

## The NIA and Wisconsin Rhesus Calorie Restriction Studies – Some Comments

Mark F. McCarty, Catalytic Longevity, markfmccarty@gmail.com

*The National Institutes of Aging study of calorie restriction in rhesus monkeys surprisingly failed to observe a longevity advantage in the severely restricted animals. This may reflect the fact that, in this study (as contrasted to the Wisconsin rhesus study which did observe a longevity advantage in restricted animals), both groups were calorie restricted – albeit the control group only to a modest degree sufficient to prevent obesity and metabolic syndrome. The modest calorie restriction of the monkeys in the control group might be analogized to that of Okinawans during the mid-twentieth century, who now enjoy a significant advantage over Americans with respect to both average and maximal longevity. Jointly, the NIA study and the Okinawan experience suggest that a modest degree of calorie restriction may benefit longevity in humans and primates, but that more severe restriction may provide little if any additional benefit. Hence, the modest calorie restriction likely achievable with carb-concentrated diets, when complemented by health-protective food choices, might achieve about as much longevity benefit as humans can attain by dietary measures alone.*

The discrepant results of the rhesus calorie restriction studies conducted at the National Institutes of Aging (NIA) and the Wisconsin National Primate Research Center (WNPRC) have caused perplexity and perhaps a measure of consternation among advocates of calorie restriction. Here are some pertinent comments:

**Study Design Differences** – A key difference in the design of these two studies is that the control group in the WNPRC study truly received ad libitum feeding – they were allowed to eat whenever they wished, as much as they wished, not unlike many modern Americans – whereas the control monkeys in the NIA trial received fixed daily calorie allotments intended to protect them from obesity. So, in effect, the NIA study compared monkeys who were mildly calorie restricted with those who were severely calorie restricted.

Ad libitum feeding, as used in the WNPRC study, is likely to result in overweight and its attendant complications – metabolic syndrome. Some health authorities have referred to metabolic syndrome as “accelerated aging”. So the calorie-restricted monkeys in the WNPRC study were compared with monkeys who were at relatively high health risk owing to calorie overconsumption. It’s not surprising that they enjoyed superior survival – whereas no significant difference in survival has emerged between the two groups of monkeys in the NIA study.

Another key difference in study design is that all of the monkeys in the NIA study received a healthy diet – essentially a whole-food diet rich in phytochemicals and omega-3 and low in added sugars or oils – whereas the monkeys in the WNPRC study received diets laced with added sugar and corn oil. Intriguingly, so far 5 of the monkeys in the NIA study (4 in the restricted group, and 1 of the controls) have achieved an age in excess of the previously reported maximal lifespan of rhesus monkeys, 40 years. Arguably, this may reflect an interaction between a mild or more substantial calorie restriction and health-protective food choices.

The authors of the NIA study also note that their monkeys were more genetically diverse, whereas the monkeys in the WNPRC study were all obtained from a single colony in India. Whether this was key determinant of the discrepant outcomes is unclear.

**Health Outcomes** – So far, in the NIA study, the monkeys calorie-restricted at an early age are enjoying notable protection from cancer – none of them have yet developed cancer, as opposed to 6 control animals enrolled at a young age. The calorie-restricted monkeys enrolled at a more advanced age are however about as prone to cancer as their control cohorts. As might be expected, diabetes so far is less common in the calorie-restricted group – though not absent.

What really stands out is the fact that, in the NIA study, the calorie-restricted group is not less prone to cardiovascular (CDV) disease – indeed, there is a trend toward more such disease in the restricted group. This tends to bear out our contention (see p. 16 of the essay *Could Carbohydrate -Concentrated Diets Mimic Calorie Restriction in Slowing the Aging Process?* posted on this website) that calorie restriction per se is not inherently beneficial for CDV health, in light of the fact that growth factor activities down-regulated by calorie restriction (IGF-I and insulin) act directly on the vascular endothelium to provoke release of protective nitric oxide. The fact that calorie-restricted monkeys in the WNPRC study were less likely than control monkeys to experience CDV disease probably reflects the fact that the ad libitum fed monkeys were much more prone to metabolic syndrome, which quite notably increases CDV risk. The control monkeys in the NIA study were unlikely to experience this problem.

In regard to the impact of IGF-I on cardiovascular health in humans, it is notable that Laron dwarves, in whom circulating IGF-I levels are dramatically decreased owing to a genetic defect in their growth hormone receptor, appear to be almost immune from cancer, but don't enjoy increased average longevity relative to other humans owing to increased risk for cardiovascular disorders.

Importantly, these findings do not imply that dietary choices can't have huge impacts on CDV risk. The Framingham study indicates that people who maintain low LDL levels throughout life – analogous to those seen in many quasi-vegan Asian or Third World populations – are at extremely low risk for coronary disease; such low risk was also observed in these quasi-vegan populations, and whole-food plant-based diets are clearly therapeutic in patients with pre-existing coronary disease. On the other hand, vegan diets do not inherently confer protection from stroke, and stroke is indeed highly prevalent in many Asian cultures which salt their food heavily. The good news is that stroke appears to be uncommon in societies where salt consumption is relatively low and potassium consumption relatively high; so stroke may also be inherently preventable by optimal dietary choices.

**Comparisons to Mice** – When mice are protected from predators and infectious agents in the context of longevity studies, their predominant cause of death is cancer. Hence, the increase in average and maximal lifespan seen in mouse calorie restriction studies is primarily reflective of cancer prevention. In mice, calorie restriction notably decreases circulating IGF-I levels; diurnal insulin levels are also decreased, and the bioactivity of the circulating pool of IGF-I is decreased by an up-regulation of hepatic production of IGF-BP-1, an IGF-I antagonist. This marked reduction in plasma growth factor activity tends to boost apoptosis (cellular suicide) in pre-cancerous cells, restrain cellular proliferation, and aid control of oxidative stress – effects which likely are key mediators of the prevention or postponement of cancer associated with calorie restriction in mice.

Surprisingly, in humans, calorie restriction *does not* lower plasma IGF-I levels – albeit IGF-I bioactivity should be somewhat lower owing to increased IGFBP-1. This suggests that calorie restriction might be less effective for cancer prevention in humans than in mice. So far, I have found not data pertaining to the impact of calorie restriction on IGF-I levels in rhesus monkeys. However, it is notable that a plant-based diet of moderate protein content – entailing a modest degree of essential amino acid restriction – has been shown to decrease IGF-I levels in humans, by about 30%. Arguably, this phenomenon helps to explain why age-adjusted death rates from “Western” cancers were many-fold lower in lean quasi-vegan Third World cultures in comparison to Western society during the 20<sup>th</sup> century.

If rhesus monkeys are similar to humans with respect to the impact of calorie restriction on IGF-I levels, it would be reasonable to predict that calorie restriction would have a less dramatic impact on cancer risk than it does in mice. Moreover, in both humans and rhesus monkeys, CDV disease is a major cause of mortality – in marked contrast to mice. As we have seen, calorie restriction per se does not appear to confer much protection from CDV disease – save to the extent that it prevents metabolic syndrome. These considerations may help to explain why the impact of calorie restriction on average and maximal longevity in primates can’t be expected to be nearly as dramatic as it is in most strains of mice.

It should be noted that the 30% level of calorie restriction tested in the rhesus studies is wholly impractical for humans – even the most dedicated practitioners of calorie restriction would be hard-pressed to achieve this through voluntary choice. And it is quite conceivable that 30% restriction is too extreme for primates. Longevity tends to decline in many strains of rodents as calorie restriction surpasses the 40% level – who is to say that this threshold may not be lower in primates? Also to be noted is the fact that calorie restriction was actually a bit less severe in the WNPRC study, since these monkeys were restricted relative to the excess consumption of the ad libitum-fed controls.

**The Okinawan Experience** – Arguably, the experience of the Okinawan people over the last century is more relevant to pro-longevity researchers than are the recent rhesus monkey studies. A remarkable series of investigations by Willcox and colleagues have shown that the current cohort of very old Okinawans, for about half of their lifespans, ate a diet that was modestly calorie restricted – by about 11% relative to the calorie requirement for their typical BMI of 21 calculated from the Harris-Benedict equation – and currently enjoy an average and maximal lifespan about 5% longer than that of Americans. It is also notable that the traditional Okinawan diet was almost entirely vegan – only about 4% of calories from animal sources, primarily fish – with protein constituting only 9% of total calories; this would have been expected to achieve a notable down-regulation of IGF-I levels. Moreover, their diet consisted mostly of whole foods, with yams as the dietary staple; yams are low in glycemic index and caloric density, and high in potassium – features which contrast markedly with those of the white rice favored on the Japanese mainland. One of Willcox’ most intriguing observations regarding this cohort of Okinawans is that their age-related decline in serum DHEA – considered a marker of the aging process – is considerably lower than in Western controls, suggestive of a genuine slowing of the aging rate.

The slightly calorie-restricted monkeys in the NIA study, enjoying a whole-food diet which is primarily plant based aside from some fish, seem remarkably reminiscent of the classic Okinawans! Perhaps the results of this study imply that it might be difficult for humans to top the longevity benefit conferred by the traditional Okinawan diet - at least by dietary means alone.

**Relevance to Carb Concentrated Diets** – It seems likely that, owing to superior appetite control associated with long periods of low insulin and stable glucose levels, many people eating carb-concentrated diets are indeed achieving a modest degree of calorie restriction – possibly analogous to the 11% restriction which the Okinawans practiced via will power or scarcity. It would be desirable to confirm this in clinical studies. Optimizing the calorie restriction achieved with such diets might require refraining from over-consumption of high-fat foods during accessory low-carb meals, however, as the Hellers advised; not all of the Hellers’ patients lost weight on a carb-concentrated regimen. If the food choices employed with such a diet are primarily whole food and plant-based – or at least Mediterranean (featuring animal products low in saturated fat, as also advised by the Hellers) – such a diet might represent a practical way of achieving all or most of the health and longevity benefits associated with a traditional Okinawan diet, without the necessity of calorie-counting. Hence, a carb-concentrated diet featuring health-promoting whole foods arguably might provide about as much life extension benefit as humans could expect to achieve via dietary choices.