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Beyond Interventions: Caloric Restriction as a Scientific Model

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Caloric restriction is a major component of most life-style interventions. Beyond its use as an intervention tool, caloric restriction can also serve as a scientific model to study important research questions. Caloric restriction in nonhuman animals can dramatically extend the life span, and this can also be tested in humans. In addition to conducting randomized controlled trials of caloric restriction, there is much knowledge to be gained by studying already existing conditions of very long-term caloric restriction. The Cronies, members from the Calorie Restriction Society, are one such model. In addition to studying biological markers relevant to aging in the Cronies, we can also study them to understand what makes them so successful at long-term eating behavior change. This information is invaluable given the difficulties people from the general population face in adhering to calorie reduction interventions. **Key words:** dieting, caloric restriction, aging.

Calorie restricting interventions are one of the primary intervention tools that researchers in psychosomatic medicine use to affect biobehavioral health. In the life-style intervention tool kit, calorie reduction is as central and ubiquitous as the Phillips screwdriver. We use it to induce weight loss in the those who are overweight and obese (1–3). We use it to treat diabetes symptoms (4). We use it to improve cardiovascular and other health outcomes (5,6). In some cases, we avoid it to avoid triggering eating disorder pathology (7,8).

Caloric restriction, however, can be more than an intervention. We can use the effects of caloric restriction to critical questions related to the determinants of longevity. In nonhuman animal models, the way to most dramatically extend normative life span is in fact caloric restriction (9). A normal *Caenorhabditis elegans* worm lives around 14 days. With caloric restriction, the same worm will live up to 40 days—on average, two to three times longer (10)—while remaining active and vital until the very end (11). The stunning photographs of calorie-restricted versus free-eating rhesus macaques published in *Science* in 2009 also underscore the power of caloric restriction (12). Indeed, the effects of caloric restriction are conserved across several species from yeast to fruit flies, nematodes, fish, rodents, and old world monkeys. Whether caloric restriction will work as radically, or if at all, in humans is still an open question.

There are two general strategies that researchers might use to determine whether caloric restriction increases life span. The first is to randomly assign participants to either a calorie restriction or control group and measure markers of longevity/aging. This is precisely the strategy of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) study, which involves a 25% calorie-restricted diet in normal-weight to overweight participants (13). The CALERIE intervention, after 6 months, seems to beneficially affect some measures of aging such as oxidative stress (14). The strengths of the CALERIE study are numerous. The CALERIE study is a rigorously piloted, multisite endeavor with comprehensive outcome measures and rich resources. Above all, it is a randomized controlled trial, which allows for causal inference.

The CALERIE study intervention, however, lasts only 2 years. As caloric restriction studies go, this is a very long intervention period, but it may not be long enough to test the hypothesis that caloric restriction extends life span. The CALERIE investigators, based on several pilot studies, found that "…an intricate and detailed screening process is required to screen out volunteers unlikely to persevere with the rigors of the CR (caloric restriction) intervention over the full 24 months" (13). This approach maximizes the likelihood that the manipulation is successful, but this underscores the difficulty that human participants face in adhering to caloric restriction over long periods.

A second strategy is to find already existing calorie reduction models of humans, which parallel the nonhuman animal models. However, human research precludes full control of food intake and complete adherence to a caloric restriction manipulation. Cultural, societal, technological, and biological forces conspire to make humans eat. Just the biological forces alone are not trivial. In response to caloric restriction, hunger drive intensifies, and food consumption can rebound higher than pre-restriction levels (15). Plasma leptin and insulin levels decrease, which result in the stimulation of central anabolic pathways such as the hypothalamic neuropeptide *y* axis, as well as the inhibition of central catabolic pathways such as the hypothalamic melanocortin system (15,16). Ghrelin levels increase, further stimulating hunger centers in the hypothalamus (17–19). Individuals become less sensitive to the meal-suppressing action of meal-generated signals such as cholecystokinin and eat larger meals (16,20).

The effects of caloric restriction can also be investigated by examining a unique self-selected group of individuals who voluntarily engage in long-term caloric restriction, that is, members of the Calorie Restriction Society. This group has labeled itself as *Cronies* (derived from "caloric restriction with optimal nutrition"). The life-style regimen of this group entails long-term caloric restriction, without engaging in strenuous exercise that could act as a potential confounding factor. The research that inspired the Cronies was that of Dr. Roy Walford, who was forced along with the crew to practice caloric restriction in Biosphere 2, when the crew was unable to grow enough food to feed themselves at conventional calorie levels. The Biosphere crew apparently had greatly improved health (21). The Cronies aspire to go beyond "improved health" and aim for life span extension (one participant stated, "I would like if possible to be immortal"). In our laboratory and in others (22–24), we are studying selected

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highly compliant members of this group, in which the average length of caloric restriction is approximately one decade.

In the study, we are using the Cronies as a model of caloric restriction, measuring a broad range of biological and behavioral markers related to aging processes, including telomere length and up- or down-regulation of genes related to life span extension in nonhuman species. Unlike in the CALERIE intervention study, observational studies such as the systematic investigation of this particular cohort cannot answer questions about causality. However, observational designs are an efficient approach to gain knowledge about special populations.

Caloric restriction as a scientific model, and the group of Cronies in particular, offers even more exciting opportunities to advance understanding in psychosomatic medicine. We can learn, for example, what helps this group of humans sustain caloric restriction over years and years. This may offer insight into how to increase adherence to calorie restricting interventions. This type of information is highly valuable because a) adherence to prescribed caloric reduction seems to be a principal component of weight loss (25); b) in the area of life span extension, it seems that 2 years is currently the upper limit of the duration that free-eating humans can sustain caloric restriction (13); and c) challenges remain in using caloric restriction to effect weight loss beyond 2 years (26).

This study will reveal characteristics that set the Cronies apart from the general population in which dietary interventions typically take place. Possible explanations include the following. The motivation that drives the Cronies—longevity with the possibility of immortality—is very different from a typical "dieter," whose motivation may be weight loss, perhaps to change one's appearance. Macro factors such as socioeconomic status may also distinguish the Cronies from the general population. The average calorie restricted participant in our study has at least a graduate degree, and the group has attained remarkable levels of achievement in business, academia, and music. Perhaps the Cronies are genetically predisposed to have blunted hunger signals, possibly combined with high levels of leptin and low levels of ghrelin.

In sum, we have much to gain from broadening our focus from using caloric restriction as a life-style intervention tool to using caloric restriction as a scientific model. Systematic research on caloric restriction may reveal important information about the aging process and the factors that underlie long-term eating behavior change. Caloric restriction provides a model that integrates the psychology, behavior, and biology of food consumption, weight control, and health.

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