Human Implications of Caloric Restriction’s Effects on Aging in Laboratory Animals: An Overview of Opportunities for Research

Evan C. Hadley,1 Chhanda Dutta,1 Judith Finkelstein,2 Tamara B. Harris,3 Mark A. Lane,4 George S. Roth,4 Sherry S. Sherman,1 and Pamela E. Starke-Reed5

1Geriatrics Program, 2Neuroscience and Neuropsychology of Aging Program, 3Epidemiology, Demography and Biometry Program, and 4Biology of Aging Program, National Institute on Aging, NIH, Bethesda, Maryland.
5Gerontology Research Center, National Institute on Aging, NIH, Baltimore, Maryland.

For more than 60 years it has been known that restricting caloric intake below ad libitum levels in several species of experimental animals extends life span and slows numerous aging changes. Descriptive research on these effects continues to expand and is being extended to nonhuman primates. However, there has been little research to explore the implications of these findings for the development of interventions to affect human age-related changes and diseases.

In 1999, the National Institute on Aging, in collaboration with the National Institute of Diabetes, Digestive, and Kidney Diseases, convened the Caloric Restriction Clinical Implications (CRCI) Advisory Group to consider opportunities for such research. The group included expertise in gerontology, epidemiology, clinical trials, nutrition, metabolism, endocrinology, neuroendocrinology, genetics, pharmacology, and behavioral medicine. It was composed of six panels, whose reports follow this overview. In brief, the six panel topics were:

- Current epidemiologic and intervention data
- Metabolic interventions
- Anorexiant and neuroendocrine manipulations
- Physical activity and body composition changes
- Genetic variability in responses to caloric restriction
- Effects of lowering caloric intake in nonobese persons.

These panel reports were developed before the CRCI Advisory Group’s March 1999 meeting, discussed in its plenary session, and modified thereafter. Three members of the group (Barbara Hansen, Leo Lutwack, and James Greenberg) served as “at large” members and contributed substantially to several panel reports. The reports follow a standard format, including background information and recommendations for studies in nonprimates, studies in nonhuman primates, studies in humans, recommendations on methodologic approaches, and recommendations regarding resources and infrastructure.

The following discussion of some of the main themes running through the Advisory Group’s considerations and recommendations emphasizes themes that cut across contributions of several panels. Numerous equally important ideas appear in the individual panel reports.

In regard to identifying interventions with potential human application, Panels 2 and 3 focused on an approach that complements the increasing interest in learning the mechanisms responsible for the effects of caloric restriction (CR) on aging in experimental animals. One way to probe these mechanisms in experimental animals is to examine how interventions that produce one or more of CR’s physiologic or biochemical effects (e.g., lowering circulating glucose levels) affect life span or age-related changes. Such interventions are referred to in the following reports as “CR-mimetic” interventions. If a CR-mimetic with a known mechanism of action produces effects on life span and aging similar to those of CR, this would implicate this mechanism as a likely mediator of CR’s effects.

Testing effects of CR-mimetic interventions in animals also provides an experimental therapeutic strategy to explore potential human interventions: Examining how they affect life span and aging in experimental animals can indicate potential endocrine or pharmacologic agents that might be used in humans to produce some or all of CR’s beneficial effects in delaying or preventing age-related diseases. Some CR-mimetics (e.g., oral hypoglycemic agents) have been studied extensively in humans as agents to treat or prevent specific diseases. In such cases there may be opportunities for human studies to examine other effects on age-related changes.

The amount of information derivable from studies of CR-mimetic interventions has increased greatly with the development of array technologies to determine effects on expression of a large number of genes. Using such techniques, effects of CR-mimetics could be compared with effects of CR itself, which have recently been studied with such methods (1). As evidenced by the opportunities discussed by Panel 5, possibilities for testing CR-mimetic strategies also have been expanded greatly by techniques to produce transgenic animals. Transgenic strains that on ad libitum diets have physiologic features similar to those seen in CR wild-type strains can be used to probe the mechanisms for CR’s effects on aging, analogous to pharmacologic or endocrine manipulations noted above. In addition, the role of physiologic responses hypothesized to regulate CR’s effects can be probed by examining differences among effects of CR on aging in transgenic strains that differ in these responses.
A second general strategy for probing human implications of CR’s effects in animals involves short- or medium-term human intervention studies. In recent years, considerable knowledge has been gained from human studies of weight-loss interventions lasting as long as several years. These interventions frequently include increased physical activity as well as lowered caloric intake. Nonetheless, the targeted reduction in caloric intake has been as much as 25% (2). The interventions have been designed for weight loss in overweight or obese persons, but recently, studies of obesity-prevention interventions have begun as well. The outcomes addressed by these studies have been mainly metabolic and cardiovascular risk factors associated with overweight or obesity, some of which are modified similarly to the effects of CR in experimental animals.

Thus, medium-term human intervention studies in non-obese persons, recommended by Panel 6, may be viewed in one light as an extension of lines of research that were developed to test benefits of weight loss interventions against obesity. The hypotheses to be tested are more specific in that the intervention is confined to reducing caloric intake (rather than changing both diet and physical activity, as in most earlier studies). On the other hand, the range of outcomes recommended for these studies is broader than that in most human weight-control intervention studies, including many age-related changes and risk factors affected by CR in experimental animals, and potential adverse effects. It is also worth noting the recommendations to study psychosocial and quality-of-life outcomes. These are particularly important in view of the major cultural roles of eating and associated activities, as well as attitudes toward body shape and weight.

The distinction between “pure” caloric intake-reducing interventions and alternative weight-loss interventions relates to an issue of practical and mechanistic importance addressed by Panel 4: Is CR’s effect on weight the crucial mediator of its effects on aging in laboratory animals? If so, other interventions to control weight, such as physical activity in human weight-control intervention studies, including many age-related changes and risk factors affected by CR in experimental animals, and potential adverse effects. It is also worth noting the recommendations to study psychosocial and quality-of-life outcomes. These are particularly important in view of the major cultural roles of eating and associated activities, as well as attitudes toward body shape and weight.

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As noted by Panel 1, one aspect of the laboratory animal paradigm of CR as clearly not applicable to human intervention studies: its involuntary nature. In contrast to calorically restricted laboratory animals, almost all humans have free access to food, so that some degree of volition (either limiting intake below former levels through willpower or by taking anorexiants) must be involved in lowering calorie intake. This has implications in regard to considerations discussed by Panel 3, noting that neuroendocrine effects of long-term involuntary food restriction could be essential mediators of its delay of aging changes. These effects might not occur in conditions where voluntary intake was diminished either by self-restraint or by anorexiant administration. These considerations reinforce the need for better understanding of the neuroendocrine effects of long-term involuntary CR, voluntary CR, and anorexiant administration, and their relevance to long-term human studies of anorexiants and other weight control agents.

The panel reports illustrate differences in how researchers on CR in humans and in laboratory animals customarily address its effects on mortality and disease incidence. Researchers on humans generally have dealt with effects on rates over a small fraction of the life span—rarely longer than 5 years, generally in middle age or early old age. Researchers on CR’s effects in laboratory animals customarily consider effects on survival curves over the entire life span after sexual maturity or early middle age, in particular the rates of rise in mortality and disease incidence with age. Although the term “caloric restriction” has been applied to both human and animal studies, it is important to bear the distinction in mind, particularly in regard to the lack of human data on the effects of CR that are particularly important to aging researchers—the “rightward shift” of the survival curve and increased maximum life span. To show conclusively that a human CR-mimetic intervention mimicked CR’s effects in laboratory animals, one would need to determine its effects on survival curves into advanced age.

As presented in the following reports, there are abundant clinical and basic research opportunities to clarify the potential for human interventions having some or all of the beneficial effects on age-related changes that caloric restriction produces in laboratory animals. Although it is still uncertain whether such interventions can be developed and tested, the research recommended by the panels could do much to reduce this uncertainty. We are very grateful to all members of the CRCI Advisory Group for their energy, insight, and clarity in reviewing the pertinent scientific information and developing their recommendations.

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Address correspondence and requests for reprints to Evan C. Hadley, MD, Geriatrics Program, NIA, Gateway Building, Suite 3E327, 7201 Wisconsin Avenue, Bethesda, MD 20892-9205. E-mail: ehadley@nih.gov

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