Calorie Restriction and Aging in Nonhuman Primates

Joseph W. Kemnitz

Abstract

In the 75 years since the seminal observation of Clive McCay that restriction of calorie intake extends the lifespan of rats, a great deal has been learned about the effects of calorie restriction (CR; reduced intake of a nutritious diet) on aging in various short-lived animal models. Studies have demonstrated many beneficial effects of CR on health, the rate of aging, and longevity. Two prospective investigations of the effects of CR on long-lived nonhuman primate (NHP) species began nearly 25 years ago and are still under way. This review presents the design, methods, and main findings of these and other important contributing studies, which have generally revealed beneficial effects of CR on physiological function and the retardation of disease consistent with studies in other species. Specifically, prolonged CR appears to extend the lifespan of rhesus monkeys, which exhibited lower body fat; slower rate of muscle loss with age; lower incidence of neoplasia, cardiovascular disease, type 2 diabetes mellitus, and endometriosis; improved insulin sensitivity and glucose tolerance; and no apparent adverse effect on bone health, as well as a reduction in total energy expenditure. In addition, there are no reports of deleterious effects of CR on reproductive endpoints, and brain morphology is preserved by CR. Adrenal and thyroid hormone profiles are inconsistently affected. More research is needed to delineate the mechanisms of the desirable outcomes of CR and to develop interventions that can produce similar beneficial outcomes for humans. This research offers tremendous potential for producing novel insights into aging and risk of disease.

Key Words: baboon (Papio spp.); calorie restriction; diet; glucose regulation; health; longevity; rhesus macaque (Macaca mulatta); nonhuman primate (NHP); cynomolgus macaque (Macaca fascicularis)

The phenomenonology and mechanisms of action of calorie restriction (CR1; also called dietary, food, or energy restriction) to reduce morbidity and extend the lifespan of yeast, worms, flies, and rodents have attracted increasing attention among scientists during the last several decades (McDonald and Ramsey 2010). Studies in the lower-order organisms have sparked interest in the possibility that CR or a CR mimetic can have similar effects on health and lifespan in larger, more complex, and longer-lived species and potentially in humans. To explore this possibility, studies of the effects of CR on aging in nonhuman primates (NHP2) formally began nearly 25 years ago.

In this review I consider the design and methodology of these studies, summarize the main findings of these and related studies on aging in NHP, identify challenges and limitations of this work, and reflect on the implications of this knowledge for future research in this area. Other articles in this issue examine the utility of smaller NHP species (Fischer and Austad 2011), including the marmoset (Tardif et al. 2011), for studies of aging.

Prospective Studies of CR and Aging in Rhesus Monkeys

Only two projects have been prospectively designed to evaluate the effects of moderate CR on general physiology, healthspan, and lifespan in NHP. One is being conducted under the auspices of the intramural research program of the National Institute on Aging (NIA) of the National Institutes of Health (NIH) and the other by the University of Wisconsin-Madison through extramural program funding from the NIA. These studies began in 1987 and 1989, respectively.

Both projects have relied on rhesus monkeys (Macaca mulatta), an Old World species (indigenous to the Indian subcontinent and ranging into China) commonly used in biomedical research because of its similarity to humans in terms of genetics, endocrinology, physiology, neuroanatomy and cognitive function, and course of aging (Colman and Kemnitz 1998). Rhesus monkeys experience puberty at 2½ to 4½ years of age and are physically mature by 6 to 10 years. Females undergo menopause in their mid- to late 20s. In the protective confines of research colonies, where the animals have nutritious food, clean water, and excellent veterinary care, median life expectancy is approximately 26 years, 10% survive beyond 35 years, and maximum lifespan is approximately 40 years (Colman and Kemnitz 1998).

A wealth of background information is available for rhesus monkeys of Indian origin and Chinese rhesus monkeys are very similar in most respects. Because there may be subtle differences based on geographic origin, a distinction is

1Abbreviations used in this article: CR, calorie restriction; NHP, nonhuman primate(s); NPRC, National Primate Research Center

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1Abbreviations used in this article: CR, calorie restriction; NHP, nonhuman primate(s); NPRC, National Primate Research Center.
made between them in Table 1, which summarizes the general characteristics of the animals discussed in this review.

The use of macaques in these studies does present certain challenges. They are large (body weights of 10-20 kg for adults), strong, and not always cooperative, so anesthesia (which can be a confounding variable) is often necessary for certain physical procedures. They are highly social species but have strict social hierarchies and can be very aggressive with each other, so housing conditions require special consideration. They are intelligent and inquisitive, so they need various forms of environmental enrichment to keep them occupied. They often harbor pathogens that are dangerous to themselves and also to humans, so there are occupational safety concerns related to their care (ILAR J 2008). And their size and long lifespan make it expensive to study them in the context of aging.2

### NIA Intramural Study

This project was spearheaded by investigators at the NIA’s Gerontology Research Center in Baltimore, Maryland, and the monkeys were maintained indoors at the NIH Primate Unit in Poolesville, Maryland. An independent cohort designated for short-term studies was managed at the Oregon

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Table 1 General characteristics of rhesus macaques used in long-term aging studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Speciesa</th>
<th>Source</th>
<th>Sex</th>
<th>Sample size (C/CR)</th>
<th>Age (yrs) at entry (date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute on Aging (NIA)</td>
<td><em>M. mulatta</em></td>
<td>Perrine, FL</td>
<td>Male</td>
<td>12 (6/6)</td>
<td>0.5-1.0 (1986-1987)</td>
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<tr>
<td></td>
<td>(Indian)</td>
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</tr>
<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>Alice, TX</td>
<td>Male</td>
<td>12 (6/6)</td>
<td>3-5 (1986-1987)</td>
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<tr>
<td></td>
<td>(Chinese)</td>
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</tr>
<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>Perrine, FL</td>
<td>Male</td>
<td>6 (3/3)</td>
<td>18-25 b (1986-1987)</td>
</tr>
<tr>
<td></td>
<td>(Indian)</td>
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<td>(Chinese)</td>
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<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>Morgan Island, SC</td>
<td>Female</td>
<td>20 (10/10)</td>
<td>1-3 (1992)</td>
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<tr>
<td></td>
<td>(Indian)</td>
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<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>Alice, TX or Aberdeen</td>
<td>Female</td>
<td>20 (10/10)</td>
<td>6-14 (1992)</td>
</tr>
<tr>
<td></td>
<td>(Chinese)</td>
<td>Proving Ground, MD</td>
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<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>Morgan Island, SC</td>
<td>Female</td>
<td>20 (10/10)</td>
<td>16-21 b (1992)</td>
</tr>
<tr>
<td></td>
<td>(Indian)</td>
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<tr>
<td>University of Wisconsin-Madison</td>
<td><em>M. mulatta</em></td>
<td>WNPRC</td>
<td>Male</td>
<td>30 (15/15)</td>
<td>8-14 (1989)</td>
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<tr>
<td></td>
<td>(Indian)</td>
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<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>WNPRC</td>
<td>Female</td>
<td>30 (15/15)</td>
<td>8-14 (1994)</td>
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<tr>
<td></td>
<td><em>M. mulatta</em></td>
<td>WNPRC</td>
<td>Male</td>
<td>16 (8/8)</td>
<td>6-14 (1994)</td>
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<td>(Indian)</td>
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<tr>
<td>Wake Forest University</td>
<td><em>M. fascicularis</em></td>
<td>Bogor, Indonesia (feral)</td>
<td>Male</td>
<td>32 (16/16)</td>
<td>8 b</td>
</tr>
<tr>
<td>NIA</td>
<td><em>S. sciureus</em></td>
<td>Peru (feral)</td>
<td>Male</td>
<td>12 (7/5)</td>
<td>1-4 b (1987)</td>
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<tr>
<td></td>
<td><em>S. boliviensis</em></td>
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<tr>
<td></td>
<td><em>S. sciureus</em></td>
<td>Peru (feral)</td>
<td>Male</td>
<td>13 (7/6)</td>
<td>5-9 b (1987)</td>
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<tr>
<td></td>
<td><em>S. boliviensis</em></td>
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<tr>
<td></td>
<td><em>S. sciureus</em></td>
<td>Peru (feral)</td>
<td>Male</td>
<td>8 (C)</td>
<td>&gt;10 b (1987-1988)</td>
</tr>
<tr>
<td></td>
<td><em>S. boliviensis</em></td>
<td></td>
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</tr>
<tr>
<td>University of Maryland</td>
<td><em>M. mulatta</em></td>
<td>Various</td>
<td>Male</td>
<td>8 (CR)</td>
<td>12-19</td>
</tr>
<tr>
<td></td>
<td>(Indian)</td>
<td></td>
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</tbody>
</table>

C, control group; CR, calorie restriction group; M., *Macaca*; S., *Saimiri*; WNPRC, Wisconsin National Primate Research Center

aA distinction is made between Indian and Chinese derivation for rhesus monkeys.
bAges are estimates based on dentition and other physical characteristics.

2Some of these challenges can be mitigated by the use of neotropical primates, as discussed elsewhere in this issue (Fischer and Austad 2011).
Selection of Subjects and Animal Procurement

The initial study involved 30 male rhesus monkeys of varying ages assembled in December 1986-February 1987 (Ingram et al. 1990): 12 were 6 to 12 months old (acquired from a NIH facility in Perrine, Florida, via New Mexico State University); 12 were 3 to 5 years old (obtained from a research colony in China via the Texas Primate Center, Hazelton Research Primates, Alice, Texas); and 6 were older monkeys (18–25 years) either born in captivity (n = 5) or captured as a young adult (n = 1) in India and maintained in a breeding colony at Perrine. Records of the animals’ previous histories were extensive, but not necessarily complete; ages were determined by dental records and other documentation.

In 1988 these three age groups were supplemented with an additional 30 rhesus males, almost all of which were of Chinese origin (Lane et al. 1992), and in 1992 three cohorts of rhesus females were added. These new groups were added to increase statistical power and to allow comparison of aging and CR between sexes. The three female groups (n = 20 each) were 1 to 3 years old (obtained from Labs of Virginia on Morgan Island, South Carolina), 6 to 14 years old (from China via Texas Primate Center or the US Army Medical Research Institute of Chemical Defense at Aberdeen Proving Ground in Maryland), and 16 to 21 years old (also from Morgan Island). The general background characteristics of these monkeys are summarized in Table 1.

The male monkeys in the younger groups were initially housed as pairs except during the period of food availability, but because of repeated instances of aggression all subjects were housed indoors individually by year 6 of the study (Lane et al. 1996). The 120 monkeys in this project (60 male and 60 female) had disparate genetic backgrounds and variable experiences before entering the protocol, although none had undergone any invasive procedures. It is perhaps important that many of the animals were of Chinese origin, while the others were of Indian origin, in light of potentially significant genetic and phenotypic differences between these geographically separated populations (Smith and McDonough 2005). For example, there is deep divergence in mitochondrial and nuclear genomes between Indian and Chinese rhesus, including sequences for the major histocompatibility complex (Kanthaswamy et al. 2008). Phenotypic differences, including behavioral differences such as less aggressiveness in Indian versus Chinese rhesus, have also been reported (see Kanthaswamy et al. 2008).

Diet and Implementation of CR

The diet used in this study, specially formulated by Joseph J. Knapka, PhD, laboratory animal nutritionist at the NIH, was a modification of the standard high-fiber diet of monkeys at the NIH (Agway, Ithaca, New York) and was manufactured as an extruded biscuit with natural ingredients (Ingram et al. 1990). Nutrient concentrations were based on published estimates of requirements for nonhuman primates (NRC 1978) and on previous experience with commercially available NHP diets. The approximate macronutrient composition (by weight) was 15% protein, 5% fat, and 5% crude fiber, with a gross energy density of 3.77 kcal/g. Standard vitamin and mineral premixes added to the diet were increased by 40% to guard against possible deficiencies when the diet was fed in reduced amounts. All the animals also received a low-calorie treat daily and fresh fruit on a weekly schedule.

Food allocations were established by estimated energy requirements based on individual ages and body weights (NRC 1978) over the preceding 3-month period. Half of the daily allocation was provided at 7:00 AM and the other half at 1:30 PM; at 3:00 PM unconsumed food was removed. Twice a year for 5 days/week the unconsumed food was measured to assess actual caloric intake. The food allotments of the CR monkeys were incrementally reduced by 10% per month over a 3-month period to achieve 30% CR (this level of restriction was considered moderate in the context of a large number of rodent studies, which provided the benchmarks for this kind of work). Measurement of food intakes approximately 6 months after the beginning of CR revealed that the degree of restriction was actually 23-24%, because the control animals were not eating all of their allocation, so the amount fed to the CR groups was further reduced to achieve the targeted level of restriction.

University of Wisconsin-Madison Study

This project is being conducted at one of the eight National Primate Research Centers (NPRCs1) supported by the NIH National Center for Research Resources (NCRR), an arrangement that offers some important advantages. All of the NPRCs maintain breeding colonies to provide well-characterized cohorts for prospective studies and have staff with interdisciplinary expertise in NHP and use consistent and established methods for assessment. In addition, the NIA provides support for set-aside colonies of older rhesus monkeys at four NPRCs (including the Wisconsin center) and these colonies have been invaluable for cross-sectional studies of geriatric monkeys that continue to pave the way for prospective investigations of aging.

Selection of Subjects and Animal Procurement

Initially 30 young adult (8- to 14-year-old) male rhesus monkeys were selected from the colony at the Wisconsin NPRC for this project, which began in 1989 (Kemnitz et al. 1993). These animals, entirely of Indian derivation, were born and lived their entire lives at this facility. Their pedigree and complete electronic health records are available and, together with physical exams, revealed that potential subjects were healthy and had not undergone any procedures that would be
expected to alter the course of aging. The animals were fed Purina Monkey Chow (#5037 or 5038) at approximately ad libitum levels from weaning until entry into this study, when they were housed indoors in individual cages (to control and measure food intake accurately and to protect them from aggression, as explained above).

In 1994, with an expanded renewal of the grant from the NIA extramural program, 30 females and 16 males of ages similar to those of the initial cohort at the onset of CR and drawn from the same multigenerational colony using the same screening procedure, were added to the study (Ramsey et al. 2000a). Females were selected to have had at least one but no more than three healthy infants.

Animals were randomized between control and CR groups in equal numbers with the goals of achieving balance in terms of age, body weight, and baseline food intake.

**Diet and Implementation of CR**

A defined diet was developed for this study so that nutrient intakes could be precisely known and controlled (Kemnitz et al. 1993). The diet (#85387, Teklad, Madison, Wisconsin) was formulated with the guidance of Ron Rose, PhD, research nutritionist at Harlan Teklad, to contain 15% lactalbumin (88-89% protein) by weight, 10% fat (primarily corn oil), and 5% cellulose, providing 3.9 kcal/g. This diet contains roughly the same protein level as the Purina Chow that the monkeys had been fed before the study, but has about twice as much fat (primarily corn oil) and less roughage.

The initial group had ad libitum access to the semipurified diet between approximately 8:00 AM and 4:00 PM for several months before the study. We carefully measured the daily consumption of individual animals and used their average intake for at least 6 weeks as their baseline intakes. Individualized restriction was progressively imposed by reducing food allotments to CR animals by 10% per month from their baseline intakes for 3 months, consistent with the NIA study. An important difference between the NIA and UW-Madison projects is that baseline food allocations were determined by formula for the NIA monkeys and based on individualized measured intakes for the Wisconsin project.

After the first 18 months of restriction the intake of the CR animals was only 18% less than that of the controls (which gained weight during the first several months of the experiment) because the latter gradually ate less than they had during the baseline phase; in fact, animals with the highest baseline intakes voluntarily reduced their intakes the most. Allocations to the CR animals were adjusted based on the statistical relationship between their baseline intake and the control animals’ actual intake in order to reestablish the intended 30% differential in the consumption of the two groups. The unexpectedly high intake of the animals during the first year or so of the study was attributed to a transient response to the greater palatability of the semipurified diet compared to the standard chow used to maintain the colony (Kemnitz et al. 1993).

When the additional animals were added to the study after 5 years, the dietary protocol was changed in two ways. First, individualized baseline caloric intakes were measured while the animals in the new groups were on the chow diet rather than after switching them to the semipurified diet, to avoid the complicating factor of palatability and weight gain for determining food allocation. Second, the diet for the CR animals in all groups was supplemented with the vitamin and mineral mix by 30% in order to equate the intake of these components across the CR and control groups (Ramsey et al. 2000a). Individual intakes have been measured daily throughout the course of this project.

**Challenges in the Long-Term Management of Animals in the NIA and UW-Madison Studies**

Issues emerged during the conduct of the NIA and Wisconsin studies that are inherent to such long-term experiments. One pertains to strategies for dealing with chronic conditions and diseases. The policy of the Wisconsin team has been to treat the monkeys much as would be done in human clinical medicine to alleviate discomfort and prolong life. This approach—which entails, for example, the treatment of incipient or frank type 2 diabetes mellitus with insulin sensitizers or exogenous insulin, treatment of endometriosis by hormonal suppression of ovarian function, and surgical resection of malignant tumors when feasible—enables assessment of the course of clinical conditions in control versus CR animals. The NIA policy, on the other hand, has been to euthanize animals diagnosed with chronic disease because they become more like “case studies” and difficult to incorporate into continuing statistical contrasts of control and CR data (Mattison et al. 2007).

Another important issue arises from the fact that, beginning in middle age, monkeys spontaneously decrease their food intake. An initial restriction of 30% between CR and control animals, with the assurance of good nutrition for the CR monkeys, therefore requires periodic adjustment in order to maintain this difference. As intakes of control monkeys progressively decline, it is inevitable that further reductions in CR allocations will eventually not sustain complete nutrition. A more complex formula is necessary to maintain CR without malnutrition in later years and any restriction must be implemented very carefully in late life, particularly beyond 30 years of age.

**Related Studies**

Several recent studies that are thematically similar to the two studies described above were designed to test short-term hypotheses related to the beneficial effects of CR in reducing morbidity and extending lifespan in nonhuman primates, or to provide meta-analysis of existing data, or used dietary interventions similar to the CR paradigm. They have generated important ancillary data.
Wake Forest University

Wake Forest University School of Medicine has a long and productive history of cardiovascular research using cynomolgus monkeys (Macaca fascicularis). In this context, Cefalu and colleagues (2004) tested the hypothesis that increased insulin sensitivity consequent to CR reduces the progression of atherosclerosis.

Cynomolgus monkeys are closely related to rhesus monkeys but slightly smaller and their ancestral territory is southeast Asia. Colonies of these monkeys are now found outside their native territory (e.g., on the island of Mauritius and in China). 3

The Wake Forest study involved 32 adult male cynomolgus monkeys imported from an Indonesian research institute. The animals were estimated to be 8 years old based on dentition. They were housed indoors as pairs except at meal time, when a partition was inserted in the cages to separate the animals in order to control access to food and measure intake.

The animals’ moderately atherogenic diet (30% of calories as fat, 0.25 mg cholesterol/kcal) was provided at 100 kcal/kg body weight during the initial baseline phase. As in the NIA and Wisconsin projects, the 30% CR was gradually imposed during a 3-month period of stepwise reduction of food allocation and the animals’ diet was supplemented with a vitamin/mineral mixture and cholesterol so that intake of these components was equivalent in the two groups. Food intake and body weights were carefully monitored and fully documented.

The monkeys on CR exhibited reduced body fat and increased insulin sensitivity, but were not different from controls in terms of lipid profile or atherosclerosis extent after 4 years of study. It appears that diet-induced hypercholesterolemia overwhelmed the putative protective effects of reduced visceral fat mass and enhanced insulin sensitivity.

NIA Squirrel Monkey Study

A study of squirrel monkeys (Saimiri sciureus and S. boliviensis) was initiated concurrent with the NIA rhesus monkey study (Ingram et al. 1990; Weindruch et al. 1995). Squirrel monkeys are small (adult body weight of 0.6-1.3 kg) arboreal primates widely distributed throughout Central and South America.

Twelve juvenile (0.3-4 years old), 13 adult (5-10 years old), and 4 older (>10 years old) monkeys were acquired either from a commercial dealer or from a Peruvian research facility; all but one had been wild caught in Peru. A wide range of age estimates had been provided by the vendor so ages were re-estimated on the basis of morphological assessments, including dentition, after the study began. This resulted in some discrepancies in reporting data in the first years of the study. The study design was similar to that used for the rhesus monkeys, but the diet was modified to be more appropriate for the New World tropical species (manufactured by Zeigler Bros., Inc., Gardners, Pennsylvania). It was higher in protein (20% by weight) and fat content (8%) and energy density (4.03 kcal/g). The monkeys were pair housed.

Food allocations based on individual ages and body weights (NRC 1978) appear to have been too generous, as the squirrel monkeys assigned to the CR group (as well as the controls) consistently left approximately 10% of their food uneaten in the early phase of the project (Ingram et al. 1990). During the next few years, however, the control group monkeys tended to increase their intake, so on average over a period of 5 years the CR group ate 21-23% less than controls instead of the targeted 30%.

There was no reliable effect of CR on body weight or growth after 5 years of study (Weindruch et al. 1995). Much of the data remain unreported, but an extensive pathology assessment of these animals is currently under way.

University of Maryland

Barbara Hansen and her colleagues have been studying obesity and the development of type 2 diabetes mellitus in rhesus monkeys for several decades, during which they acquired a small number of older animals whose access to food had been restricted in order to control their body weight. All monkeys were fed commercial monkey chow (Purina Mills, St. Louis, Missouri) composed of 17% protein and 13% fat by weight. Some of the control monkeys were occasionally fed a liquid diet (Ensure, Ross Laboratories, Columbus, Ohio) for related studies. All monkeys received a chewable multivitamin daily and fresh tap water was freely available.

Eight male rhesus monkeys subjected to CR for more than 10 years and aged 21 to 30 years at the end of the analysis were compared to 88 male and 21 female monkeys that served as historical controls (Bodkin et al. 2003). All of these animals were of Indian derivation. The control monkeys had been acquired from various sources, including academic research facilities and commercial vendors in the US, over a period of approximately 25 years beginning in 1977. Among the control animals, some maintained fasting plasma glucose levels in the normal range, some exhibited hyperinsulinemia and moderately elevated glucose levels, and some became overtly diabetic.

Food was available ad libitum to the control animals 24 hours/day except for times of fasting for assessment procedures. Food allocation for the monkeys undergoing CR was titrated for each animal with the goal of maintaining body weights between 10 and 11 kg. This “weight clamping” approach for determining food allocation is more like that used in the pioneering studies of McCay and different from that used for the other studies reviewed here. The CR animals were fed in three equal meals at approximately 8:00 AM, 1:00 PM, and 4:00 PM. Intake was measured and was approximately 60% of control levels in absolute terms, but did not differ between groups when expressed per kilogram of body weight (Hansen et al. 1995). In addition to assessments

3 More information about this species and others discussed here is available at pin.primate.wisc.edu/factsheets.
of glucose regulation and insulin levels, the monkeys were monitored in terms of age-related conditions (discussed below) and potential impact of CR on mortality (Bodkin et al. 2003).

SNPRC Baboon Study

The effects of maternal nutrient restriction have been studied in baboons (Papio spp.) at the Southwest National Primate Research Center (SNPRC) in San Antonio, Texas (Schlabritz-Loutsevitch et al. 2007). Baboon species are widespread in equatorial Africa. They are large (10-25 kg) and have a lifespan similar to that of macaques.

The purpose of the SNPRC study is to assess fetal growth and metabolism during the pregnancies of dams that eat either ad libitum or 70% of contemporaneous controls on a per-kilogram basis from day 30 of gestation to cesarean section delivery at day 90 (when placental physiology changes and dramatic growth of the placenta begins) or at term of the 165-day gestation (Li et al. 2009; Schlabritz-Loutsevitch et al. 2007). The baboons’ diet was commercial monkey chow (Purina #5038), provided during a 2-hour feeding session daily. Tap water was available ad libitum.

Maternal CR in this regimen decreased maternal weight by 11% but did not affect fetal body weight or length or fetal liver or kidney weight. However, placental weight was lower at term and villous volume and surface area and capillary surface area were reduced, suggesting decreased placental transport of nutrients to the fetus (Li et al. 2009; Schlabritz-Loutsevitch et al. 2007). In addition, there were marked changes in hepatic insulinlike growth factor (IGF) pathways that might be predictive of growth retardation in the infant (Li et al. 2009). These observations require further study.

Aggregated Observations

Functional Assessments

Energy Intake

The studies reviewed here that entailed restriction averaging 20-30% of food intake less than ad libitum-fed control monkeys in young adult and middle-aged monkeys demonstrated that this intervention can be safely implemented during the age range of approximately 8 to 30 years (i.e., about half of their lifespan). In immature monkeys, however, this level of CR impairs growth (Weindruch et al. 1995) and in elderly monkeys it can exacerbate the loss of lean tissue. Because NHP food intake steadily declines after middle age (Mattison et al. 2005; Schroederus et al. 1999) it is probably highly inadvisable to attempt to maintain a 30% differential in intake indefinitely, but rather to titrate allocations in already fat-depleted animals in order to guard against drawing on lean tissue for energy.

It is difficult to precisely impose CR relative to a control group because of day-to-day variability of intake among control animals (which eat ad libitum) and the potential effects on intake of novelty and palatability of experimental diets during the first several months. It is critically important to closely monitor and report intakes along with experimental outcomes to enable appropriate interpretation of the data. It can be misleading to describe consequences of “30% restriction” when that is only the intent, whereas in fact the difference between control and experimental groups is either not known or is something less. Also, animals’ intake is not truly restricted if they are not routinely consuming all their allotted food. Findings of no difference between groups must be viewed skeptically if it is not clear that the CR group was actually restricted according to the defined goal (e.g., 30%).

A related point pertains to effects of short-term (hours) versus chronic restriction. Some measures, such as growth hormone and cortisol (glucose counterregulatory factors), can be markedly elevated after fasting and changes or differences in levels may be a function of time since the last meal rather than sustained outcomes of CR. It is important, therefore, to standardize the period of fasting between groups before measuring labile endpoints and to consider integrated measurements over longer periods of time (e.g., 24-hour measurements of hormones and metabolites in urine) where appropriate.

Under ad libitum conditions in a controlled laboratory environment water intake is highly correlated with food intake, with approximately 4.5 ml water consumed per gram of chow eaten by adult rhesus monkeys (Schroederus et al. 1999). Monkeys on CR have markedly greater 24-hour urine volumes than controls both in absolute terms and relative to food intake (JWK, unpublished observations). Water intake of monkeys on CR has not been reported, but the increased excretion of urine suggests that intake is elevated. Studies of water balance and associated variables (e.g., serum concentrations of electrolytes, minerals and water soluble vitamins) are needed.

Body Weight and Composition

Body weight, body fat and distribution of fat, skeletal muscle mass and anatomy, and bone mass and density are important dependent variables and covariates in studies of CR and aging. Body fat in CR monkeys has been variously assessed by anthropometry (e.g., skinfold thicknesses and circumferences of trunk and limbs), labeled water dilution, dual-energy X-ray absorptiometry, and computed tomography. A healthy range of body fat for adult rhesus monkeys seems to be approximately 10-20% (Raman et al. 2005); at the lower end of this range further weight loss is accompanied by loss of lean body mass and at the upper end insulin action is impaired.

Not surprisingly, all studies that document CR (i.e., all food is consistently eaten, at a minimum) also report decreases in body weight and body fat, especially in the abdominal region, including visceral fat (Cefalu et al 2004; Colman et al. 1998, 1999a). These reports accord with those of weight reduction and avoidance of obesity in humans and other species.
Muscle mass declines with aging, a condition known as sarcopenia that develops in both control and CR monkeys but more rapidly in controls, suggesting relative preservation of skeletal muscle function by CR (Colman et al. 2008). Studies of the vastus lateralis, a major muscle of the upper leg, in non-CR middle-aged male rhesus monkeys demonstrated significant loss of muscle mass and muscle fiber cross-sectional area associated with mitochondrial enzyme abnormalities due to mitochondrial DNA deletion mutations (McKiernan et al. 2009). Perhaps CR slows the progression of sarcopenia by protecting against oxidative damage to mitochondria (Anderson et al. 2008; Zainal et al. 2000).

Bone mass also declines with aging in both female and male rhesus monkeys (Colman et al. 1999b,c), but 6 years of CR in seven 27-year-old rhesus monkeys did not detectably affect bone mineral density or content for either total body or lumbar spine or radius sites, osteocalcin, 25-hydroxyvitamin D, 125-hydroxyvitamin D, or parathyroid hormone concentrations (Lane et al. 2001). Longer-term (11 years) CR resulted in lower total bone mass, but this could be accounted for statistically by factoring in age and lean body mass (Black et al. 2001). Taken together, these and similar unpublished observations suggest that moderate CR does not adversely affect skeletal health.

Energy Expenditure

Metabolic rate has long been regarded as a potentially important factor in controlling the rate of aging, but the effects of CR on metabolic rate have been controversial because of methodological considerations and interpretation of observations. Studies of CR and metabolic rate in rhesus monkeys have used respiration chambers and doubly labeled water for indirect calorimetry over periods of one to several days while the animals lived in typical laboratory conditions, together with periodic measurement of rectal temperatures of briefly anesthetized animals and continuous recording of subcutaneous temperatures and heart rate for 1 week. Physical activity of the animals has also been monitored by direct observation or automated systems.

Direct behavioral observations in a cross-sectional study of male and female monkeys aged 7 to 9, 13 to 17, and more than 23 years (n = 6 per group) indicated that the oldest group spent more time resting and much less time engaged in vertical movement than the younger groups (Ramsey et al. 2000b). The oldest group also had less lean body mass and lower 24-hour oxygen consumption than the younger groups.

After 30 months of CR male rhesus monkeys in the Wisconsin study exhibited lower total energy expenditure than controls during the overnight period when the animals are inactive (Ramsey et al. 1997). This effect remained significant when differences in body size and composition were taken into account by analysis of covariance. Overall physical activity of the two groups did not differ. An analysis of the same animals after 11 years of CR revealed lower total energy expenditure measured by doubly labeled water and overnight (resting or sleeping) energy expenditure using respiration chambers (Blanc et al. 2003), and a longitudinal analysis of data from male and female animals ranging in age from 11 to 29 years showed that 24-hour energy expenditure in both CR and control groups declined with advancing age (Raman et al. 2007b). Both lean body mass and body fat mass contributed independently to the lower energy expenditure associated with both age and CR. Decreasing total energy expenditure with age was also associated with a decline in daytime physical activity. Declining physical activity with age was also described in the NIA monkeys ranging from 6 to 26 years of age (Moscrip et al. 2000). Recent observations suggest that CR animals exhibit a slower rate of decline in energy expenditure with advanced age compared to controls (Yamada et al. in preparation).

Lower total energy expenditure was also seen in male rhesus monkeys whose body weights had remained stable at reduced levels for 10 years (DeLany et al. 1999). Physical activity of the CR group did not differ from that of younger weight-matched controls but was higher than that of older age-matched controls. Rectal temperatures did not differ among groups.

The NIA study did not find an effect of CR on metabolic rate (measured with doubly labeled water) after 5 years of restriction (Lane et al. 1995b), but did see a reduction after 2 months of 30% restriction in other groups (using respiration chambers; Lane et al. 1996). The CR animals have consistently shown lower rectal and subcutaneous temperatures than the controls (Lane et al. 1996) but no difference in heart rate.

After 6 years of CR the NIA monkeys were videotaped in their home cages and scored for a range of locomotor, self-directed, and other behaviors (Weed et al. 1997). The group that underwent CR in early adulthood exhibited increased activity, particularly oral behaviors and rocking (usually regarded as manifestations of neurosis), compared to the younger groups. Interestingly, animals exhibiting stereotypies were those imported from China, suggesting that the behavioral difference may have a genetic basis or result from different early experiences.

Endocrinology and Metabolism

One of the clearest and most consistent CR effects found in the macaque studies is an improvement in insulin sensitivity and glucose tolerance. These endpoints for glucose regulation have been assessed by fasting plasma measures of glucose and insulin (all studies), glycosylated hemoglobin, simple intravenous glucose tolerance tests (Bodkin et al. 1995; Lane et al. 1995b), euglycemic hyperinsulinemic-clamp techniques (Bodkin et al. 1995; Cefalu et al. 2004), and elaborate modeling of insulin and glucose concentrations during intravenous glucose tolerance tests with frequent sampling (Cefalu et al. 2004; Gresl et al. 2001, 2003b; Kemnitz et al. 1994). Fasting plasma glucose and glycosylated hemoglobin concentrations have not immediately or consistently differed between CR and control groups within or among studies; these
measures appear to be less sensitive to the effects of CR than changes that are more dynamically modulated by insulin.

Insulin concentrations of CR monkeys are lower in the fasted state and in response to glucose or tolbutamide challenge, and insulin sensitivity as measured by the modified minimal model method is higher (Cefalu et al. 2004; Gresl et al. 2001; Kemnitz et al. 1994). Similarly, CR increases insulin-stimulated glucose uptake by the clamp technique (Bodkin et al. 1995; Cefalu et al. 2004). Modeling of pre- and posthepatic insulin secretion by concurrent measurement of glucose, C-peptide, and insulin levels indicated that in CR monkeys the pancreatic beta cell is less sensitive to glucose in the fasted state but not in the glucose-stimulated condition. Differences between groups are related to differences in (abdominal) body fatness (Gresl et al. 2003a). CR increased insulin receptor signaling as evidenced by greater IRS-1 and -2 protein abundance. There was no difference in the transcriptional regulation of these proteins, but a decrease in protein degradation via the ubiquitin proteosomal system (Wang et al. 2009).

Deterioration of glucose tolerance and an elevation in prevailing glucose levels with age is thought to increase glycation of proteins, glycoxidation, and the development of cross linkages, all of which can lead to stiffening of connective tissue. Given that CR improves insulin sensitivity and glucose tolerance, it is reasonable to hypothesize that it would also preserve connective tissue health in aging. This process has been studied extensively in the skin of the monkeys in the NIA project (Sell et al. 2003), which showed that CR significantly decreased glycation but not glycoxidation of skin collagen.

The most detailed NHP studies of the effects of CR on lipids, lipoproteins, and atherosclerosis are those of Cefalu and colleagues. In their study of male cynomolgus monkeys fed a fat- and cholesterol-enriched diet, there was no difference between control and CR monkeys in plasma triglyceride or lipoprotein levels, blood pressure, or coronary artery atherosclerosis (Cefalu et al. 2004). In contrast, triglyceride levels were lower in CR rhesus monkeys fed a lower-fat diet in the UW-Madison study (Ramsey et al. 2000a) and, in the Wake Forest study, the LDL of CR rhesus monkeys was lower in triglyceride content and molecular weight compared to controls (Cefalu et al. 2000). In the NIA study of male rhesus monkeys triglycerides increased with age, but CR reduced levels in only the young adult group (Verdery et al. 1997). Lipoprotein (a) is an independent risk factor for age-related progression of atherosclerosis and levels of Lp(a) are higher in males than in females. In the UW-Madison study, CR lowered levels of Lp(a) in males to those of females, but had no effect on Lp(a) levels in females (Edwards et al. 2001).

Dehydroepiandrosterone (DHEA), the most abundant steroid hormone in the blood of primates and primarily found in its sulfated form (DHEAS), progressively declines during adulthood but it is not clear whether CR affects the rate of decline. A survey of nearly 800 rhesus monkeys in the WNPRC colony, ranging in age from less than 1 year to 36 years, indicated that the rate of decline is approximately 4% per year in mature animals (Kemnitz et al. 2000). Lane and colleagues (1997) measured DHEAS in a single time-point sample from the monkeys of the NIA project and reported that CR slowed the rate of its decline, proposing that DHEAS levels might serve as a marker of aging. A follow-up assessment of the same animals but using a different sampling method (24-hour indwelling catheter) failed to confirm the earlier finding and reported an age-related decline in DHEAS that was enhanced by CR (Downs et al. 2008). Results from the Wisconsin CR study did not indicate any effect of CR on either DHEA or DHEAS levels in single time-point samples (Ramsey et al. 2000a). No consistent effects of CR on cortisol values have been found (Downs et al. 2008; Ramsey et al. 2000a).

DeLany and colleagues (1999) reported that thyroxine (T₄) levels were lower in CR monkeys, but there was no difference between CR and control monkeys in triiodothyronine (T₃) concentrations. Similarly, there was no effect of CR on T₃ levels in the Wisconsin project (Ramsey et al. 2000a). Plasma T₄ was reduced by CR in the NIA study, but there was no detectable effect on T₃ levels (Roth et al. 2002). In light of the major role of the thyroid hormone axis in modulating metabolism and other physiological functions, these disparate findings clearly indicate the need for further study.

Melatonin is secreted primarily by the pineal gland in a pulsatile fashion, with the highest levels in the middle of the night in both humans and rhesus monkeys. Levels decline with age. According to a report of the NIA study, blood collected from 96 male and female rhesus monkeys (aged 2 to 17 years at the onset of restriction) after 12 or 7 years of CR, respectively, showed that CR appeared to have prevented age-related decline in peak melatonin levels (Roth et al. 2001).

Questions about the effects of CR on reproductive function frequently arise. In the early years of the Wisconsin study we examined the frequency of menstrual cycles in control and CR female rhesus monkeys and did not find evidence of disrupted cycles in the latter (Kemnitz et al. 1998). The female monkeys on CR in the NIA study also continued to have normal menstrual cycles (Lane et al. 2001). Both CR and control monkeys exhibited lower estradial and increasing FSH with advancing age, as is typical of the primate aging process. The females in the Wisconsin and NIA studies were not allowed to breed while in the study, so it was not possible to assess the possible effects of long-term CR on fertility and pregnancy. Short-term CR in baboons, however, did not interfere with conception or gestation (up to the surgical delivery of the fetuses; Li et al. 2007).

Recent studies of testicular function in young males in the NIA study did not reveal a significant effect of CR on 24-hour plasma testosterone levels or on indicators of semen quality, such as sperm viability and function (Sitzmann et al. 2010a,b).

**Immunology**

The immune system of aging NHP and the immunologic responsiveness of monkeys on CR both warrant more study (Nikolich-Zugich and Messaoudi 2005). NHP T cell subsets change with age in ways that are similar to the changes that
occur in rodents and humans: naïve CD4 and CD8 T cell numbers decline and memory cells increase, limiting flexibility in responsiveness to new infections. An exciting finding from studies of the monkeys in the NIA project indicated that naïve cell populations were preserved in animals that began CR in early adulthood compared to age-matched controls (Messaoudi et al. 2006). Subsequent analysis of the younger and older cohorts, however, revealed that CR begun earlier in life (1-2 years of age) or when the animals were older adolescents (3-5 years old) had the opposite effect, increasing T cell senescence or producing lymphopenia and reduced proliferative capacity, respectively (Messaoudi et al. 2008). There are also suggestions that CR decreases the production of inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6), but further work on this topic is clearly needed.

Brain Morphology and Behavior

Brain atrophy is a characteristic of aging humans that is not accurately reproduced in smaller mammals but is mimicked in rhesus monkeys. Grey matter volume measured in vivo by magnetic resonance imaging (MRI) declined generally in the frontal and temporal cortex during the third decade of life for monkeys in the Wisconsin project, but for the CR animals there was relative preservation of volume in the midcingulate cortex, lateral temporal cortex bilaterally, and right dorsolateral frontal cortex, as well as various subcortical regions, including the caudate, putamen, and left insula (Colman et al. 2009). Proinflammatory cytokites are associated with neural atrophy in humans and in the UW-Madison monkeys peripheral IL-6 levels were associated with less global grey and white matter of the brain and with smaller parietal and temporal grey matter volume (Willette et al. 2010). CR monkeys, however, had significantly lower IL-6 levels and less associated atrophy and there was evidence that CR mitigated the effect of elevated IL-6 on brain changes in several regions that are sensitive to aging.

Diffusion tensor imaging showed preservation of white matter in CR monkeys in the fronto-occipital fasciculus, superior longitudinal fasciculus, external capsule, and brainstem (Bendlin et al. 2010). In addition, both CR and control monkeys in the Wisconsin study showed iron deposition in the globus pallidus and substantia nigra, but CR animals had significantly less iron in these regions and in red nucleus and parietal, temporal, and perirhinal cortex (Kastman et al. 2010). The beneficial effect of reduced iron deposition in areas associated with motor performance was indeed borne out by improved scores on standardized movement assessments. Studies of the NIA monkeys using brain MRI have yielded results that are less clear (Matochik et al. 2004).

Effects of CR on Morbidity

Geriatric diseases and late-life conditions of rhesus monkeys maintained under laboratory conditions at the WNPRC include coronary sclerosis, emphysema, degenerative joint diseases, cancer, brain changes, and ocular cataracts (Uno 1997).

Cardiovascular diseases in macaques are readily induced by feeding high-fat, cholesterol-enriched diets, but monkeys fed standard laboratory chow, which is low in fat, do not display marked atherosclerotic pathology. Intimal fibrous plaques in the aorta increase in incidence and extent with age, but ulcerative changes and deposition of cholesterol in the plaques are rare for animals on the low-fat diet. Coronary arteries commonly show sclerosis in monkeys 25 years of age and older.

Peripheral regions of the lungs of aged monkeys often show expansion of alveolar cavities, but these changes do not markedly compromise the animals’ health (and they may be secondary to earlier lung mite infections in animals that lived outdoors when young). Spondylosis, kyphosis, osteoarthritis, and osteopenia are common among older animals. Cancer does not often occur in monkeys younger than 25 years, but incidence increases dramatically for monkeys older than 30 years. Most common is adenocarcinoma of the colon, which also occurs in some younger adult monkeys (Simmons and Mattison 2011); other cancers include ductal carcinoma of the breast, squamous cell carcinoma of the cervix and skin, and cancers of various other organs (Simmons and Mattison 2011; Uno et al. 1998).

Brain changes include multiple small infarctions in the parietal and temporal lobes and, occasionally, cerebellar cortex and thalamus. As mentioned above, pallidonigral iron deposition and beta-amyloid plaques also appear in the brains of old monkeys.

Cardiac pathology—endocarditis, aortic valve calcification, fibrosis, cardiac hypertrophy, myocardial infarction, acute cardiac arrest, and congestive heart failure—was a major contributor to death in the control animals of the University of Maryland program (Bodkin et al. 2003). Gastrointestinal, renal, and hepatic-related disease were also seen. In addition, lung mites were common among these animals, many of which came from outdoor corral-housing conditions, and probably contributed to pneumonia, bronchiolitis, and emphysemic changes. Insulin resistance and diabetes were common among the control group, and the risk of death for a hyperinsulinemic monkey from all other causes (except gastrointestinal) was greater than for those that maintained normal insulin levels. Other pathologies of the older control monkeys in this program were similar to those reported by Uno (1997) for the Wisconsin colony.

Marked protective effects of CR on age-related pathology have been seen in the Wisconsin project thus far (Colman et al. 2009). The incidence of cancer, neoplasia, cardiovascular disease, and endometriosis was 50% lower in the CR monkeys compared to the control group and also lower relative to general colony statistics. For example, there are eight cases of cancer (seven of which were colonic adenocarcinoma) among the 38 control animals and only four (two colon cancer) among the 38 CR monkeys.

The protective effect of CR on the development of insulin resistance and diabetes has been striking. There have
been five cases of diabetes and 11 additional cases of insulin resistance among the 38 control monkeys in the Wisconsin project and no cases of diabetes or insulin resistance in the CR group, and there were few or no cases of insulin resistance and diabetes among the eight CR monkeys in the University of Maryland project (Bodkin et al. 2003).

An interim analysis of the animals in the NIA project showed that the incidence of diabetes as well as neoplasia, cardiovascular disease, endometriosis, fibrosis, amyloidosis, ulcers, cataracts, and kidney failure was lower among CR compared to control animals (Mattison et al. 2003).

Sarcopenia, dried and wrinkled skin, tooth decay, and cataracts occur in older monkeys, as is typical with elderly humans. But the CR monkeys “look younger” than controls: their skin has fewer wrinkles and age spots, and their hair is less grey.

In general the results from these three studies of the effects of CR are very consistent and point to an important contribution of lower insulin levels to the beneficial effects of CR.

Effects of CR on Lifespan

The NIA, Wisconsin, and Maryland studies are still under way, so it is too early to identify the precise extent of CR on the animal’s lifespan. However, interim analysis of the Wisconsin study data indicate that control animals at any time had three times the rate of death from an age-related cause compared to the CR monkeys (Colman et al. 2009)—median survival of the control animals has been approximately 27 years, whereas more than 50% of CR monkeys are still living at 31 years of age (all-cause mortality). Interim analysis of the NIA data indicated that twice as many controls as CR monkeys have died of age-related causes (Mattison et al. 2003). And in the Maryland program the median survival for all ad libitum–fed monkeys is approximately 25 years and for the eight CR animals 31 years (Bodkin et al. 2003). Based on the data from these three studies, it seems likely that lifespan will be extended for the monkeys undergoing CR.

Lessons Learned and Future Directions

CR is the only intervention that has been consistently shown to reduce the incidence, delay the onset, and slow the progression of age-related disease and extend lifespan in short-lived species. The studies described in this article indicate that these effects also occur in long-lived nonhuman primates and suggest that similar mechanisms would be operative in humans.

Evaluation of the study results is complicated, however, by differences in protocol design, methods, and implementation. In addition, it has proven difficult to arrive at and maintain intended levels of CR for these very long term studies. Differences in genetic backgrounds of the animals, diets, and policies for handling chronic health conditions have sometimes frustrated interpretation of results within and between studies.

On the other hand, there is remarkable consistency in the fundamental findings: CR can be safely implemented at levels of 20-30% for periods of decades in adult monkeys, it improves many aspects of physiological function and reduces age-related disease processes, and it extends median lifespan in rhesus monkeys.

For similar projects in the future, it will be advantageous to have better characterization and control of the backgrounds and baseline health (e.g., genetic, microbial, behavioral) of the monkeys at the time of entry into the protocol as well as improved monitoring and reporting of caloric intake throughout the study. Shorter-term, precisely conducted studies of macaques and baboons will be useful for uncovering answers to mechanistic questions about the effects of CR. Lifespan studies of New World nonhuman primate species, such as the common marmoset (with a maximum lifespan of approximately 15 years), are more feasible.

Several aspects of the NHP model of CR merit further investigation. For example, although the health of these animals improved in important ways, the research has occurred under benign conditions of controlled moderate temperature, minimal need for physical exertion, and protection from infectious disease. Do primates maintained on long-term CR have sufficient energy reserve capacity to cope with reduced ambient temperature or exercise stress? What is their immunological competency? Another important area for future research is the identification of CR mimetics (e.g., pharmaceuticals and nutriceuticals) that are effective in NHP.

There has been a great deal of effort to determine the effects of CR on aging in NHP and much has been learned, but in many ways the work is just beginning. This area of research has tremendous potential for yielding insights into aging, age-related pathogenesis, and longevity in humans. Studies of CR in humans of normal body weight are just getting under way (Rochon et al. 2010) and should reveal much about effects of CR on health in the short term.

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