to such a frenzied degree that averaged 24-hour activity scores can be elevated despite depressed levels of movement during the much longer food-free periods of the daily schedule (Duffy, Feuers, Leakey, & Hart, 1991; Hart & Turturro, 1998). In other words, the high rates of activity generated by CR animals appear less a measure of their irrepressible *joie de vivre* than their hunger.

It also turns out that the tendency towards liveliness on CR is more species-specific than initially appreciated. The primate projects have so far yielded a muddled pattern of findings for our closer kin, reporting more, less and equivalent gross motor behaviour in CR compared to AL groups in different studies, cohorts and time periods (DeLany, Hansen, Bodkin, Hannah, & Bray, 1999; Ingram et al., 2001; Kemnitz et al., 1993; Moscrip, Ingram, Lane, Roth, & Weed, 2000; Ramsey, Roecker, Weindruch, Baum, & Kemnitz, 1996; Weed, Lane, Roth, Speer, & Ingram, 1997). One of the few observations on which studies generally agree is that the differential is sharpest around mealtime: like CR rodents, CR monkeys are especially restless before and after the food arrives.

Topography of Spontaneously Emitted Behaviour

Crude levels of motoric activity address only one of the behavioural questions of interest. The difference between pacing and purposeful movement, between agitation and ebullience, between foraging and play, cannot be discerned by the ultrasonic motion detectors used to measure total activity. In order to make these sorts of distinctions, the animals' behaviour must be observed as it unfolds and then categorized into clusters that are meaningful for the species under study. A variety of methods and conventions has developed for use in field and laboratory settings (Altmann, 1974).

Few studies have simply watched and classified what rodents do all day when on CR versus AL regimens. Perhaps the daily routines of rats and mice—at least when constrained within small cages or tubs—do not offer a lot of scope, on or off CR. With the exception of research on the time spent eating, sleeping and running, comments on rodent behaviour in CRL research are usually informal and parenthetical. For example, in the context of a study on blood profiles and tumour development, the investigators remarked that both steadily underfed and intermittently fed CR rats 'appeared to be more sensitive and aggressive' than normally fed controls (Imai, Yoshimura, Hashimoto, & Boorman, 1991, p. 89). It has also been noted in passing that CR rats are more prone to escape than their complacent AL fellows (Hart & Turturro, 1998)—which seems like a sensible inclination in view of their straitened circumstances and lack of insight into the extra time they are buying through their imposed asceticism. In another observation that we find poignant, it appears that CR mice at leisure are inclined towards the species-uncharacteristic behaviour of hanging from the ceiling. In connection with one study of muscular strength on CR (Means, Higgins, & Fernandez, 1993), investigators noted anecdotally that underfed mice were frequently seen clinging to the wire tops of their home cages. None of the control animals had ever been observed to behave similarly. The researchers did not speculate as to whether these self-initiated calisthenics represented high spirits or another form of attempted escape behaviour.

There are a few data on the general behavioural profiles of food-deprived primates, under both free-range and laboratory conditions. When suddenly cut off from usual food sources in the wild, rhesus monkeys and baboons become more passive, showing a sharp decrease in all categories of beha-

viour—including play, fighting, mating, and social grooming—with the notable exception of foraging activities (Hall, 1963; Loy, 1970). The nature of the food shortage in these instances did not satisfy CRL criteria, since it involved deficits in nutrients as well as calories and was initiated abruptly. In the lab, rhesus monkeys with protein-calorie malnutrition display more stereotyped behaviours, less social and sexual activity and more aggression than controls (Zimmermann, Steere, Strobel, & Hom, 1972). The prompt reversal of some of these abnormalities with refeeding suggests that they are secondary to the deprived monkeys' almost exclusive focus on food-oriented behaviour (Zimmermann, Geist, & Ackles, 1975). Again, however, it is not clear to what extent these findings would apply to animals on correct CRL regimens.

Thus far, a single paper on the topography of spontaneously emitted behaviour has been published out of the three long-running studies of true CRL in non-human primates. (As discussed in the following section on food-related behaviour, there have been several additional references to qualitative data from one of these projects; however, they have appeared as brief narrative insertions in summary articles, and provided minimal information about procedures or results.) In the sole detailed report, Weed et al. (1997) collected and coded data from videotaped segments obtained during a 1-week period after the animals had been in the study for more than 6 years.

The authors' reflections on their own results are instructive with reference to the need for closer collaboration between the CRL and ED fields:

'There is little reason to predict that monkeys subjected to CR should exhibit more stereotypies [i.e., repetitive behaviours] than controls; however, we did observe that CR resulted in increased stereotypies [in the adult group]... Examination of the data revealed that this effect was due largely to increased levels of licking or sucking coupled with a higher incidence of rocking... Increased licking or sucking provides non-nutritive oral stimulation, and may be contributory toward satiety. It is reasonable to assume that animals on restriction may be hungrier than ad lib fed controls, and thus engage in more food oriented behaviour. No systematic research has been conducted to confirm this assumption. [Because] this issue of possible motivational differences can also affect analysis of calorie restriction effects in other behavioural tasks... the control of such variables will have to be considered for future behavioural analysis in our primate study'. (Weed et al., 1997, p. 101)

A couple of points caught our attention in the conventionally dry scientific prose of this passage. We estimate that something like nine out of 10 ED specialists *would* have seen some 'reason to predict' that monkeys on CR might exhibit more stereotypic behaviour than well-fed controls. Indeed, licking, sucking and rocking would likely garner most of the votes if ED experts were presented with an inclusive list of primate pastimes and asked to guess what an underfed monkey might do between meals. The two other variables that differentiated groups—increased pacing and self-grooming by animals on CR—would be among the probable runners-up. Such foresight would not require specialized knowledge about the habits of monkeys in captivity—just a close familiarity with the practices and preoccupations of a related species under the pressure of semi-starvation. If Weed et al. (1997) had sought the counsel of those with expertise on the hungry higher primate, they could have seemed prescient too.

Then there is the acknowledgement that while it is 'reasonable to assume' that CR animals feel hungry, 'no systematic research has been conducted' to confirm the suspicion (Weed et al., 1997, p. 101). With the exception of the scanty material outlined below, that remains an accurate but astonishing summary—70 years into the CRL animal research programme and more than 15 years into the primate projects. The disinclination to pursue this topic is especially surprising when the sole impediment to human CRL that many enthusiasts concede is the annoying complication of a persistent urge to eat. It is encouraging that Weed et al. (1997) plan to start considering the variable of hunger in future—if not altogether clear how they anticipate that it can be successfully 'controlled'.

Food-Related Behaviour

In CR rodents, intensified hunger can be inferred to some extent from a number of indicators, including the high rate of activity around feeding time, noted earlier, and the complex relationship between food availability and aggression, discussed below. Other observations suggest that rodents have a different behavioural repertoire (and presumably cognitive set) around food when they are receiving too little. CR shifts rats away from the normal rodent pattern of 'nibbling' behaviour, characterized by a large number of brief, low-volume eating episodes, towards 'meal-like' feeding behaviour, characterized by longer bouts of eating with higher food consumption per episode (Duffy et al., 1991; Duffy, Feuers, Nakamura, Leakey, & Hart, 1990). Most

rodents are not gastrointestinally suited to true binge eating comparable to that of humans (Woods & Strubbe, 1994), but those on CR pack in as much as they can when food is available. If experimental protocols permit, they also stash whatever they can carry. Rats do not typically hoard when supplies are continuously available, but begin to do so when bodyweight is decreased, stockpiling food in proportion to the amount of weight lost (Fantino & Cabanac, 1980; Lore, Gottdiener, & Delahunty, 1986).

Perhaps the most basic indicator of the proposition that CR animals 'feel hungry' is that—given the opportunity—they all eat substantially more than they are allocated on CRL regimens. Rodents reprieved from CR show significant hyperphagia and rapidly regain weight (along with cyclicity and fertility). Unlike humans in the aftermath of semi-starvation (Keys et al., 1950; Walford, Mock, MacCallum, & Laseter, 1999), they do not tend to overshoot expected weight. Indeed, because rats continue to grow larger through adulthood, veterans of CR generally end up slightly behind continuously AL controls, matching their ongoing rate of growth without achieving the same mean weight (Brownlow, Park, Schwartz, & Woods, 1993). There is no evidence, however, that they have been reprogrammed to forget that they used to want more food than their CR assignment permitted. Nature would be remiss if it allowed animals to feel satisfied with a dietary intake that hampered reproduction. An organism that did become indifferent to underfeeding would be withdrawn from the genetic pool, failing to pass its easily placated appetite to the next generation.

What is most striking about the evidence in primates is that it is exceedingly difficult to find. Certainly, investigators had reason to anticipate from the outset that monkeys who drew the short straw during random assignment would end up dissatisfied. Several allusions suggest that researchers did see differences in the food-related behaviour of CR and AL animals. For the first full decade of the primate projects, however, such observations were mentioned only in passing, sometimes in oddly elliptical terms that contrasted with the scientific language used in the rest of the reports. For example, in an article summarizing the success of the University of Wisconsin and National Institute on Aging (NIA) primate studies, Weindruch wrote that 'the dieting animals in both projects seem healthy and happy, albeit eager for their meals' (Weindruch, 1996, p. 49).

A more vivid description of the food-related behaviour of underfed monkeys came from an outside source who toured the Wisconsin primate facility while preparing a *National Geographic* article on longevity. The visitor used much stronger terms than Weindruch to depict the scene he witnessed:

'There is a downside to caloric restriction, however, which is obvious even to a casual observer who visits during mealtime. The monkeys go crazy when the food shows up, grasping at their meager rations'. (Weiss, 1997, p. 24)

Presumably, responses 'obvious even to a casual observer' had long been evident to laboratory staff, as Weindruch's reference to the monkeys' 'eager' preprandial attitude suggests. In fact, project investigators had more than anecdotal evidence about the salience of food cues to underfed primates. At least three separate behavioural studies have been conducted by the Wisconsin team, all yielding clues about the experience of hunger on CR. For unknown reasons, another characteristic these studies have in common is that they have never been published in conventional formats, each appearing only as a narrative aside in overviews of the primate research.

The first reference to qualitative research on behaviour indicates that such work was already underway more than 10 years ago. In a general article describing project findings, the Wisconsin investigators reported that they were recording the behaviours exhibited by monkeys given 30-minute opportunities to explore larger, more complex environments outside their home cages (Kemnitz et al., 1993). The early returns were already coming in: 'Preliminary results indicate that the restricted animals do engage in more food-oriented behaviour, suggesting that they feel hungrier' (Kemnitz et al., 1993, p. B25). Unfortunately, this single sentence remains the only summary of these data after more than a decade.

The other two studies from the same project were also referenced as unpublished datasets, this time in an overview paper (Ramsey et al., 2000) that appeared 7 years later (but made no mention of the dusty 'preliminary results' on reactions to novel environments). According to the brief description provided, one of these studies coded the monkeys' behaviour in their home cages for 15-minute periods immediately before and after the morning feeding, with the following findings:

'All monkeys walked more before feeding than afterwards, but restricted monkeys paced twice as much as controls prior to eating and six times

more after food was offered. Before feeding, restricted monkeys also exhibited more threatening displays, and also cooing, than controls. The restricted monkeys ate and drank more intensively than controls after food was given to them'. (Ramsey et al., 2000, pp. 1142–1143)

It appears that the author of the *National Geographic* piece was not taking excessive literary licence when he reported that 'the monkeys go crazy when the food shows up' (Weiss, 1997, p. 24). The combination of threat displays, cooing, pacing and intensive eating seems to match that colloquial description fairly well—and suggests that the CR subjects Weindruch calls 'eager' are perhaps not quite as 'happy' as he indicates, at least during the periods before and after meals.

The other unpublished study subsumed within the Ramsey et al. (2000) summary was apparently designed to assess the motivational punch of food rewards for CR and AL monkeys. A plexiglass puzzle-feeder was mounted on the front of the animals' home cages and they were given 15 minutes to sort out how to extract a small food pellet by guiding it through a maze with their fingers. Unsurprisingly, restricted monkeys showed shorter latencies than controls in retrieving the first piece, spent more time working the puzzle and retrieved more food during the test period.

The snippets of information available from these three references and the Weed et al. (1997) article on spontaneous behaviour converge to suggest that food looms large in the life of underfed monkeys. When observed in their home cages between meals, they are more likely than fully-fed controls to be licking, sucking and rocking; when their rations arrive, they coo, threaten, pace and eat intensively; when allowed to explore new environments, they search for something edible; when offered a chance to earn additional calories, they set to work avidly. The data seem to suggest that the fact of underfeeding dominates the experience of primates on CR, just as it distorts the daily lives of semi-starving humans and individuals with AN.

Perhaps the picture that emerges from these fragments of information is misleading. More complete data would be welcome, and we hope they will be provided in future. The scientific community should not have to depend on *National Geographic* or brief asides about unpublished material for depictions of the behavioural response to deprivation. The urgency and intensity of concern for food are relevant both to evaluating the full range of CR effects and to estimating the feasibility of transfer

to free-living humans. Such patterns should be communicated along with the regularly updated bulletins on insulin levels and metabolic rates released by the primate projects.

Avoidance of the topic of hunger in CRL research may be attributable to a number of factors. As noted in the companion article (Vitousek, Gray, & Grubbs, 2004), some investigators see food deprivation protocols as a transient phase of basic research, imposed on animals solely for the purpose of identifying mechanisms which can then be manipulated through 'mimetic' drugs that bypass the need for restraint (e.g. Ingram et al., 2004). Another contributor may be concern about attracting attention from animal rights activists. The fact that 50% CR can be translated as 'half-starved' sounds bad enough; the admission that CR animals appear 'half-crazed' when half-starved' might provoke demonstrations.

Above all, one gains the impression that hunger is a nuisance variable to CRL investigators, in every sense of the term. It interferes with the assessment of behavioural and cognitive phenomena in animals, discourages widespread adoption of the regimen by humans, and generates negative publicity for a truly miraculous paradigm. It is indeed 'reasonable to assume' that organisms on CR 'may be hungrier' (Weed et al., 1997, p. 101)—but it is also quite vexing.

An interesting irony attaches to the neglect of food-related behaviour in the CRL field. Recently, some experts have begun to suspect that the experience of ungratified hunger may not be a nuisance variable after all, but an essential trigger for the body's defensive responses to CR (Hadley et al., 2001; Mobbs et al., 2001; Roberts et al., 2001). Indeed, there is concern that any 'mimetic' drugs that successfully eliminated the pain of semi-starvation would also eliminate its gains. If hunger is reconstrued as a desirable consequence of CR—or at least a necessary means to the benefits it provides—it is a good guess that research on the topic will receive a higher priority rating in future.

Aggressive Behaviour

The most accurate prediction about the effect of food deprivation on aggressive behaviour is that 'it all depends'. From an evolutionary perspective, we might expect to see an increase in aggression under some conditions and a sharp diminution under others. To avoid the error of non-falsifiability, we should be able to specify the conditions that tip the balance in opposing directions.

One crucial variable is the amount of food available. In general, a curvilinear relationship is likely

to obtain, with limited resources eliciting maximal aggression while both the complete absence and the bountiful presence of food reduce the incidence of conflict. The inclination to engage in territorial defence is a function of cost-benefit considerations about the density of resources protected versus the energy expended to secure them (e.g. Carpenter, 1987; Carpenter & MacMillen, 1976; Gill & Wolf, 1975). Other contributing factors include: the dispersion of individuals and groups for foraging, which shifts the odds of potentially combative encounters; the suppression of oestrus and mating, which eliminates some common precipitants of wrangling among conspecifics; the erosion of social networks maintained through displays of dominance; the decline in strength and stamina with depletion; and perhaps an increase in non-specific irritability as part of the affective response to hunger.

There is a substantial literature on these phenomena among animals in the wild, where fluctuating conditions provide frequent natural opportunities for observation. The linkage between hunger and aggression has also been studied extensively in the lab—not by CRL investigators, who have shown little interest in this behavioural outcome of CR, but by other animal researchers. In most such studies, experimental animals are simply food-deprived, rather than placed on technical 'CRL' regimens. There is no reason to anticipate, however, that micronutrients in profusion would have a pacifying effect. Aggressive underfed animals are not vying for the right to their recommended daily allowance of vitamins and minerals. They are battling over access to calories.

Available data affirm that the calorically deprived rat is a bad-tempered rat, trip-wired for combat with intruding conspecifics and prone to bite the hand that underfeeds it. Rats on CR attack strangers more fiercely and persistently than do AL controls and are more disposed towards muricide (mouse-killing) (Lore et al., 1986). When there is not enough food for one, two is a crowd; the only adaptive courses of action are to oust the invader or, perhaps, convert it into calories. In contrast, rodents pampered with constant access to unlimited sucrose solution lose their edge, acting more like hosts than besieged defenders when newcomers are introduced into their well-stocked cages (Lore et al., 1986). (On the basis of these data, it is disconcerting to speculate that the trend towards tolerance in many contemporary human cultures may owe less to the maturation of values than the ubiquity of fast-food outlets.)

Observation of free-ranging primates indicates that they are less fractious than normal when no food is available and more when inadequate amounts are supplied (Loy, 1970). As noted in the section on spontaneous behaviour, laboratory monkeys on protein-calorie deprivation are both hyper-aggressive and socially avoidant; no comparable research has been conducted with subjects on true CRL. Apparently, some scrapping did develop in the early phases of one of the primate projects (Weed et al., 1997). The initial arrangements had involved pair-housing; however, 'due to increased fighting and experimental protocol [?], all subjects were subsequently separated and single housed after approximately 3 years' (Weed et al., 1997, p. 98). The investigators did not clarify whether the squabbling was more, less or equally prevalent between paired CR monkeys as between paired AL monkeys. Certainly, information on the congeniality of hungry versus replete roommates is one of the kinds of data sought by those keen to understand the full range of CR effects. The notation about 'threatening displays' by CR monkeys at mealtime (Ramsey et al., 2000) does hint at the possibility of conflict if the bars came down and fellow subjects made any sudden moves on the rations distributed.

It does not follow from the animal data that people on CRL would begin assaulting fellow citizens in an attempt to drive them away, seize their food, or eat them. The privileged human subgroups likely to find CRL appealing are rigorously socialized not to wrestle over dinner or eat their own species. Of course, such inhibitions predictably break down under the pressure of imposed starvation (Petrinovich, 2000), but the case before us is voluntary semi-starvation. The deprivation involved in CRL would be perpetually optional. The paradox of deliberate hunger is that access remains *ad libitum*—it is consumption that must be restricted. In a very real sense, the struggle over the right to resources is *internal*: the opponent is the self-denying self rather than an outside competitor.

On the other hand, the fact that hostile actions would be gratuitous under such circumstances does not mean that they would be eliminated. Nature made no provision for purposeful semi-starvation (outside of circumstances such as hibernation and migration), since intact animals are neither wise nor foolish enough to self-impose extreme restraint. In the absence of a 'special exceptions' clause that waives the usual instructions if an organism elects to stay hungry for the sake of its health, it is probable that the contentious bias would remain even though it had no objective to fulfill.

This is one prediction that cannot be tested with animals, since it would require convincing an experimental group of hungry rats or monkeys to decline ample portions placed in their cages, in order to compare their dispositions with those of unwillingly-deprived and fully-sated controls. The best we can do is to extrapolate from chronically hungry humans who have made a prior decision, for other reasons, not to eat resources they can readily secure. Marked irritability has been associated with extreme restraint in the semi-starving volunteers in the Minnesota study (Keys et al., 1950) and in patients with AN. Some of these individuals also develop uncharacteristic impulsive behaviours and, interestingly, an increased incidence of aggressive acts directed against the self (Fessler, 2002)—the agent of their deprivation. Although it may be tempting to attribute these untoward effects to inadequate diet in the Minnesota study and to psychopathology in AN, they are consonant with the less subtle and more externalized forms of aggression shown by animals on CR.

Moreover, anecdotal evidence already hints at a feisty trend in individuals who adopt the recommended CRL regimen (Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press). Roy Walford is one prominent CRL researcher who has written extensively about his personal practice of restriction (and does a brisk business on the side in proselytizing, cookbooks and diet-planning software).² In his own writing, Walford insists that hunger is a trivial impediment to the practice of CRL (Walford, 1983, 2000). Others who have observed his behaviour, however, suggest that he is not immune to its effects (Alling & Nelson, 1993; Austad, 1997). A fellow expert in the longevity field commented: 'The word in the gerontology community was that on the days [Walford] was eating you risked losing a hand if you reached for

²After this article was written, CRL researcher, popularizer and practitioner Roy Walford died of amyotrophic lateral sclerosis (ALS) at the age of 79. There is no basis for speculating that his two decades on CR contributed to the development of his disease—or that earlier or more stringent CR could have prevented it. Although some obituaries noted the discrepancy between his quite ordinary age at death and his promotion of 'the 120-year diet' (Walford, 1986, 2000), Walford always emphasized (correctly) that his own longevity was merely a single data point in the study of human CRL. He strayed from the evidence, however, when he persisted on CR after the onset of his illness and credited the diet for slowing its progression. An animal model of ALS suggests that CR not only fails to protect against the disease but accelerates its clinical course once it is underway (Pedersen & Mattson, 1999).

the food at the same time he did' (Austad, 1997, p. 194). Gossip (even among scientists) makes a poor data source, and this may be slander—but it does converge with the harder evidence on pugnacious rats and irritable anorexics. Regrettably, ill-temper may be just as robust a consequence of prolonged CR as decreased blood pressure or increased lifespan.

Prosocial Behaviour

Although it is reasonable to infer some conclusions about the social impact of CRL from the data on aggression, many parameters of social behaviour have yet to be investigated—in part because of the data on aggression. As noted earlier, it is both inconvenient and hazardous to house CR animals together. Although group caging can be managed successfully with mice (e.g. Harrison & Archer, 1988; Idrobo, Nandy, Mostofsky, Blatt, & Nandy, 1982), the few investigators who attempt the arrangement with other species seem to have paid just enough attention to subjects' activities to remove weak specimens deemed especially vulnerable to cannibalism (Roe, 1991) or to modify living arrangements when social relations became persistently strained (Weed et al., 1997).

The failure to examine social outcomes is troubling in view of the fact that some experts already endorse dissemination of CRL to our own highly social species. Even in the simplified social spheres of rodents, it has been established that basic processes such as food selection cannot be understood when detached from the normal context of community life (Galef & Beck, 1990; Rozin, 1990). Studying CR effects in isolated animals is also likely to yield distorted answers to critical questions.

Again, data on the social consequences of CR in primates would be far more instructive for the extrapolation to humans than material on interrodent relationships. To our knowledge, however, all monkey members of the three long-running rhesus projects remain strictly segregated in individual cages within same-sex facilities. In the wild, hungry monkeys have been observed to curtail their socializing outside the matrilineal group (Loy, 1970). This observation is reminiscent of commentary about the human response to semi-starvation. During periods of famine, the circle of interpersonal concern progressively shrinks from the community to close associates, then to immediate family members, and finally contracts to contain only a hypervalent interest in feeding oneself (Keys et al., 1950; Lipscomb, 1945). For a variety of sound reasons, the semi-

starving organism tends to be an inward-turning organism, focused on the securing and private enjoyment of food, suspicious of others and disinclined to waste its energy on the maintenance of social relationships.

Parenting responsibilities are typically the last interpersonal investments to be withdrawn, just as Nature would have it, but they too are managed less conscientiously as hunger settles in. Unlike rodents, starving humans are not disposed to consume their young; however, they may share the hungry rat's tendency towards inconsistent parenting. Undernourished rodent mothers are less efficient in retrieving their pups and do less maternal licking. In connection with the well-studied preprandial burst of activity (and corticosterones), they also tend to abandon their nests approximately 30 minutes before feeding (Smart & Preece, 1973). It should be noted that underfed rat dams are not neglectful of their offspring across all situations. Decreased maternal attentiveness is seen principally when food-directed behaviour competes with caretaking responsibilities (Crnic, 1976).

The rodent data resonate with observations of human parenting behaviour in semi-starvation and AN. A review of childrearing patterns in anorexic mothers concluded that the attitudes, preoccupations, and behaviours associated with (and, indeed, required by) extreme dietary restraint often distract parental attention (Stein, 2002). Like the restlessly roaming rats on CR, undereating human mothers may find it difficult to respond patiently to children's needs when their own hunger is especially salient. The glimpses provided by both the animal and human data suggest that it is insufficient for CRL advocates to advise prospective recruits to suspend the regimen for the duration of pregnancy (e.g. Walford, 1983, 2000). The responsibilities of parenting extend beyond the prevention of nutritional blighting in the womb; for humans, they also last a good deal longer.

Sexual Behaviour

In previous sections, we have noted that researchers seem disinclined to study phenomena relevant to human CRL. The topic of sexuality is a striking exception. The effects of CR on hormonal status, pubescence, mating, fertility and gestation have been recognized since Darwin's time (DePaolo, 1993) and extensively documented in animals within and outside the context of CRL. Clearly, investigators are not disinclined to collect data on these issues; indeed, they have accumulated a

substantial body of evidence that allows them to anticipate human responses in this domain with at least as much confidence as they predict decreased disease and increased longevity. And yet, for the most part, they do not. Except for infrequent references to the possibility of amenorrhea, the implications of CRL for human sexuality are almost never mentioned in scientific or popular discussions of the paradigm. A sampling of three prominent summary articles and one popular book failed to turn up a single allusion to loss of sexual interest as a relevant consideration for the human case (Pinel, Assanand, & Lehman, 2000; Roth, Ingram, & Lane, 2001; Walford, 2000; Weindruch, 1996). All underscored what CRL would do for health, vitality and longevity; all fell discreetly silent about what it would do to libido.

Summaries of CRL typically do describe its impact on sexuality and fertility in animals. Indeed, it is difficult to discuss the paradigm without mentioning these consequences, since the shunting of resources from generativity to maintenance helps explain the desirable effects that are featured in such reviews. Material on the compromise of reproductive function rarely strays out of the section on animal data, however, to darken the bright prospects outlined for human CRL. It is almost as if advocates hope that readers will not make the connection if it is not explicitly stated. They want the audience to be impressed by the robustness of *positive* effects across species, and sometimes emphasize the point in language that is only slightly more restrained than our paraphrase:

Heaps of data show that animals on CR retain their youthful vigour, avoid many diseases and enjoy remarkably long lives—and if you make the commitment to undereat for decades, YOU CAN TOO!

Reviewers do not similarly connect the dots with reference to sexuality. No summary article on CRL includes a parallel statement that extrapolates the *bad* news from animals to people:

Heaps of data show that animals on CR have decreased levels of sex hormones, little interest in mating, and impaired fertility—and if you make the commitment to undereat for decades, YOU CAN TOO!

The problem here is not a lack of information, but an absence of candour. Even if there were no data on the human sexual response to CR, researchers could readily predict the direction of the effect, although it would be difficult to forecast the details. As noted in the first paper in this series (Vitousek, Gray, &

Grubbs, 2004), species differ in the extent to which reproduction is impacted by CR. Rats show delayed maturation and reduced fertility, but do not go out of business altogether; mice, in contrast, become reproductively dormant on fairly modest levels of CR.

But of course there *are* data about how CR affects human sexuality, from natural and experimental semi-starvation, from short-term research on dieting in normal-weight women, from AN and, very recently, from freelance practitioners of the CRL paradigm. All of these data suggest that our own species falls out on the mouse end of the spectrum. Human females show a marked sensitivity to CR in terms of both suppression of libido and loss of fertility. Cyclicity is almost immediately disrupted by sharp CR; even mild dietary restraint is associated with shortened luteal phases and anovulatory cycles (Barr, Prior, & Vigna, 1994; Fichter & Pirke, 1995; Schweiger et al., 1987, 1992). The available evidence suggests that human males take a mouse-like hit in terms of libido, but preserve a more rat-like capacity to procreate (perhaps with reduced fertility)—if they can stir up enough motivation to participate in the necessary act. One CRL practitioner described the consequences succinctly: 'My plumbing is working fine, so I can do it, it just seems I almost never want to' (Pomerleau, 2000). During the Minnesota experimental study of semi-starvation, sexual inclination and activity were 'virtually extinguished in all but a few subjects' (Keys et al., 1950, p. 839). After 6 months on half-rations, the men were no longer interested in dating, stopped masturbating, reported few nocturnal emissions and were more excited by fantasies and images of food than by sexual stimuli.

The obligatory sacrifice of sexuality on CR would clearly dissuade many potential recruits from embarking on the regimen if they were accurately informed about the predictability and magnitude of the effect. Exchanges among practitioners on CRL listserves are full of troubled references to the loss of libido—sometimes accompanied by reproach of CRL researchers (who are otherwise lionized by disciples) for failing to disclose this expected consequence. As one strong supporter of the movement wrote:

'Although I had to steel myself when I first posted my libido problems, it was amazing how many other CR folks were suffering in silence. This is a really serious issue, which Walford has swept under the rug in his books'. (Sherman, 2000)

Although Walford certainly deserves censure from his readership (see below), he is not solely

responsible for the information blackout. Avoidance of this topic is universal among CRL researchers and proselytizers. As it seems improbable that each has failed to mention sexual side-effects by coincidence, the question of *why* this issue is so consistently 'swept under the rug' requires explanation.

Through their silence, CRL researchers seem to assume a *prim* sort of indifference to the forfeit of sexual pleasure and intimacy. The implication is that doubts about trading in sexuality for longevity should not arise among serious-minded people with well-ordered values who are responsible stewards of their own health. Avoidance of the topic is not plausibly attributed to a belief that it is up to each individual to balance advantages and disadvantages according to his or her own priorities. One cannot make an informed decision without information.

The most likely explanation for silence on the subject of sexuality is that the CRL field has strayed away from science and into advocacy. The forfeiture of sexual desire is not mentioned because it makes bad press for the paradigm CRL researchers wish to promote. However they rank-order sexuality in their own hierarchy of human attributes, proponents cannot be unaware that it would be a relevant consideration for most of those they seek to persuade of the merits of CRL. In their warranted enthusiasm for the discoveries they are making, the prospect of seeing CRL negated on the grounds of lost libido must be difficult to bear. Accordingly, this cluster of effects is simply dropped from discussions of the human application.

The strategic omission of sexual consequences tips the hand of the CRL field much more clearly than its overall pattern of selective emphasis by topic area. Perhaps researchers' neglect of other behavioural and social variables is purely a function of their physiological orientation. Perhaps their disregard of existing data on human semi-starvation is based on the conviction that better nutrition would prevent negative effects. But the blighting of sexuality by CR is well within their domain of interest and expertise, and unequivocally attributable to a deficit in *calories*. Sexual consequences are not mitigated by proper CR, as investigators know from their own research, but caused by proper CR and proportionate to its severity, just like the benefits they enumerate. Since CRL researchers realize that these effects will occur in the human case, their failure to say so is worrisome—not least because the investment it reveals may influence other aspects of the investigation and interpretation of CRL.

A few of the most fervid proponents go beyond tactful avoidance of the reproductive costs of CR to invert them into assets. Weindruch and Walford (1988) suggest that CR can serve as a useful birth control technique, since women may develop amenorrhea on the regimen. Pinel et al. (2000) misrepresent the delay of reproductive senescence as a sign that CR might fulfill the 'overriding criterion of adaptiveness' by increasing reproductive success; in fact, all experts (including Walford) agree that total progeny output is decreased by extended CR. Under natural conditions, CR is not more advantageous than an absence of CR; rather, when CR is imposed by adverse environmental circumstances, shutting down the system is more adaptive than keeping it running (Holliday, 1989).

The most egregious example of spinning the bad news is provided by Walford (1986). In defiance of all the human and animal data (and, for that matter, the conservative logic of the CRL effect), he asserts that the underfed organism is an especially randy organism:

'You may have to give up angel food cake [on a CR regimen], but to those for whom sight, sense, and sexuality are less important than angel food cake, I have nothing to offer . . . If you must have a certain measure of sin, I suggest you give up gluttony and accentuate one of the [other seven sins]: lust, for example. [Critics of CR] and all you other sinners, give up gluttony and double your lust!' (Walford, 1986, p. 30)

Whatever is going on here, it has nothing to do with the science of CRL. We assume that more temperate researchers find such flights of fancy as troubling as we do—but they have not said so, at least publicly. Moreover, if they are less inclined to distort the data on sexuality, they are no more disposed to discuss them.

COGNITION ON CRL

How do animals on severe CR fare cognitively? On the sorts of variables measured in rodents, the answer is generally 'just fine'. During youth and mid-adulthood, restricted animals perform as well as AL controls on tests of learning and memory. That conclusion may surprise ED specialists, but it shouldn't. Data from semi-starving humans indicate that basic cognitive abilities are largely spared from the widespread psychological devastation incurred through CR, even in the absence of fully satisfactory nutrition (Keys et al., 1950). Underfed humans may

feel stupid, subjectively—and sometimes strike observers the same way—but for the most part they do not test stupid.³ The sensed decline in cognitive capacity seems to be a function of distractibility, narrowing of interests and depressed mood rather than true loss of intellectual ability (Keys et al., 1950).

With reference to long-term effects, in fact, most of the animal research suggests that CR is advantageous. Later in life, CR rodents begin to pull ahead of their AL counterparts as the latter show the expected declines of advancing age. A number of studies have documented greater preservation of cognitive function in older animals on CR (e.g. Algeri, Biagini, Manfredi, & Pitsikas, 1991; Dubey, Forster, Lal, & Sohal, 1996; Goodrick, 1984; Gould, Bowenkamp, Larson, Zahniser, & Bickford, 1995; Idrobo et al., 1987; Ingram, Weindruch, Spangler, Freeman, & Walford, 1987; Pitsikas & Algeri, 1992; Pitsikas, Carli, Fidecka, & Algeri, 1990). For example, Ingram et al. (1987) found restricted and fully-fed mice equally adept in middle age at learning to avoid footshock in a 14-unit T-maze; elderly AL mice made 35% more errors than animals in their prime, while ageing CR subjects proved just as competent as their younger counterparts.

The factors that support the retention of cognitive faculties on CR are unclear. Presumably, age-related declines are attenuated by some combination of benefits observed on the cellular and physiological levels, such as increased cerebral blood flow and heightened resistance to neurotoxins (for reviews, see Casadesus, Shukitt-Hale, & Joseph, 2002; Mattson, Chan, & Duan, 2002; Mattson, Duan, & Guo, 2003). It is also possible that CR seniors test smarter than AL controls in part because they are less handicapped by illness and infirmity (Ingram, 1991;

Markowska, 1999). Some of the tasks used to measure cognitive skills in rats and mice put a premium on moving fast and seeing well in addition to thinking clearly; therefore, the widening *physical* gap between CR and AL animals with advancing age may give the former an unfair advantage in showing off their intellect. Another difficulty is that many rodent aptitude tests offer food or water rewards for correct performance, which is obviously problematic in the context of CRL research. There are alternatives, mostly involving the avoidance or termination of aversive stimuli—but a variety of evidence suggests that CR (or even a history of CR early in life) may also influence responses to pain or stress, again confounding motivational variables with cognitive capabilities (Forster & Lal, 1991; Smart, 1981; Zimmermann, Geist, & Wise, 1974).

Other studies have yielded mixed or negative findings about CR's power to prevent age-related cognitive decline (Beatty, Clouse, & Bierley, 1987; Bellush, Wright, Walker, Kopchick, & Colvin, 1996; Bond, Everitt, & Walton, 1989; Dubey et al., 1996; Markowska, 1999; Means et al., 1993; Scalzo, Holson, Ali, Sullivan-Jones, & Hart, 1989; Stewart, Mitchell, & Kalant, 1989; Yanai, Okaishi, & Okaishi, 2004). For example, Stewart et al. (1989) determined that CR rats outperformed AL controls on a task that involved working memory within a trial, but showed expected decrements with increasing age on a test that required retention of information over long intervals. Markowska (1999) reported severe and equivalent memory deficits in aged CR and AL rats on two tasks assessing different memory processes. Noting that rats on CR are also not exempt from retinal deterioration, O'Steen and Landfield (1991) conclude that dietary restriction has selective effects on age-related changes in the central nervous system, suggesting that different ageing mechanisms may modulate some aspects of cognitive function. Dubey et al. (1996) concur that CR has inconsistent effects on brain regions, contradicting the view that it represents a true 'anti-ageing' paradigm that retards deterioration across domains.

It should be emphasized that to date only one study of cognitive function (Yanai et al., 2004) has indicated that CR rodents are in *worse* shape than AL peers when tested at the same age. In view of the fact that there are no replicated liabilities and some clear advantages, it may seem peculiar to characterize the patchy data on protection against cognitive decline as a potential cost of CRL. Yet where brain function is concerned, failure to find differences favouring CR is not a neutral outcome. If the ageing underfed organism is not *better* off than its

³While cognitive function is also fairly well preserved in AN, the picture is not benign in severely ill patients. Neurocognitive impairments and structural brain changes are often detected (e.g. Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996; Lambe, Katzman, Mikulis, Kennedy, & Zipursky, 1997; Mathias & Kent, 1998; Moser et al., 2003; Swayze et al., 2003). Many (but not all) of these abnormalities tend to reverse with weight restoration. It should not be assumed that the same changes would occur on the recommended CRL regimen; however, too little is known about the mechanisms that produce them to rule out the possibility of untoward effects, particularly in human practitioners who reduce too fast, too far, or through resort to disapproved techniques. The first published MRI study of restricted monkeys determined that subjects on moderate, nutritionally correct CR had lower volumes of the putamen compared to controls, although the opposite pattern had been predicted (Matochik et al., 2004); the significance of this finding remains unclear in the early stages of primate research.

AL fellows, there is a problem—because it is likely to live a good deal longer. Since deterioration is progressive, unprecedented lifespans may also permit unprecedented cognitive decay. One investigation reported that when the brains of ancient CR rats were autopsied after their long-deferred deaths, they sometimes revealed degenerative phenomena that are virtually never observed in AL animals with shorter lifespans (West, Volicer, & Vaughan, 1984). On the other hand, recent studies using rodent models of stroke, Alzheimer's disease and Parkinson's disease suggest that CR may reduce the incidence and/or decrease the impairment associated with these conditions (Mattson et al., 2002). Clearly, alleviation of the suffering caused by neurodegenerative disorders would be an enormous advantage of CR—yet if the sparing of cognitive function turns out to be uneven across domains, the implications would also be profound. Few people would drink from a fountain of youth that might leave them sprightly but demented for an additional two or three decades. A lifetime of hunger in exchange for a chance at extended senility and extra years in a nursing home seems a poor bargain.

Because the retention of cognitive powers is a make-or-break issue for human CRL—and the rodent data thus far look mixed—one would anticipate that researchers would be working assiduously to sort out the problems in animals more like ourselves. Since monkeys are much cleverer than mice, their availability as CR subjects broadens the range and increases the complexity of cognitive processes that can be examined, while reducing dependence on physical skills as means of demonstrating intellectual competence. But for reasons unfathomable to outsiders, the primate projects are purportedly stymied in their efforts to study learning and memory in monkeys. In an interview, one of the lead investigators in the NIA group alluded to the problem:

'George Roth... who is testing the monkeys' behavior, says progress is frustrating. "It's taking a long time to train the monkeys to do the tasks," he says. "We hope to get faster, but it's agonizingly slow," and he has no results to report.' (Devitt, 1998, p. 1)

The failure to devise any suitable means of gauging primate intelligence is as mystifying to us as it was frustrating to Roth. Without information on the pattern of problems encountered, it is difficult to sort out why investigators with more than a decade of continuous access to CR and AL monkeys at the time of Roth's interview (and 6 additional years since)

have had *no* results to report, while numerous studies have been published in the interim on the cognitive function of shorter-lived and less versatile rodents. There have been no intimations that the CR monkeys are disproportionately responsible for the cohort's poor performance, keeping the whole colony stuck in remedial education through their failure to progress. More to the point, there are no reasons to expect that underfed monkeys would be disadvantaged in this domain, on the basis of data from lower *or* higher animals on CR.

As the older primate cohorts approach the age at which any cognitive advantages of CR might emerge, it is probable that CRL researchers will become increasingly invested in solving the assessment problems they have encountered. Regrettably, any solutions that may be devised at this point will come more than 15 years too late. The experimental method requires not only random assignment and control over the independent variable, but some means of determining the equivalence of groups before the manipulation was introduced. Particularly with the small sample sizes feasible in primate research, the absence of pretest data will remain problematic, no matter what pattern of results is observed at post-test.

Examples of the variety of questions that should be addressed by the CRL field are illustrated in the work of Zimmermann and colleagues (Zimmermann et al., 1972, 1974, 1975). Their research examined the cognitive, behavioural, emotional and social effects of protein-calorie malnutrition in juvenile rhesus monkeys as a model for the relationship between deprivation and developmental outcomes in undernourished children. The results cannot be extrapolated directly to animals (or humans) on CRL protocols, as the low protein regimen produced animals that were not only underweight but precariously poised on the edge of clinical illness. Nonetheless, the project is instructive on several levels.

First, the programme of research suggests what could be explored by investigators who were interested in the psychological consequences of nutritional manipulations. Over a period of 4 years, the experimenters carried out at least 23 individual studies with 62 rhesus monkeys (Zimmermann et al., 1974). These included seven studies on learning and memory, three on attention and distractibility, five on curiosity and reactions to novel stimuli, six on the motivational power of food, two on activity level and six on sociability and dominance (the total sums to more than 23 because some studies assessed more than one of these categories). Working with the same species of monkey used in the CRL projects,

these researchers were apparently able to devise multiple means of testing cognitive abilities—even though their malnourished subjects were younger and less healthy than the animals on CR.

In addition, some of the results are relevant to the CRL paradigm precisely because of the differences in dietary regimen. The findings provide a 'worst case' (or at least a 'worse case') example of the disruption caused by CR with inadequate nutrition—affording CRL investigators the potential opportunity to demonstrate the protective power of CR with adequate nutrition. The malnourished monkeys showed diminished curiosity, heightened anxiety, distractibility, neophobia and markedly abnormal social behaviour. If similar patterns are *not* evident in calorically deprived animals who receive sufficient protein, CRL advocates would bolster the case that many ill-effects attributed to semi-starvation are a function of specific deficits and not underfeeding *per se*. To do so, however, they will need to collect data.

On the other hand, the fact that the wretched and wizened little monkeys on protein-poor diets performed *well* in several domains is also germane from the perspective of CRL. On most measures of learning and memory, the malnourished animals showed no impairments despite their debilitated condition—indeed, they outshone their well-fed age-mates on food-rewarded tasks and performed comparably when other contingencies were used. Such findings strengthen the prediction that CR with sound nutrition is unlikely to produce major deficits in these areas, since CR with poor nutrition does not do so either. It is less clear, however, that better CR would raise animals' scores in the one domain where the malnourished monkeys obtained low marks: the capacity to pay close attention to test stimuli when fine discriminations were required (Zimmermann et al., 1974). In this instance, protein deficiency is an improbable explanation for their lacklustre performance. The problem seemed traceable to a competing tendency to glance toward the food dish into which rewards would be dispensed for accurate responding.

Indeed, over and over, across task types, *hunger* appeared to account for much of the variance in the superior, inferior or anomalous performances displayed by the malnourished monkeys. They chose food rather than toys, opened fewer puzzle boxes until these were baited with visible treats and showed no flicker of interest in shiny objects that the well-fed monkeys found enticing. They looked keen and clever when working for extra intake, but appeared average or a bit slow when calorie-free

contingencies were employed. They ranked low on the dominance hierarchy during spontaneous social interactions or when vying to avoid an aversive stimulus, yet held their own with far stronger peers—or even outmatched them—when edible prizes were at stake. Because CR with excellent nutrition remains CR all the same, it is unlikely that the hunger factor would be ameliorated on CRL regimens—and the hunger factor, by itself, seemed to provide the best account for many of the findings observed.

Finally, it is informative that underfed animals can look absolutely fine on the few behavioural dimensions in which CRL researchers have demonstrated a degree of interest (activity level and cognitive performance), while simultaneously appearing abnormal on a range of variables to which they have been indifferent (including curiosity, emotionality and social interaction). If the CRL paradigm is to be extended to people, concern for all of these outcomes is obligatory.

The cognitive effects most certain to afflict humans on sustained CR cannot be assessed in non-verbal animals—although both the data outlined above and the glimpses of food-related behaviour on CRL are suggestive. By all accounts, semi-starvation disrupts cognitive software to a greater extent than cognitive hardware, changing what underfed people think *about* much more than how well they think. What they think about, of course, is food—monotonously, perseveratively, and at the expense of abstract, creative and interpersonal thought content. The same preoccupations are reported by stranded arctic explorers (Greely, 1886), prisoners of war (Daws, 1994), concentration camp internees (De Silva, 1996), patients with AN (Vitousek, Gray, & Gonzalez, 2004, 'Hunger in anorexia nervosa', in preparation), restrained eaters (Jones & Rogers, 2003), normal volunteers on short-term or long-term CR (Keys et al., 1950; Laessle, Platte, Schweiger, & Pirke, 1996), crew members in the Biosphere 2 project (Alling & Nelson, 1993) and freelance CRL practitioners (Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press).

If CR mice and monkeys could verbalize their stream of consciousness, it might well include more images of pellets and bananas than the cognitive content of their AL counterparts. It seems plausible that underfed animals may spend somewhat less time fantasizing about food than underfed humans, as our species is both blessed and cursed with greater capacity to brood about stimuli we cannot see. It is difficult to guess whether hungry animals find such ruminations pleasant or aversive; hungry humans disagree. But however animals experience

this effect, there is one difference with significant implications for projecting the outcome of human CRL. To the extent that restricted mice and monkeys become obsessed with food, this hijacking of their cognitive content is not interfering with more productive lines of thought. Singly-housed animals with no occupational, social or parental obligations can afford to while away the hours anticipating the next caretaker-provided meal. For humans, the displacement of other concerns by the trivia of CR-driven cognition is far more consequential.

Moreover, the need to plan and enforce one's own CR regimen when semi-starving in an AL world demands the allocation of additional cognitive resources not expended by confined animals (or humans) on premeasured, externally imposed CR. Individuals with AN often identify the constant calculations and anxious uncertainties of self-regulated restriction as among the most debilitating aspects of their disorder. Anyone who minimizes the workload of long-term CR is unfamiliar with the job requirements. It would take a lot of years of extended lifespan to compensate for the time lost along the way to food-related rumination.

AFFECT ON CRL

Most of the data relevant to this heading have already been reviewed under subcategories such as 'Aggressive behavior'. No studies have been designed specifically to assess emotional experience on CR. Obviously, the nuances of mood state are difficult to measure in animals, on or off dietary restriction. Investigators cannot administer symptom checklists or quality-of-life scales, but only observe and infer. To date, there has been more inference than observation in the CRL field—and it shows a relentlessly optimistic bias. Across sources, the positive skew of CRL investigators sets a high threshold for the signalling of distress. When animals described as 'going crazy' by outside observers (Weiss, 1997, p. 24) are depicted as 'happy, albeit eager for their meals' by project staff (Weindruch, 1996, p. 49), it is not clear what a mouse or monkey would need to do to communicate its displeasure.

Within the limited scope available to singly-housed laboratory animals, both rodents and primates on CR give some hints that they might fall outside the normal range if measures of subjective well-being could be administered. They bite, they fight, they escape, they pace, they rock, they hang from their cage tops, they fall on their food. They do *not* huddle miserably in the corner or lie on the

floor howling; certainly, they do *not* lose their appetites. In fact, both the presence of some conventional indicators of distress (such as stereotypic behaviours) and the absence of others (such as passivity and decreased appetite) are difficult to interpret in food-deprived organisms. Behaviours that generally correspond to negative emotional states may not carry the same meaning in the context of CR.

For example, repetitive behaviours such as licking, sucking, and rocking are ordinarily construed as abnormal (Erwin & Deni, 1979). In the underfed primate, however, it is conceivable that such activities simply substitute for the oral gratification of eating, as Weed et al. (1997) suggest, with no implications for overall adjustment. On the other hand, the temptation to assume that the busy animal is a happy animal should be resisted by CRL researchers. Activity level is not a reliable index of state of mind under CR conditions. Many individuals with AN are hyperactive, and virtually all are depressed; most of the semi-starving Minnesota men became less active, and virtually all were depressed. The malnourished monkeys studied by Zimmermann's group emitted just as much spontaneous movement as those on protein-enriched diets and took similar advantage of runwheels—while also showing signs of emotional disturbance that seemed attributable to their chronic hunger (Geist, Zimmermann, & Strobel, 1972; Zimmermann et al., 1974).

Although CRL researchers may have a number of reasons for wanting underfed animals to be 'happy', Nature almost certainly disagrees. Just as it would be foolish to build an organism that forgot to feel hungry under conditions of chronic deprivation, it would be careless to construct one that remained equally cheerful when famished or well-fed. In general, emotions are used to nudge animals into selected patterns of behaviour. The regulatory system is far from perfect, and can go seriously awry in individual cases (as mental health professionals often witness). But on the species level, evolutionary forces have done an excellent job of making organisms feel good when they are pursuing adaptive strategies and bad when they are not. A tendency to keep one's equanimity at a subfertile, antisocial, low-strength weight would be an egregious programming error unlikely to survive natural selection. All the evidence on human semi-starvation suggests that it did not. The chronically hungry person is a chronically dysphoric person. If we knew how to solicit their input, we would probably learn the same from the chronically hungry mouse and the chronically hungry monkey.

With reference to the affective costs of CR, we might obtain more useful information by extrapolating downwards on the evolutionary scale, getting tips about what to look for in animals from semi-starving humans who are able to describe what they feel. Human sources suggest that the changes will be subtle, at least when viewed from the outside. Underfed people seldom lie on the floor howling either—but they are decidedly *not* ‘happy’.

Of course, a different sort of assessment problem arises when dealing with human informants who are invested in continuing the practice of CR. Animals may be poor reporters of their mood state, but at least they do not dissemble—and are unlikely to be committed to staying on short rations no matter what the cost. Individuals with AN often insist that they feel perfectly fine when they are manifestly miserable, only to disclose their suffering to a more sympathetic interviewer and/or after they recover. Presumably, some of the people who are inspired to implement CRL will be similarly motivated to minimize its price to themselves and others (Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press).

In this connection, ED specialists have a lot to offer to CRL researchers as they move into the human arena. Clinicians have substantial experience in the art of eliciting more accurate self-report from defensive individuals on voluntary CR (Vitousek, Daly, & Heiser, 1991). First, however, CRL experts will need to resolve their *own* reluctance to recognize the disadvantages of food deprivation. Researchers who are disinclined to see or to study adverse effects in animals are unlikely to probe positive self-reports from humans pledged to CR. Indeed, some specialists manage to convert AN itself into encouraging evidence for CR, stressing how splendidly anorexic patients feel and do (until they get a bit too carried away with their semi-starvation). According to Weindruch and Walford (1988), individuals with AN are not only ‘symptom free’ (p. 303) at BMIs of 15–16, but positively thriving:

‘Clinically, anorexics do surprisingly well despite their growing emaciation... Far from being lethargic, they are typically hyperenergized. Serious problems do not generally occur until 30 to 40 percent of [body weight] has been lost’ (Weindruch & Walford, 1988, p. 303)

If the definition of ‘serious problems’ is restricted to complications like cardiac failure or collapse of the immune system, Weindruch and Walford (1988) have their facts straight. If, however, amenorrhea, osteopenia, food preoccupation, binge

eating, depression, irritability, social isolation, asexuality and shrinking horizons count as costs, the ‘symptom-free’ zone of CR is considerably narrower. If CRL researchers are unaware of these effects, ED experts should bring the facts to their attention; if CRL researchers believe such consequences trivial in view of the health benefits CR provides, we may want to take the lead in a discussion of values.

CONCLUSION

CRL: An Ethical Option for Human Use?

More than 15 years ago, excited proponents of CRL wrote that ‘we see no reason not to recommend [CRL] for humans’, holding that the regimen was already established as ‘an ethical option for human use, on existing evidence’ (Weindruch & Walford, 1988, pp. 335, 336). More cautious investigators advised deferring human applications until findings had been replicated with animals higher on the evolutionary scale than rodents. The primate studies were initiated at about the same time, and are now yielding convergent data. On the basis of the preliminary results, a conference convened by the National Institute on Aging (NIA) and other agencies concluded that human research was feasible, desirable and likely to provide ‘immense benefits’ (Hass et al., 1996, p. 90). The panel recommended beginning with the recruitment of healthy male volunteers between 25 and 30 years of age who were ‘near ideal body weight’ (p. 86). A few years later, NIA solicited grant proposals for exploratory CRL research with non-obese participants who were ‘at risk’ for obesity (National Institute on Aging, 2000). Several projects are currently underway.⁴

At least with reference to short-term indicators that correlate with the CRL effect, we have little

⁴In the end, the funding agency blinked when it came to supporting CRL research with young, normal-weight participants, as advised by the Hass et al. (1996) panel, opting instead to fund studies of middle-aged and older volunteers who were overweight but not obese. We agree that this was a more ethically sound decision; however, the results may yield limited information about the potential of human CRL (Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press). Such research will also underestimate the costs of CR for normal-weight individuals. ED experts disagree about whether dieting is advisable for people who are overweight (see discussions in Brownell & Rodin, 1994; Foster, 2002; Garner & Wooley, 1991; McFarlane, Polivy, & McCabe, 1999; Wadden, Brownell, & Foster, 2002; Wilson, 2002). All concur, however, that CR by the underweight and normal-weight elicits distinctive and much more negative effects.

doubt about what such studies will report. A substantial body of evidence already demonstrates that CR with excellent nutrition, CR with middling nutrition and CR with dreadful nutrition all lower blood pressure, glucose, insulin, body temperature and central adiposity, in humans as well as in animals. We are prepared to stipulate that CR will produce each of these desirable changes just as reliably when called 'CRL' as when called 'semi-starvation', 'anorexia nervosa', or a 'very strict diet'. We also think it highly likely that CR will extend the lifespan of rhesus monkeys, and would do the same for people as well if enough could persist for the decades required to test the prediction. We consider the mechanisms underlying these effects fascinating too, and deserving of thoughtful research on multiple levels and from many different perspectives.

We dissent, however, from the opinion that the CRL regimen is established as 'an ethical option for human use, on existing evidence' (Weindruch & Walford, 1988, p. 336). It was not an ethical option 16 years ago, it is not at present and, unless there is a radical shift in the nature of CRL research, it will not be 50 years in the future, after all the initial and added cohorts of primate subjects have reached the end of their lengthened lives. CR leading to subnormal weight will never be 'an ethical option for human use' until CRL investigators begin to examine the full range of questions relevant to those humans who might opt to use it—and until they stop avoiding or rejecting answers they do not wish to receive.

In fact, a great deal is already known about the effects of CR in the species to which researchers hope to generalize the findings obtained in animals. The weight of the evidence they have amassed across mice, rats and monkeys does indeed support the claim that the physiology of CR should hold for humans too. The weight of the evidence accumulated by others, however, suggests that the *psychology* of CR is equally robust. Along with the 'well-coordinated, multilevel networks of various [physiological] defenses to maintain homeostatic mechanisms' that make up the CRL effect (Yu & Chung, 2001, p. 40), natural selection built in some impressive psychological defences that are just as lawful, predictable and powerful. Their purpose is to get the organism to eat, by keeping it narrow-minded, self-centred, goal-directed, food-obsessed and at least moderately miserable until that mission is accomplished. Nature knows her business on all of these levels: the molecular, cellular and physiological *and* the behavioural, cognitive and affective. CRL researchers focus on the

former and ignore the latter to the peril of their own paradigm.

The specialists who know most about the cluster of effects CRL researchers disregard are experts in the eating disorder field. (There is an obvious and relevant reason—the defensive system works so splendidly that 'disorder' is required to throw it off more than briefly or involuntarily.) Our familiarity with the neglected elements of the CR response should make us valuable resources to CRL investigators. Our exposure to the suffering those elements cause confers a responsibility to take our knowledge to them if they do not come to us. We are in a position to recognize the irony involved in the current situation. Governmental agencies are on the verge of supporting research designed to get the general population down to 20% below normal weight—while simultaneously (if inadequately) funding our own efforts to get the few people who have successfully achieved weights 20% below normal back up to average. In view of the public policy implications of CRL research, this is a debate we are obligated to enter.

Initially, the discussion may not go smoothly. Both sides are invested in their respective positions on CR, and both have considerable evidence supporting their views. The ED field is not free from biases of its own. Indeed, it may be just as difficult for AN specialists to acknowledge that CR does make semi-starved organisms 'healthy' in some important ways as it will be for CRL experts to concede that CR does not make them 'happy' after all. Keenly aware of the price our patients pay for restriction, we do not want to recognize any benefits that would give individuals with AN more reason to continue semi-starving—or might encourage others to begin. Keenly aware of the benefits other species can derive through restriction, CRL researchers are loath to recognize any costs that could deny humans the same opportunity.

At least by putting our biases together, a more complete picture of CR effects will emerge. Eventually, both fields may develop a genuine scientific and clinical curiosity about the 'other side' of CR. Each would profit from doing so: CRL experts because their paradigm will stand or fall on the basis of *all* of its consequences, no matter what it does for physiology; ED experts because our ignorance of the benefits of restriction only handicaps our efforts to treat it. The reality is that the CRL paradigm is essentially, irreducibly a 'good news/bad news' paradigm. Efforts to exclude either set of consequences from consideration distort a complex phenomenon that we should be invested, most of all, in understanding.

A Broadened Agenda for Animal CRL Research

From the perspective of the ED field, what kinds of animal research would provide a stronger basis for judging whether CRL is 'an ethical option for human use'? The guiding principle is straightforward: we need to maximize what we can learn from non-human subjects about matters of direct relevance to the feasibility and cost-benefit calculations involved in human CRL. Of course, we cannot anticipate or resolve all the issues, but more thoughtfully designed animal studies could be much more informative than those conducted to date.

Examples are easy to generate for each of the categories covered in this review. For instance, the topography of animal behaviour on CR is at least as important to projecting the human response as research on raw activity levels. We are not interested solely in whether CR affects the disposition to move about, but whether it changes the inclination to explore, to interact and to play. We need to know more about how CR impacts pair-bonding, parenting and group cohesion. We should investigate whether CR impairs frustration tolerance or resets the threshold for aggression. We must examine how CR versus AL animals cope with a range of acute and chronic stressors, using the variety of protocols for bedevilling rodents that are already applied in other contexts of animal research. We should be keen to find out how CR affects initiative and persistence in tasks that are unrelated to food, as well as curiosity about novel stimuli or situations that hold no potential for incrementing caloric intake. We should also examine what happens under the same circumstances when competing food cues are simultaneously present. After all, there is a banana in plain sight, metaphorically speaking, in every corner of the world that will be inhabited by humans on CR.

Research on hunger and food-related behaviour should continue (and preferably, in future, be published). To better approximate the conditions under which human CR would be practised, investigators must become more creative. They might analyse what happens to the behaviour and stress hormones of CR versus AL animals when exposed to the sight and smell of food they are prevented from consuming. Rather than doling out precisely measured portions at regular fixed intervals, researchers could periodically serve up rich and highly palatable foods in lavish quantities and record the behavioural and physiological consequences of such intermittent indulgence. All the evidence suggests that the small group of humans who are able to persist in extreme

CR generally end up with that sort of consummatory pattern: ongoing restraint punctuated by episodes of overeating (Eddy et al., 2002; Vitousek, Gray, & Talesfore, *European Eating Disorders Review*, in press). Except for a tiny subgroup of the most super-obsessional individuals within a pool already selected for obsessiveness, *that* is real-world human CR—which should be examined before it is advised.⁵

In fact, the outcome of most human efforts to practise CR will be *failed* CR. Investigators who are interested in the real public health implications of CRL should recognize the responsibility to anticipate and study the usual case in the laboratory as well as the ideal. Very little research has been done on the status of animals on faulty CR or on the fate of formerly CR animals who are returned to AL schedules. There needs to be much more, and it should be conducted systematically, examining the health and behavioural outcomes of subjects exposed to varying durations and severities of CR at different ages. (Existing evidence already suggests that animal research will underestimate the deleterious effects of abandoned CR, since humans appear to have more difficulty controlling food intake in the aftermath of deprivation than less sensitive or more forgetful species.)

This research agenda may seem overly ambitious, expensive and time-consuming. In our view, it is modest and mandatory. Some of the studies proposed could be conducted in conjunction with ongoing CRL investigations, with little added expenditure beyond the cost of videotape and coding time. Others would require more substantial changes in experimental protocols. For example, to examine social interaction most meaningfully, we cannot simply put two animals into the same cage and film while the fur flies, but must analyse the

⁵As noted in the companion article (Vitousek, Gray, & Grubbs, 2004), recent evidence indicates that at least one strain of mouse does enough catch-up eating on every-other-day feeding schedules to maintain near-normal caloric intake and weight—yet profits from the life extension bonus of CR all the same (Anson et al., 2003). Apparently, restricting-subtype AN is not the only eating disorder that may provide health benefits. The general pattern associated with non-purging bulimia nervosa can also be endorsed, as long as fasting and binge eating are appropriately spaced and adequate nutrition is assured. A different set of problems arises, however, when the same organisms who are *experiencing* the CR regimen are also *administering* the CR regimen. Individuals who intend to fast all day often fail to make it past mid-afternoon before the bingeing begins. Once again, proponents of CRL would do well to consult the ED field about the foreseeable fate of intermittent feeding schedules in free-ranging humans.

effects of CR on established social units. The additional expense and delay are warranted.

It is crucial to remember that CRL investigators consider it ethical to proceed with human research because they have demonstrated, to their satisfaction, that the physical problems associated with nutritionally inadequate CR do not occur on correct CRL regimens—indeed, spectacular benefits accrue. They have not yet demonstrated that the psychological and social consequences of semi-starvation are similarly resolved. It has often been observed that chronic hunger changes individuals and societies more profoundly, predictably and uniformly than any other circumstance humans commonly encounter. Advocates of CRL have the burden of proof that processes known to go awry on CR of varying quality will *not* be disrupted by the regimen they recommend. They cannot make that case without paying close attention to variables they have thus far ignored.

We anticipate that once CRL researchers do so, they will be unable to make the case at all. It is already clear—in part from research conducted within the framework of CRL—that the food focus and asexuality of semi-starvation are not mitigated with micronutrients. There are insufficient data to gauge whether consequences such as depression will be reduced; it is a good guess that effects such as decreased sociability and a narrowed scope of interests will not. Indeed, it would be astonishing if vitamin-enriched CR elicited the desired physiological elements of the CRL syndrome while neatly excising its inconvenient psychological components. The vigorous behavioural, cognitive and affective defences against undereating are not side-effects but central effects of Nature's reaction to the crisis of caloric deficit, as firmly embedded in the 'well-coordinated network' as changes on the cellular level. The physiology of CRL may be the preferred focus of specialists in this area, but the phenomenon they have chosen to study does not give them the freedom to pick and choose. The CRL effect comes as a package deal for any organism in which it is elicited; accordingly, it comes as a package deal for any investigator who hopes to describe, understand or exploit it.

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