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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.