Nonhuman primate advances in nutrition research$^{1,2}$

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Abnormal or disturbed nutrition levels cannot be experimentally tested in humans to determine the consequences of varied maternal nutrition on fetal and neonatal or later outcomes. The role of undernutrition or disturbed nutrition in humans must therefore be limited to such testing as can be done under well-controlled conditions in nonhuman primates (NHPs). The similarities of the gastrointestinal and the endocrine/metabolic systems between humans and NHPs ensure that the results of such studies performed in NHPs are highly relevant to human nutrition. Such key comparisons of similarities between human and NHPs include the determinations that many key molecules are effectively identical across these primate species, including, for example, the insulin molecule (identical) and C-peptide (single amino acid substitution), and many other features that allow especially high translational potential for results obtained in NHPs, as summarized in Table 1.

Two articles in this issue of the Journal (3, 4) report on nutritional studies carried out in NHPs, and both bring challenging new evidence related to hypotheses of nutritional consequences for human health. Uniquely, both studies were “opportunistic,” taking positive advantage of the existence of ongoing long-term primate studies to superimpose additional focused questions.

Kavanagh et al (3) performed a well-controlled study of the consequences of fructose feeding and found that in NHPs with calories controlled to be identical in 2 groups, fructose itself was not obesifying and did not produce hepatic steatosis. Thus, they concluded that the negative health consequences of fructose ingestion may occur only in the setting of excessive caloric intake. One diet used was very high in fructose (~25% of calories), whereas both the high-fructose and the control diets were relatively low in fat (17% and 13%, respectively). It should be noted that the sources of fat in the diets of the 2 groups were highly disparate (vegetable oils and butter compared with pork fat) and the sources of protein were completely different. The calories per kilogram of body weight provided to the NHPs also differed by >10%. Thus, conclusions must be drawn carefully from 2 very different diets not solely differing in the source of carbohydrate. In the Kavanagh et al study, 17 monkeys fed a high-fructose diet for 3 mo to 7 y had succumbed to non–diet-related issues and their livers became available for histologic examination. Similarly, 10 control monkeys fed the standard primate diet also had livers available for evaluation. The outcomes must be viewed with some caution because the fructose-fed monkeys were significantly older than the controls (middle-aged compared with elderly), and they weighed significantly more as well. Thus, the findings related to diabetes cannot yet be accepted because both weight and age strongly influence the onset of type 2 diabetes in both humans and monkeys.

In a second study also reported by Kavanagh et al (3), 2 monkey groups were prevented from gaining weight by a stable calorie allotment of 70 kcal · kg$^{-1}$ · d$^{-1}$; fructose was fed acutely for 6 wk, and liver histology was compared with control monkeys via surgically obtained liver biopsies. This is clearly not a study that could be performed in human subjects, but it is highly relevant to the consequences of high fructose intake in humans. Again, there was no significant increase in hepatic steatosis with the fructose feeding. Interesting hypotheses were generated, implicating possible microbial translocation that produced higher endotoxin concentrations in the fructose-fed monkeys. There was, however, no change in the microbiome induced by the fructose feeding. This study provides an excellent model for designing and performing further mechanistic studies to understand the roles of this important nutrient in the human diet and follows on a previous study of fructose feeding in primates (2).

The second NHP study in this issue, by Keenan et al (4), is an example of the evaluation of a nutritional intervention during pregnancy and lactation on fetal and early infant outcomes, and is a study that could never be performed in human subjects. In this study, 32 female baboons were assigned to 2 cohorts, one ad libitum fed and the other restricted to reduced caloric intake during both pregnancy and lactation. The 16 restricted mothers delivered 7 offspring (3 females), and the 16 ad libitum–fed control mothers delivered 12 offspring (8 females). Because this was an opportunistic study, the young were tested over a very wide age range (2.6–5.1 y, possibly equivalent to testing children once between their 7th and 15th birthdays). Because of the small sample size and differential distribution of sexes, age stratification was not possible in the analysis. In a fascinating approach, the investigators appear to have successfully adapted for baboons a behavioral psychology test used in humans (the progressive ratio task of the Cambridge Neuropsychological...
appeared to be increased variability in testing behavior and in divided and analyzed by sex. Interestingly, the primary effect finding and likely an artifact of the small sample sizes when 3 female baboons in the present study, which is also a puzzling sentence and attention were decreased across sessions only in the excessive arousal was seen only in the control group. Persistence and attention were decreased across sessions only in the 3 female baboons in the present study, which is also a puzzling finding and likely an artifact of the small sample sizes when divided and analyzed by sex. Interestingly, the primary effect appeared to be increased variability in testing behavior and in activity level and less emotional arousal, which were hypothesized to be the result of early undernutrition (1). The offspring of deprived primate mothers showed low arousal, and excessive arousal was seen only in the control group. Persistence and attention were decreased across sessions only in the 3 female baboons in the present study, which is also a puzzling finding and likely an artifact of the small sample sizes when divided and analyzed by sex.

Clearly, such findings are of concern and deserve to be replicated and examined further. Importantly, such replications should address the conditions regularly confronted by clinicians in managing pregnancy; for example, in overly obese or overly thin mothers. The study raises a warning flag concerning the manipulation of calorie amounts during pregnancy, but the findings are not sufficient in themselves to be conclusive. NHPs are likely the only model that can produce findings relevant to humans related to the consequences of pregnancy-related manipulations of food intake.

Keenan et al (4) titled their article using the words “poor nutrition”; however, there are many ways that maternal nutrition may not be optimal. What constitutes “poor” compared with “under” nutrition? These terms cannot be used interchangeably either in the design or in the interpretation of such studies. Essential to future NHP nutrition and pregnancy trials is isolation of the component or components of nutrition that are under study, the time periods of insult (fetal, early infancy, childhood), and the timing of outcome evaluations. An analysis of mediating effects is essential to supporting or refuting hypotheses of nutritional effects, and the present study identified itself as having an insufficient sample size to examine this. Studies either to confirm or to refute the role of fetal nutrition in neurodevelopment will always be difficult in humans due to the many confounding and often immeasurable correlates, such as low income, substance use, and physical or mental problems of the mother. The hypothesis that attention-deficit/hyperactivity disorder in children is a result of maternal nutritional underfeeding requires much further study, and the baboon model appears to be ideal for examining this further. It is likely that the only interventional studies in humans will have to be limited to supplemental or enhancement of nutritional features and of course not be restrictive interventions. Thus, greater investment in primate studies of the nutritional consequences of fetal and neonatal nutritional insults together with preventive or therapeutic interventions in these well-controlled and human-like models are to be encouraged.

The author had no conflicts of interest.

REFERENCES