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OPINION

The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies

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Abstract Based on results emerging from long-term studies of dietary restriction in rhesus monkeys, we offer our views regarding whether dietary restriction can increase longevity in humans. Because lifespan data in monkeys remain inconclusive currently, we respond that ''we do not for sure.'' Based on the vast literature regarding the effects of healthy, low calorie diets on health and longevity in a wide range of species, including humans, and based on data emerging from monkey studies suggesting that dietary restriction improves markers of disease risk and health, we respond that ''we think so.'' Because it is unlikely that an experimental study will ever be designed to address this question in humans, we respond that ''we think we will never know for sure.'' We suggest that debate of this question is clearly an academic exercise; thus, we would suggest that the more compelling discussion should focus on whether basic mechanisms of DR can be discovered and if such discoveries can lead to the development of effective DR mimetics. Even if proof that DR or DR mimetics can increase longevity in humans will likely never emerge, we would suggest that endpoints regarding disease risk and disease incidence as well as maintenance of function can be examined in human clinical trials, and that these will be highly relevant for evaluating the effectiveness of such treatments.

Keywords Nutrition · Aging · Obesity · Diabetes · Cancer · Heart disease · Insulin · Glucose · Primates

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Regarding the question posed for debate in this special issue, ''Do you think that dietary restriction can increase longevity in all species, particularly in human beings?'' we will focus our discussion on whether dietary restriction will increase longevity in humans as this is the most salient question from our perspective. To this point, we can offer our most informed response as follows: (1) we do not know for sure; (2) currently we think so; (3) we think we will never know for sure.

Remarkably, the dietary restriction (DR) paradigm has become so ingrained into the framework of gerontological research that studies of DR in humans using both epidemiological (Fontana et al. 2004; Meyer et al. 2006; Suzuki et al. 2001) and experimental

approaches (Heilbronn and Ravussin 2003, 2005; Heilbronn et al. 2005; Smith et al. 2004) are beginning to emerge. Under the support of the National Institute on Aging (NIA), experimental investigation of DR, known as the Comprehensive Assessment of the Long-Term Effects of Reducing Intake of Energy (CALERIE) study, has been initiated at three sites including the Pennington Biomedical Research Center at Louisiana State University, Washington University School of Medicine, and Tufts University/USDA Human Nutrition Research Center on Aging (Smith et al. 2004). Pilot studies involving short-term assessments of various DR regimens were initiated in 2003. Results of these studies are emerging in the literature (Pittas et al. 2005), and have been judged to be sufficiently significant as to prompt NIA support for long-term studies to be coordinated among all three sites.

In 1987, our research group at NIA began a study (Ingram et al. 1990) to evaluate the long-term effects of DR on aging and longevity in rhesus monkeys (*Macaca mulatta*). The study was initiated after much discussion about the question of human relevance and the best approach for addressing it. That discussion generated several relevant conclusions. At that time, a long-term human study of DR was considered impractical for the following reasons: (a) length of time and costs required for such studies; (b) compliance to DR regimens over the long-term; (c) safety of such interventions, particularly for very young and old subjects; (d) disagreement about how to evaluate the effectiveness of any aging intervention.

For these reasons, the decision was made to plan a study utilizing nonhuman primates. The use of a nonhuman primate offered several advantages over human studies, including shorter lifespan and greater control over experimental variables. Environment and diet could be controlled to a very high degree. In addition, a variety of measures, some of them invasive, could be collected longitudinally. Most importantly, the aging phenotype of rhesus monkeys appears so remarkably similar to that in humans (Roth et al. 2004) that findings about DR in this study should apply well to the question of the relevance of CR to human health and longevity.

When fully operational by 1992, the NIA study employed both male and female monkeys (N=120), and included ages of DR initiation that ranged from juvenile, adult, and old groups (Mattison et al. 2003). This range was designed to consider that the effectiveness of DR might be age dependent. At the outset, we were skeptical that DR initiated in old monkeys could be beneficial. The target for DR in the NIA study was a 30% reduction in calories. Because many monkeys were still in a growth phase, how to impose DR was problematic since caloric requirements changed with development. Therefore, dietary amounts provided to each monkey had to be adjusted for age and body weight. The diet was formulated to be highly nutritious incorporating low fat, low protein, high fiber together with extra supplementation of essential vitamins and minerals (Ingram et al. 1990). In general, we have found that rhesus monkeys tolerate the DR regimen very well with no untoward effects (Mattison et al. 2003).

In 1989 investigators at the University of Wisconsin (UW) initiated a similar DR study in rhesus monkeys but focused on initiation of 30% DR in only adult animals (Kemnitz et al. 1993). Their monkeys also appear to have adapted to a 30% DR without any unhealthy side-effects (Ramsey et al. 2000).

Addressing the question about whether DR can increase longevity in rhesus monkeys is a very difficult challenge. The median survival age of rhesus monkeys in captivity is about 25 years and the maximum age has been estimated to be 40 years (Bodkin et al. 2003). The original objective of the NIA study was to rely upon evaluating biomarkers of aging to assess whether aging rate could be attenuated by DR in rhesus monkeys (Roth et al. 1991). A strategy was developed for identifying biomarkers of aging and for assessing their reliability and validity (Ingram et al. 1991). As the study evolved, advice emerging from the gerontological community, including formal input from a Scientific Advisory Committee for the study, shifted the focus away from reliance upon biomarkers of aging for assessing the effects of DR and towards assessing whether this intervention could increase lifespan, reduce disease, and maintain function longer than the control diet. This change in emphasis was consistent with a new NIA initiative designed to evaluate aging interventions in mice (Warner et al. 2000).

Thus, regarding whether DR will increase longevity in rhesus monkeys, the studies at NIA and UW should be able to address this question eventually. The majority of monkeys in both studies are now approaching the median lifespan for the species where the force of mortality increases exponentially.

Preliminary reports from both studies indicate higher survival rates among monkeys in which DR was initiated at adult ages (Ramsey et al. 2000; Roth et al. 1999); however, survival data for aged monkeys in the NIA study currently do not indicate enhanced longevity will be achieved in DR monkeys (Ingram et al. 2005). So, currently, even regarding the question about whether DR will increase longevity in rhesus monkeys, the most informed response is ''we do not know for sure.''

This statement must be balanced against those made in the recent report by Bodkin et al. (2003) who concluded that their results in a study of rhesus monkeys at the University of Maryland (UMD) suggested ''...that dietary restriction leads to an increased average age at death in primates, associated with the prevention of hyperinsulinemia and the mitigation of age-related disease (p. 212).'' This report was intriguing in view of the subject at hand; however, the validity of their conclusion was later addressed. Specifically, Lane et al. (2004) pointed out several methodological issues with the UMD study including the study design, subject characteristics, and statistical methodology, any of which could limit the generalizability of the conclusions offered by Bodkin et al. The primary problem was a statistical one in that the study included only eight monkeys that had been weight stabilized as the DR manipulation, and only three deaths had occurred in this group. Thus, the results were far from conclusive regarding effects of DR on longevity in rhesus monkeys. However, regarding the possibility of DR enhanced longevity in rhesus monkeys, the data do appear supportive of our statement that ''we think so.''

Moreover, the data on health and function emerging from both the NIA and UW studies as well as the UMD study also would support the conclusion that enhanced longevity should be expected in rhesus monkeys. As these results have been reviewed in previous publications, we will not review them here; however, it is clear that several measures of health including indices of risk for cardiovascular disease and diabetes are enhanced in monkeys on DR (Bodkin et al. 2003; Hansen et al. 1999; Mattison et al. 2003; Ramsey et al. 2000; Roth et al. 2004). Importantly, these indices, such as blood pressure, blood lipids, glucose tolerance, and insulin sensitivity, have also been reported to be improved in humans who practice DR (Fontana et al. 2004; Meyer et al. 2006).

A general conclusion from the primate studies, human and nonhuman, is that DR produces physiological, metabolic, and hormonal effects in higher species similar to those observed in rodents on DR. Clearly the changes in body composition are similar among mammalian species placed on DR, including reduced body weight and adiposity. Given the proven relationship between body weight and adiposity to general mortality and morbidity in humans (Samaras et al. 2002; Shiner and Uehlinger 2001), these data would support the belief that DR should enhance longevity in humans. In addition, when imposed early in life, DR also produces shorter monkeys with later reproductive development. Indices of shorter stature and later development are also predictive of longevity in humans (Samaras et al. 2003). Moreover, key metabolic and hormonal indices, such as reduced body temperature and triiodothyronine (T3) as well as reduced insulin, that are observed in rodents on DR are noted in rhesus monkeys on DR (Mattison et al. 2003; Roth et al. 2004), and apparently are also observed in humans in the CALERIE study (Ravussin, personal communication). As additional support for our belief that DR should increase longevity in humans is the previous report from NIA that lower levels of insulin and body temperature were predictive of better survival among healthy men involved in the Baltimore Longitudinal Study of Aging (Roth et al. 2002). Additionally, epidemiological studies support the view that lower calorie diets in humans can decrease the incidence of many age-related diseases, including cardiovascular disease, diabetes, cancer, and neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Mattson 2005; Roberts and Barnard 2005). In regard to the latter disease, a recent report demonstrated that DR in rhesus monkeys could attenuate the effects of a neurotoxin in a model of Parkinson's disease similar to observations in rodents (Maswood et al. 2004).

Thus, all evidence emerging from human and nonhuman primate studies are suggestive that DR should enhance longevity in a wide range of species including humans. However, even if the NIA and UW studies had run their course and all data were collected to allow a definitive conclusion that DR extended longevity in rhesus monkeys, there would remain lingering questions about whether similar results could be expected in humans. Therefore, we offered our response that ''we think we will never

know for sure.'' No doubt, there will continue to be epidemiological studies examining a variety of human populations presumably on nutritious, low calorie diets that will address this question. However, we do not anticipate that any life-long experimental study of DR will ever be attempted. The same issues that motivated the NIA study of DR in rhesus monkeys will endure. Such a human study of DR will be far too expensive and too impractical to undertake. However, if the CALERIE study and similar, well-planned experimental studies emerge and move forward, we will gain considerable information on whether DR in humans can reduce established risk factors for disease and perhaps even the incidence of certain age-related diseases, such as cardiovascular disease, diabetes, and cancer. We will also gain considerable information on whether long-term DR can maintain function later into life. Such indices might include vision and audition, motor performance, and cognition. These findings alone would have major clinical significance above and beyond definitive evidence that DR could increase longevity in humans.

Beyond this academic exercise of considering whether there will ever be definitive proof that DR can enhance longevity in humans, we would argue that the more compelling discussion should be whether basic mechanisms of DR can be discovered and if such discoveries can lead to the development of effective DR mimetics (Hursting et al. 2003; Ingram et al. 2004; Roth et al. 2005; Sinclair 2005). Despite the recent evolutionary arguments that have been made to the contrary regarding the relevance of DR to longer lived species (de Grey 2005; Phelan and Rose 2005), we have become increasingly convinced that response to DR is a fundamental biological program inherent in nearly all species. Consistent with the views posited in the disposable soma theory of aging (Shanley and Kirkwood 2000), we would contend that virtually all organisms, including humans, would need to have evolved a strategy to cope with limited caloric resources. This strategy would increase the efficiency of caloric utilization by directing energy away from programs of growth and development and towards programs for protection. Discovery of the genetic programs involved in these strategies could advance our understanding of many important clinical issues, such as programs controlling growth, development, body composition, metabolism, reproductive function, stress resistance, and cancer control. The greatest upshot could be the discovery of compounds to increase longevity in humans (Hursting et al. 2003; Ingram et al. 2004; Roth et al. 2005; Sinclair 2005). However, even the field of DR mimetics continues to grow and spin-off possible clinical interventions, we will never know for sure whether any candidate compound will increase human longevity. We would have to be satisfied with the level of proof currently affecting conclusions about the effectiveness of DR in humans, specifically, whether risk factors for disease would be lowered and measures of function maintained.

Thus, we maintain, ''we will never know for sure.'' Moreover, regarding the question of relevance of DR to humans, there remain several caveats. The age dependence of effects would be highly relevant. The effectiveness of DR in older rodents remains a controversial issue (Spindler, 2005). It is likely that DR would be most effective in immature humans and lose its effectiveness in older humans, even to the point of becoming detrimental if maintained late into life. The NIA study of DR in older rhesus monkeys will be able to address this possibility to some degree. There could also be gender differences to consider. In the NIA study, gender differences do appear in response to DR in a number of variables, including body composition (Mattison et al. 2003). Gender differences in response to DR have been noted in other species as well (Magwere et al 2004). Thus, research would have to be directed to these issues of age and gender. In addition, the level of DR requires investigation and might have to be adjusted at different ages. Concern about effects on bone density and reproductive function again would require additional research. In a very nice review, Dirks and Leeuwenburgh (2006) have raised other health concerns about long-term DR in humans, including hypotension, cold sensitivity, loss of strength and stamina, slower wound healing, and psychological conditions, such as depression, emotional deadening, and irritability.

In summary, many questions and caveats will clearly affect future DR research, particularly regarding its application to humans. However, because of the compelling and robust nature of findings regarding DR as an aging intervention coupled with the progress being made in identifying mechanisms of DR and developing DR mimetics, we have no doubt that this research area will continue to expand and remain highly relevant regarding our

understanding of how and why aging occurs in all species, including humans.

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