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## REPORT

Compelling Evidence in Humans' Closest Relatives

Calorie  
Restriction  
In Monkeys

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Restricting the number of calories consumed has proven in lab experiments to increase life span in rodents. In previous issues, Life Extension has presented the findings of calorie restriction pioneer Dr. Roy Walford, as well as actual calorie-restriction practices by humans. But the impact of calorie restriction in human experiments is difficult to gauge, because the test subjects could well outlive the research scientists. Here, we explore first-ever calorie-restriction experimentation on some of the closest relatives to humans, and what leading scientists in the field—the authors of this report—are finding, and hope to find, about calorie restriction's impact on mankind. Part 2 of this series will deal with a similar research project.

"Eat less, live longer," a hallmark observation in aging research, is attracting increased attention. Since the pioneering studies of Clive McCay and colleagues at Cornell University beginning in the 1930s, the calorie restriction (CR) paradigm has been an intriguing and powerful tool for experimental gerontology.

What are the effects of calorie restriction? When mature laboratory rodents (rats and mice) are fed about 30 to 40 percent less than they would normally eat, the following observations almost always occur:

- The CR groups live 30 to 40 percent longer than those animals allowed to eat all they want;
- They have later and lower incidence of many age-related diseases, including cancer; and
- They maintain youthful levels of function later into life.

These observations provide legitimacy to the claim of CR as an anti-aging treatment...perhaps the only one that most gerontologists would permit to be characterized in this fashion.

Calorie restriction is intriguing for several reasons. Most gerontologists view aging as involving highly complex processes resulting from interactions of numerous genes with numerous environmental factors. But the CR paradigm offers the possibility that this treatment impacts upon a few fundamental mechanisms. If these mechanisms were identified, gerontologists might gain great insight into basic processes of aging that can be manipulated through other treatments.

For several additional reasons, calorie restriction offers a powerful tool for experimental gerontology. First, it provides "robust" effects; that is, the same results are generally obtained no matter what strain or species of laboratory rodent is being used, or what type of CR is applied. Manipulation of a particular caloric source, whether from protein, fat or carbohydrates, is not that important for achieving the expected results. The restriction of total calories is the most important factor, as long as the diet is supplied with normal or even enriched amounts of essential nutrients.

Secondly, CR can exert beneficial effects when implemented in rodents at many stages of life (although most gerontologists would agree that these effects diminish the later in life it is begun). And, although most research has been conducted in laboratory rodents, several studies have shown the extension of life span in other vertebrate and invertebrate species subjected to various CR regimens. Examples include water fleas, spiders, and guppies.

Some gerontologists have considered that the response to CR is most relevant in short-lived species such as rodents, whose evolutionary strategy of survival involves rapid gestation, quick development, and a high number of offspring. Such species live in

markedly changing environments and must take advantage of variable resources that are usually determined by seasonal factors. For example, if food is in short supply prior to a seasonal change, it would be "adaptive" (that is, beneficial) for such species to retard their growth and development, and postpone or reduce reproductive activity until food was more abundant.

The effect of this strategy is to activate mechanisms that indirectly retard aging processes and promote longevity. In species such as humans, this strategy might not have evolved.

Nevertheless, several possibilities exist for addressing the relevance of CR to human aging, including studies in humans; however, we chose to conduct our study in nonhuman primates, specifically rhesus monkeys. Under the auspices of the National Institute on Aging, we began our study in 1987 with 30 male monkeys. Over a 10-year period, we have expanded our study greatly to include male and female monkeys across a range of ages. Nearly 200 monkeys are now under investigation. In addition, CR studies in rhesus monkeys have been initiated at the University of Wisconsin and at the University of Maryland, Baltimore.

These studies have yielded important findings regarding questions about both the mechanisms of CR and its relevance to human aging. In short, emerging evidence would support the view that CR effects are relevant to primate species. We see great consistency between rodents and monkeys in the physiologic responses to CR. Because of this consistency in response, we are beginning to believe that response to CR might be a generalized evolutionary strategy for organisms that might invoke similar anti-aging mechanisms through similar signaling pathways.

Why study monkeys? In a genetic sense, rhesus monkeys and humans are closely related. These species share about 95 percent of their DNA in common. Second, rhesus monkeys have a maximum life span of about 40 years, versus 120 years for humans. Thus, the rate of aging in rhesus monkeys should be three times faster in these monkeys than humans, making any age-related differences between control monkeys and those on CR more quickly seen.

But the primary reason for studying a nonhuman primate is the ability to implement experimental control. It would be extremely difficult to conduct well-controlled studies of CR in humans; people tend to go off and on diets, for one thing. We wanted to maintain complete control over the diet to be assured of compliance.

Moreover, human studies would involve the interaction of the treatment with many genetic and environmental factors. In our study using rhesus monkeys, we can control nearly all elements of the environment. The monkeys eat the same diet and live in the same surroundings. Moreover, we were able to assign monkeys to respective control and experimental groups such that any genetic factors would be randomly placed across the groups.

The experimental design of our study included male and female monkeys spread across three basic age cohorts, since we wanted to assess the effects of CR at different stages of life, as well as to examine age differences in a wide range of variables. The groups ranged from juvenile (very young) to late adolescence/young adulthood, and old (20-year-olds, equivalent to 60-year-old humans).

Also, we have monkeys assigned to long-term longitudinal studies, some with more than 10 years of data collected, while other monkeys have been assigned to shorter-term studies. The shorter-term groups have been studied with somewhat more invasive methods, such as the implantation of telemetered devices that transmit data on body temperature and heart rate. The monkeys in the longitudinal study are used for relatively noninvasive procedures that mostly involve taking blood and skin samples on a quarterly basis, or using noninvasive procedures such as bone scans.



The study's CR goal was to reduce the caloric intake of experimental monkeys to 30 percent below what a normal healthy diet would be.

The monkeys are under the constant, watchful eye of veterinarians trained in primate biology who monitor all procedures and evaluate the health of each monkey. All procedures conducted on the monkeys must first be approved by a special committee made up of scientists and veterinarians who monitor and review all aspects of animal care.

The diet that we designed for our study is a variation of the monkey chow that has been used in laboratories for many years. In addition, the diet was enriched with 40 percent more vitamins and minerals than recommended levels to ensure that the monkeys on CR would not be nutritionally deprived.

We also wanted to avoid the possibility of obesity among our controls; hence, we use a low fat diet. Like humans, monkeys will respond to calorically rich, high fat diets, and as such are used as models of atherosclerosis and adult-onset diabetes. A massive literature exists to show the life-shortening effects of obesity and its related health problems in humans and animal models.

The goal of our study was to reduce the caloric intake of experimental monkeys to 30 percent below what a monkey of comparable age and body weight would normally eat, while avoiding obesity. This normal amount of food consumption changes as a function of

age (larger adult monkeys eat more than juvenile monkeys), so that occasional adjustments to the monkeys' diet in the experimental groups have been necessary. Control and experimental monkeys in our study are eating exactly the same diet, but the CR monkeys are receiving less.

As another feature of the study, monkeys in the experimental groups were introduced gradually to the CR regimen. Free access to the diet was allowed for the first month, and the diet was reduced 10 percent each month over a period of three months until the 30 percent reduction was implemented.

Since CR of the type we planned had never been attempted in a primate, we were concerned about keeping the animals healthy. We expected the regimen to retard growth and development in young monkeys, as had been observed in numerous studies in rodents, but it was also our objective to avoid severely stunting all normal processes as might be observed in malnutrition. And indeed, we have produced monkeys of different size and body composition, but we have concluded that the regimen we introduced had no detrimental health effects.

As expected, the calorie-restricted animals weighed less than the control animals, but the body weights of both groups took nearly a year to diverge. CR monkeys gained body weight at a slower rate, and they reached a plateau of body weight as adults that was about 1 to 2 kilograms (2.2 to 4.4 pounds) less than their control counterparts. There were small variations among the various groups.

But it should be clear that our monkeys were not placed on a crash diet. Rather, the implementation of a 30-percent reduction in diet intake produced gradual changes in body weight. Old monkeys tend to be fatter than younger ones, but CR also reduced body fat in them (but not to the same degree). In addition to being lighter in body weight, monkeys that were started on CR early in life also were shorter.

Control males from the younger groups are below 20 percent body fat, while control females are below 15 percent. CR has reduced both genders to less than 7 percent body fat. In addition, CR has also altered the distribution of fat. For example, there is not as much fat around the waist in CR monkeys, a condition that, in humans, is thought to lower the risk of heart disease.

Other developmental events that had been reported in rodents also were seen, specifically the age of puberty. By defining sexual maturity based on steadily high testosterone levels, we observed that CR delayed puberty by about a year. In summary, CR in monkeys produced similar effects on body composition and development to those that had been observed in rodent studies. These findings would not appear earthshaking by themselves. Indeed, one might expect these to occur in any mammal, including humans, subjected to a 30-percent reduction in calories; however, these results were welcomed in that they generated confidence that physiological effects similar to what had been observed in rodents should also be expected in rhesus monkeys.

Another expectation was, if we reduce energy intake in an organism, one might expect to observe metabolic consequences. Again in the monkey model, these changes in energy metabolism have paralleled what had been observed in rodent models. In fact, a reduction in metabolic rate was one of the early, leading hypotheses to explain the anti-aging effects of CR. It had long been recognized that mammalian longevity was inversely correlated with metabolic rate...the lower the metabolic rate, the longer the life span. The free radical theory of aging became the underpinning to this observation. If an organism is metabolizing less oxygen, then it stood to reason that fewer potentially damaging oxygen radicals were produced as part of this normal process.

Metabolic rate is expressed as a ratio: units of oxygen divided by lean body mass. It is clear that on a daily basis CR animals are consuming less oxygen in absolute amounts compared with controls, but since lean body mass is reduced by CR, the metabolic rates appear similar. (Other gerontologists, such as Dr. Richard Weindruch of the University of Wisconsin, have argued that this measure of metabolism ignores other physiological parameters affected by CR. For example, organs that consume large amounts of oxygen are smaller in size in CR animals, and thus differences in metabolic rate associated with CR might be observed only in certain organs.) [Ed.: Life Extension will carry details of Dr. Weindruch's studies in a future issue.] Other physiological measures indicate that the rodent or monkey on CR has altered its basal metabolism. Rectal temperature in male monkeys is reduced by about a degree in experimental groups, compared with controls. Reduced levels of glucose in the blood of CR monkeys became apparent about a year into the study.

Continuation of this article "It has been established..."

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