Commentary on Recently Published Articles

A Comment on the Comment: Relevance of Nonhuman Primate Dietary Restriction to Aging in Humans

Noni L. Bodkin,1 Heidi K. Ortmeyer,1,2 and Barbara C. Hansen1,3

1Obesity and Diabetes Research Center (ODRC), School of Medicine, Department of Physiology and
2Department of Medicine, Baltimore VA-GRECC, University of Maryland, Baltimore.
3College of Medicine, University of South Florida, Tampa.

In rodents and many other species, dietary restriction (DR), also known as calorie restriction, has been shown to prevent and/or delay the onset of many age-related diseases, and maintain healthy physiological function during the aging process. Although Lane and colleagues agree that our published report (1) provides a preliminary interesting assessment of the relevance of DR to human aging, they have also raised issues which we would like to address.

Dr. Lane and his colleagues have suggested that our study should have used "controls typically used in rodent DR studies." However, our study was initiated after more than 10 years of study in feeding regulation, body weight, and obesity in monkeys. Therefore we had a strong knowledge base from both research and experience that the "rodent" approach would not be appropriate to maintaining healthy DR in monkeys.

Primates (both nonhuman and human) have a wide range of calorie requirements, and even at the same lean body mass, individuals differ substantially in energy expenditure. Thus, an approach to DR that does not take into account these individual differences is destined for failure.

We agree that there are very important questions to be raised about the "control group" (in this case, the ad libitum-fed monkeys) including the following: 1) What diet and nutritional constraints should be placed on the control group? (We chose fully ad libitum feeding conditions. Lane and colleagues indicate in prior publications that they have chosen to compare two groups of monkeys, both of which are calorie restricted; one, however, is more restricted than the other.) 2) Shall the control group be expected to have a significant incidence of overweight and obesity similar to 60%-70% of the U.S. population, particularly in middle-aged humans, who also have ad libitum food availability? (We believe the answer is yes, and therefore permitted individual monkey body weights in the ad libitum-fed group to develop without constraint and without dietary manipulation.) 3) Shall a large proportion of the control group be expected to develop type 2 diabetes? (We believe the answer is yes—allow the control group to progress naturally with regard to aging and aging-related diseases). Thus, we acknowledge that the issues with the "control" group are obviously much more complex than the simple question of number of animals per group.

Although the study design may appear incongruent to some gerontologists, in fact, the large number of control animals and fully ad libitum feeding allowed the control group to emerge (as in humans) into the full range of metabolic possibilities—from lean metabolically normal aged monkeys to monkeys of all ages with various degrees of adiposity, prediabetes, and overt type 2 diabetes. We believe that the optimal control group must be many-fold larger than the DR group (in this case the ratio of ad libitum-fed monkeys to DR monkeys was approximately 15:1) because of the diversity of metabolic outcomes that can be expected with ad libitum feeding. In contrast, DR produces substantially greater homogeneity with regard to metabolic outcomes.

Dr. Lane and his colleagues appear to be seeking differences in the ad libitum-fed primates versus the DR primates, prior to the monkey's entry to the Obesity and Diabetes Research Center (ODRC). However, all monkeys were screened before entry to the ODRC; this screening included gathering background information from the attending veterinarian at the originating facility and reviewing the medical records of the monkey. All monkeys were research naive and tuberculosis negative and had a normal chemistry/hematology profile (indicating normal electrolyte, liver, and kidney function) and normal laboratory behavioral characteristics. Therefore, the ad libitum-fed and DR monkeys differed little, if at all, with regard to health parameters and history.

As stated, all monkeys were individually housed and maintained under identical laboratory conditions (including light cycling, temperature, and humidity) over the duration of the study, and decisions concerning treatment of disease and euthanasia were consistently made by the same principal investigator in consultation with the clinical veterinarian. Therefore, procedural and methodological variables were very well controlled. Concerning questions about the diet, the monkeys were maintained on standard primate chow. Only 16 of 109 monkeys received Ensure, and it was used only briefly to obtain exact calorie intakes. The Ensure diet contained 31% fat, which cannot be considered "high fat," particularly when used for only a brief period in the entire life of the primate. We determined and reported that the ad libitum calorie intake did not differ for individual monkeys between the two diets (2).

Food intake by all monkeys was determined a minimum of twice daily throughout this study. As described, we adjusted the calorie intake of each DR monkey on a weekly basis to maintain stable adult body weight (this is similar in humans to a “bathroom scale” method of feedback). There was no significant weight gain or loss in the DR group, as food intake was titrated to maintain a lean healthy body weight. In contrast, ad libitum-fed monkeys always had food available, much like many humans today. Many, but not all, of the ad libitum-fed monkeys gained weight over the years (as also happens to ad libitum-fed humans in middle age).
The comments by Lane and colleagues concerning the body weights and body fat of ad libitum-fed adult rhesus monkeys were not correct. Our adult monkeys have ranged in body weight from 8 kg to 31 kg. The individual body weight of each ad libitum-fed monkey was self-determined; therefore, the ad libitum-fed monkeys provide the fully relevant group for comparison to the weight-stabilized calorie-titrated DR group.

The prior commentary (10) also expressed concern about the differences between the ad libitum-fed and the DR groups, specifically with regard to adiposity and insulin levels. As noted in the published paper: “All the monkeys were metabolically well-characterized, including age, weight, fasting plasma insulin, fasting plasma glucose, glucose tolerance, acute insulin response, and insulin sensitivity. We sought to determine if there were differences in the survival of the two groups of monkeys based on AL vs. DR conditions, and to identify the major morbidity and causes of death in each group, including associations with metabolic factors. The metabolic differences between the subgroups of AL monkeys allowed the statistical testing of each subgroup vs. the DR group . . .” (1). Furthermore, the additional comparisons were requested by one of the original reviewers of the manuscript, and we followed that suggestion to include the various metabolically defined subgroups in Table 1 of our article.

By analysis of subgroups (e.g., those with hyperinsulinemia), we determined and reported that “… the risk of death for a hyperinsulinemic monkey was 3.7 times higher (p < .05) as compared with a DR monkey of the same age. Comparison of the AL-fed monkeys and the DR monkeys, after adjusting for baseline body weight, fasting plasma insulin, fasting plasma glucose, and peripheral insulin sensitivity (M), showed that the risk of death was decreased by 7% per unit increase in insulin sensitivity . . .” (1). DR has been shown to lead to improved glucose utilization in rodents (3) and in primates (4–9). Indeed, as our studies and those of many others (including Lane and colleagues) have shown, the effects of DR to improve glucoregulation and to support healthy insulin sensitivity appear to be important factors which decrease age-related morbidity and may lead to postponement of the average age of death.

Lane and colleagues expressed concern that the animals’ age of entry into the study was variable. The published paper noted that the data in the survival estimate from the Cox proportional hazards model were left truncated; therefore, a monkey contributed to the survival estimate at the age of entry to the laboratory. The secondary analysis was important to compare metabolic subgroups and diet treatment. The results of this analysis, including the confidence intervals and the power analysis, were clearly stated as preliminary and were included not as a final authority on these issues but as preliminary findings of interest to the research field.

Regarding the normal monkeys, they were defined post hoc as those monkeys who had maintained normal fasting glucose and normal fasting insulin levels. Therefore, it is not surprising that the ad libitum-fed monkeys who remained metabolically normal would not be significantly different from the DR monkeys (who were also metabolically normal), whereas the ad libitum-fed monkeys who developed age-related diseases (obesity, hyperinsulinemia, dyslipidemia, and/or diabetes) were more likely to die at a younger age than the DR monkeys. These findings were possible due to the large number of ad libitum-fed monkeys included in the study.

To our knowledge, our paper was the first to present detailed findings and analyses regarding the age at death, major cause of death, and organ pathology present at death for both ad libitum-fed and DR primates who died during study. We believe that this pathology information is valuable to the scientific community and can assist greatly in the design of future studies of the mechanisms by which DR leads to delayed onset of age-related diseases and decreased morbidity.

Lane and colleagues questioned the relevance and applicability of our findings to humans and to the likely effects of DR in humans. Ad libitum food intake is the normal practice of most Americans today and obesity-associated disorders in the United States are estimated to cost billions of dollars annually, with untold effects on decreased quality of life to millions of affected individuals. The consequent effects of obesity in humans on increased morbidity and age-related diseases are therefore clear. We believe that the weight-clamp protocol described in our study is ideally suited to humans who can use a bathroom scale to encourage the prevention of obesity and improve health.

The current study of DR in primates provides important information on the causes of death in primates under ad libitum feeding versus DR, and the possible extension of the average age of death in primates that maintain a lean adult body weight free of obesity. We propose that the number of monkeys and the richness of data collected over many years of study during the life of the primate and at death provide important insight into the relationship of diet, metabolic disorders, and aging with a clear and provocative relevance to healthy aging in humans as well.

Address correspondence to Noni L. Bodkin, PhD, Obesity and Diabetes Research Center (ODRC), School of Medicine, Department of Physiology, University of Maryland, Baltimore, MD 21201. E-mail: nbodkin678@aol.com

REFERENCES