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Continued from Calorie Restriction In Monkeys

It has been established that CR in rodents retards the development of many age-related chronic diseases. Therefore, in addition to monitoring physiological effects of CR in the monkeys, we have also followed several biomarkers that might be predictive of disease risks in humans. This approach is consistent with our objective of determining the relevance of CR to human aging.

Although none of our monkeys has developed symptoms of adult onset (Type II) diabetes, CR is exerting effects that would appear to put the animals at a lower risk of this disease...that is, insulin sensitivity remains more stable compared with controls. Levels of insulin in the blood go up with age in monkeys, but are reduced in those on CR. When insulin concentration in the blood is measured during a glucose tolerance test, the peak levels are greatly reduced in CR monkeys compared with controls.

Not only do these observations on glucose and insulin provide evidence of reduced risk of diabetes, we now believe that these changes are important components in the anti-aging mechanism involved in CR.

"Human studies of calorie restriction conducted since the initiation of our monkey project indicate that humans likely respond to long term CR similarly to what has been observed in primates and rodents."-- From left, authors DONald K. Ingram, George S. Roth and Mark A. Lane

We have also considered cardiovascular risk factors in collaboration with Dr. Roy Verdery of the University of Arizona. Although we have noted no significant differences between control and CR monkeys in total cholesterol levels, other parameters of the lipoprotein profile have shown differences that would indicate lower risks of cardiovascular disease, including lower levels of triglycerides, increased levels of high-density lipoproteins (HDLs), and reduced blood pressure.

How about aging? A general consensus exists among gerontologists that CR retards the rate of aging in laboratory rodents. This conclusion is based on the large collection of data on mortality, disease, and functional effects altered by CR. The challenge in initiating our study of CR in monkeys with a life span of 40 years was that we would likely not have the time or resources to collect sufficient data on mortality or disease incidence. Instead, we decided to rely upon functional assessments-so-called biomarkers of aging-to determine if CR slows the rate of aging in rhesus monkeys.

There are many opinions, but no consensus, among gerontologists about what constitutes a biomarker of aging. Many parameters obviously show increases or decreases with age, yet it is very difficult to conclude that a specified collection of these can be used to assess whether an intervention such as calorie restriction has altered the rate of aging. There is a concerted effort to arrive at this consensus for use in rodent models.

Working with the rhesus monkey, we were faced with precious little data to examine age-related changes. The literature on aging in any nonhuman primate is sparse. (In shorter-lived rodents, candidate biomarkers can be validated against mortality data derived from control and CR groups.) However, it stands to reason that if a parameter purports to reflect the rate of aging, then the rate of age-related change should be slower within a CR group compared with controls. If true, this rate of change is truly predictive of differences in life span.

Meanwhile, we have been successful in identifying several possible candidate biomarkers of aging. Two are the enzyme alkaline phosphatase and the steroid dehydroepiandrosterone-sulfate (DHEAS), which can be measured in blood samples. In the control group of male monkeys, both parameters show marked age-related declines...and these declines have been slowed down by CR.

Alkaline phosphatase is produced primarily by the liver, and is important for bone formation. DHEAS, produced in the adrenal gland, serves as a source for the production of many other related hormones, such as estrogen and testosterone. Many recent articles have appeared touting the possible anti-aging effects of this hormone.



Is it safe to conclude that CR has slowed the rate of aging in our monkeys? For several reasons, as measured by alkaline phosphatase and DHEAS, the data are intriguing but not conclusive. First, of course, only two variables are represented. To answer the question, we would want to evaluate data across a much wider range of function. Secondly, even though the rate of decline in these parameters is divergent, we do not know that the slowdown in the decline of either parameter will be predictive of longer life, since we do not yet know that our monkeys on CR will live longer.

Although we have no conclusive evidence that calorie restriction is retarding the rate of aging in our monkeys, we are encouraged by results produced so far. Many parallels exist between the physiological responses of rodents and monkeys to CR, and several parameters of aging appear to be retarded in CR monkeys compared with controls. In addition, human studies of CR conducted since the initiation of our monkey project indicate that humans likely respond to long-term CR similarly to what has been observed in primates and rodents.

Moreover, the promising results of our study, in conjunction with the exciting new results of other studies, have suggested the existence of fundamental cellular mechanisms affected by CR that might regulate the rate of aging in a wide range of species. Our studies of CR in monkeys have been important for exploring the possible relevance of this anti-aging treatment to human aging, as well as pointing to possible mechanisms that might be exploited to reap the potentially beneficial effects of calorie restriction without actually having to endure such a tough dietary regimen.

These are exciting times for gerontologists who have long been interested in the CR paradigm as a tool to understanding processes of aging.

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Because of the parallels that have emerged between findings in rodent and monkey studies, our current view is that calorie restriction likely operates through some very basic and universal mechanisms having to do with energy utilization. Recently, several clues to these mechanisms have emerged. In particular, the discovery and characterization of possible "longevity assurance" genes in a microscopic worm, a nematode called *Caenorhabditis elegans*, have provided great insight into possible mechanisms of CR [Ed.: see "Are Worm Genes the Key to Human Longevity," *Life Extension*, February 1998].

Seeking CR's Benefits Without Its Discomfort

It is exciting to consider whether the mechanism can be identified. Then, perhaps it can be manipulated without having to impose CR, and yet still produce the anti-aging effects that CR imparts.

All organisms need energy to survive. Depending upon their niche, they take up energy from many different environmental sources—from the air, the water, the soil, from the plants and animals that they eat. To be successful in their evolution, each organism must also develop carefully tuned responses for gauging the availability of energy to determine how much they should consume, when it should be consumed, and what should be stored for later use. Based on patterns of energy consumption, there are then decisions to be made about growth and reproduction, as well as further food-seeking behavior.

For many organisms, like *C. elegans*, expectation of low-energy availability, triggered by overpopulation, produces a dormant stage of development called the dauer larva. In this form the organism is small and reproductively immature, but can withstand environmental stressors and can live many weeks longer than it does typically. When the energy environment is more favorable, the organism reverts to its normal form and continues to develop and mature, and then finally shows signs of aging and dies. There are many invertebrates that have similar strategies for dormancy. In mammals, a possible parallel strategy is hibernation.

While CR does not produce a dauer form or a formal state of hibernation in mammals, many gerontologists are intrigued by the parallels and the evolutionary significance of this strategy. We can consider that the mammalian response to CR follows a similar strategy but does not go as far as some species have been equipped to do. What is the evidence for this? Namely, remarkable parallels between the physiological effects of CR and those of hibernation—among them reduced blood glucose, insulin, and white blood cell counts.

Recent genetic studies in *C. elegans* have shed some light on the possibility that CR might operate through a pathway similar to that which controls the formation of the dauer stage. Several genes have been identified that promote longevity in *C. elegans*. When the expression of one of these genes (called *daf-2*) is reduced or mutated, the worm can enter the dauer stage, exhibiting a nearly doubled life span (as determined by the actions of the other genes), compared with worms with the normal gene.

The key to creating the beneficial effects of CR without actually reducing food intake might be found in creating pharmacological "tricks" to fool the energy sensing systems. Such tricks already have emerged in the well established pharmacology of appetite suppression. These drugs act on neurotransmitter systems in the brain that regulate how much we eat. Again, eat less, live longer.

However, more relevant to the effects of CR, we are looking for other pharmacologic interventions that will trick energy sensing systems without affecting appetite. If we can find ways of telling cellular energy sensing systems they are not getting sufficient energy when in fact they are, the cells might turn on anti-aging mechanisms that are observed in calorie-restricted animals.

We are conducting initial studies in which we have fed rats a form of "fake" glucose, called 2-deoxyglucose. 2DG is transported into cells in a normal fashion, and is then metabolized into a different form in which its processing is halted. In effect, the cell takes in all the glucose it wants, but its metabolism within the cell is incomplete. Preliminary results from our laboratory suggest that feeding rats a diet containing 0.4 percent 2DG results in a reduction in body temperature of about 0.5 degrees C, a 30-percent reduction in fasting serum insulin levels, and about a 10-percent decrease in body weight.

The expected outcome of this pharmacologic trick is that certain cellular sensors are bypassed while others are activated. We are, in effect, looking for the mammalian equivalent of the gene that triggers the dauer stage in the worm *C. elegans*. We want to activate a longevity program without really affecting food intake.

Further Reading

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