Calorie restriction to retard aging and increase longevity

Key points
- **Calorie restriction** increases longevity in rodents, delays the onset of certain diseases and has positive effects on ageing.
- **Studies are ongoing** in non-human primates.
- **Eight persons following such a diet** for 2 years reacted as anticipated (loss of body weight and fat, decrease in glycaemia and body temperature, etc.).
- **Calorie restriction perhaps teaches us more** on the means of resisting malnutrition than on ageing in normal dietary conditions.
- **Calorie restriction is a tool for research**, but it should not be recommended by practitioners, notably in elderly patients.

Interest in calorie-restricted diets has been growing as nutritionists worry about increasing obesity rates and their harmful effects on health and life expectancy. Calorie restriction, or undernutrition without malnutrition, is often described in articles on experimental gerontology as the only method that substantially increases longevity in rodents and retards their aging. Many authors believe this method also extends longevity in fish, worms, and flies1-3, although the latter claim appears unfounded4,5. Early results from primate studies are similar to the results observed in rodents5 and have strengthened the interest of the public and specialists, but the longevity studies are still underway. Does calorie restriction in humans increase longevity and retard aging? A response to this question is all the more urgent because of publications touting the merits of such a diet in humans and holding forth the hope of a “total life expectancy of 140 years”7. The fact that malnutrition is a major factor in hospital admissions among the elderly and that an empty refrigerator is predictive of hospitalization8 makes it all the more important for physicians to know whether they should be encouraging or curbing patients’ plans for calorie restriction.

**Calorie restriction**

**IN RODENTS...**

Although some preliminary research was done earlier, serious study of calorie restriction began in 1935 when McCay’s group slowed the growth of rats by reducing the quantity of their food after weaning9. Upon repeating the experiment, they were able to avoid inducing any vitamin, mineral, or protein deficiencies10,11. Mean and maximum longevity increased in the undernourished group, with a difference in mean longevity of one year, or approximately 50% greater than the longevity of rats eating *ad libitum*. The undernourished rats had fewer age-related diseases11, but had very fragile bones9 and were less fertile11. Subsequent studies showed that the increased longevity induced by calorie restriction was not due to growth retardation12 and that calorie restriction begun in adulthood also increased longevity in rats12 and mice13. In summary, it is well established that calorie restriction has positive effects on age-related diseases, motor function, and cognitive aging.

**... AND IN NON-HUMAN PRIMATES**

Calorie restriction would be of greater interest to geriatricians if the same effects were observed in primates. Studies of longevity in primates only began in the 1980s, using a species (rhesus macaques) that can live as long as 40 years, thus no confirmation of the effects of calorie restriction in primates is possible as yet.

Nutrition

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UPDATE

Report in 2002 indicated that mortality at that point was 15% in the undernourished macaques and 24% in those fed ad libitum. But during the IPSEN Foundation “Longevity and Frailty” conference (Paris, 11 October 2004), Donald Ingram, who is conducting these studies, reported that the longevity of the undernourished macaques may turn out to be similar to that of the controls. However, several studies appear to show that the effects of calorie restriction are similar in primates and in rodents. Undernourished primates weigh less and have fewer fat stores, lower body temperatures, and lower energy expenditure, but equal levels of physical activity. Moreover, calorie restriction decreases insulin levels and fasting blood glucose and increases insulin sensitivity. Some authors have wondered whether calorie restriction might have a positive effect on cardiovascular diseases, but risk factors such as blood pressure and cholesterol levels do not appear to fall in undernourished monkeys. Although the behavioral studies have not been completed, the similarity of the reaction of primates and rodents to calorie restriction is promising in terms of its effects on their longevity and aging.

Homo sapiens: bis repetita placent

History abounds in dramatic situations in which various populations have had to cope with malnutrition or famine. However, our contemporaries who survived the famine in Nazi camps report no positive effect on their aging, and their longevity did not increase — quite the contrary! Nor do people with mild to moderate anorexia live longer. Malnutrition has only negative effects, including on human aging, and this has been confirmed in studies of longevity in rats.

BIOSPHERE-2

Experiments of undernutrition without malnutrition in humans are rare, and although most such studies do not survive critical examination, there is at least one that appears valid: Biosphere-2, a hermetically sealed compound located in Arizona that was intended to reproduce a complex ecosystem (tropical forest, desert, etc.), in which four men and four women lived for a two-year period. All their food was produced inside the compound: nothing came in from the outside. Because of some difficulties, their calorie ration fell to 1800 kcal per day at the beginning of the study and reached only 2200 kcal at the end of the experiment. Complete medical examinations were conducted regularly by one of the subjects who was a physician. During their stay in Biosphere-2, subjects’ weight, body temperature, blood pressure, blood glucose, insulin, cholesterol, and lipoprotein (LDL and HDL) levels, and LDL/HDL ratios all fell; these results are similar to those obtained in rodents and to some of those obtained in macaques. After the subjects left Biosphere-2, these variables gradually returned to their previous values. The authors of the Biosphere-2 studies concluded that severe calorie restriction does not negatively affect health as long as other aspects of nutrition remain adequate; they also noted that the subjects performed sustained physical activity even under these dietary conditions. These results, of course, provide no information about aging and longevity, apart from the fact that one of the participants was 67 years of age at the beginning of the study and experienced no particular problems (Figure 2). It would be premature, however, to conclude that a regimen of calorie restriction can be tolerated by everyone, particularly those over the age of 60. The study participants were highly motivated, or they would have left Biosphere-2

Table 1

<table>
<thead>
<tr>
<th>Species (strain, sex)</th>
<th>Effect of calorie restriction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (C57BL/6, female)</td>
<td>Fewer lymphomas</td>
<td>53</td>
</tr>
<tr>
<td>Mice (6 genotypes, 2 sexes)</td>
<td>Fewer tumors and lesions</td>
<td>54</td>
</tr>
<tr>
<td>Rats (Wistar, males)</td>
<td>Less proteinuria and fewer renal diseases</td>
<td>55</td>
</tr>
<tr>
<td>Rats (Fischer 344, males)</td>
<td>Fewer renal and cardiac diseases, late tumors</td>
<td>56</td>
</tr>
<tr>
<td>Rats (Fischer 344, males)</td>
<td>Better memory performance</td>
<td>57</td>
</tr>
<tr>
<td>Rats (Wistar, males)</td>
<td>No effect on memory</td>
<td>58</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, males)</td>
<td>Poorer resistance to cold</td>
<td>59</td>
</tr>
<tr>
<td>Rats (Lobund-Wistar, males)</td>
<td>Better resistance to heat</td>
<td>60</td>
</tr>
<tr>
<td>Rats (Fischer 344, males)</td>
<td>No effect on reflexive behaviors</td>
<td>61</td>
</tr>
<tr>
<td>Rats (Sprague-Dawley, males)</td>
<td>Protection against toxin-induced neurodegeneration</td>
<td>62</td>
</tr>
<tr>
<td>Mice (C57BL/6, males)</td>
<td>Better motor performance</td>
<td>63</td>
</tr>
<tr>
<td>Mice (C57BL/6, males)</td>
<td>No effect on learning</td>
<td>64</td>
</tr>
<tr>
<td>Mice (C3B10RF, female)</td>
<td>Better learning and motor performance</td>
<td>65</td>
</tr>
</tbody>
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once the draconian nature of the regimen became clear. Media coverage of the event reinforced this motivation, and we can imagine that the participants had a sort of American pioneer spirit searching for a new frontier. Moreover, the participants knew that the experiment would be abandoned in the event of real danger and that the risks involved were therefore minimal. Any motivated researcher would have remained in Biosphere-2, but might have not have continued this nutritional regimen once the experiment was completed. Figure 2 shows that this is exactly what occurred.

**CALORIE RESTRICTION — NEW PANACEA?**

These results appear to show that calorie restriction increases longevity in mammals, slows their aging, and enables them to avoid some age-related diseases. Studies should soon confirm the increased longevity and retardation of aging in primates, and there is no reason to think the situation will be different in humans. Because the idea of subjecting all of humanity to a calorie-restricted diet is unrealistic, some argue that we should instead find a way of “tricking” the body, making it react as though it were under caloric restriction in order to reap the benefits of this diet without suffering its disadvantages. This would require the development of what some have termed calorie-restriction mimetics, an eminently logical but wrong-headed premise, as will be shown below.

**Calorie restriction and evolutionary strategies**

Why does calorie restriction increase longevity, slow aging, and improve resistance to stressors? To answer this question, a slight detour into so-called “life history strategies” is necessary.

**NORMAL STRATEGY**

Mammals living in the wild in conditions where they are not exposed to undernutrition follow a well-known life strategy. After birth, a growth period that may be long or...
short concludes in adulthood, when reproduction can start. The length of the reproductive period also varies, depending on the species and on death due to predators, diseases, or any other environmental constraints. If the animal survives, it will grow old and eventually die, although aging as such does not really exist in the wild, except in several species with no predators.

**EMERGENCY STRATEGY**

Undernourishing animals at a young age may stop or slow their growth, as in the experiments by McCay et al.\(^9\)\(^-\)\(^11\), and retard or diminish their reproduction, if they have reached adulthood. This “emergency strategy” allows mammals to survive until living conditions improve, and to reproduce even after experiencing undernutrition (figure 3). In other words, reproduction and growth are deferred to allow survival and future reproduction, a strategy preferable to one allowing immediate reproduction with too little nutrition available\(^29\),\(^30\). An example of this would be raising young mice when the amount of food available is clearly insufficient, which would lead inevitably to their death and would therefore entail a loss of energy that would also endanger the mother’s life. Many authors, but not all (list in reference\(^30\)), share this idea that responses to undernutrition are an evolutionary adaptation. This emergency strategy is not limited to mammals, and varies according to each species’ characteristics. Thus, undernourishment reduces fecundity in fruit-flies (*Drosophila melanogaster*)\(^31\), butterflies (*Speyeria mormonia*)\(^32\), and spiders (*Frontinella pyramitella*)\(^33\). Another means of surviving undernourishment is used by the nematode *Caenorhabditis elegans*, which enters a larval stage called *Dauer* (duration, in German), in which both eating and reproduction are impossible\(^34\). The undernourishment-related increased longevity that has been demonstrated in rodents is exhibited in nematodes as well, which can remain in the larval stage for several months awaiting better living conditions, even though adults live only about twenty days\(^34\). Animals following this emergency strategy also resist stresses better. Undernourished rats are resistant to heat (but not cold, because of their very low fat stores) and lipid peroxidation by free radicals\(^35\). Similarly, the nematode *Dauer* larva resist different stressors\(^36\). This improved resistance to stress is understandable: it is helpful for an animal that has a strategy for surviving undernourishment to be able to survive other likely stressors during this period. For example, shortages of food sources may be accompanied by high heat, making it useful for underfed animals to be able to withstand heat. Once the conditions causing undernourishment are over, maintaining this heat-resistance is no longer strictly necessary, particularly since the organism will probably need to allocate a large part of its available energy to reproduction. Experimental induction of mutations has made it possible to express some, but not all, effects of calorie restriction in mice and other species (nematodes, *drosophila*)\(^37\),\(^38\). Significant increases in longevity and resistance to stress in mice are possible, often at the cost of growth and fertility\(^37\), but not always\(^39\). In any case, these studies will perhaps help us to better understand how animals resist undernourishment and how they age under normal feeding conditions.

In summary, underfed animals adopt

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**Figure 3** Life strategy of mammals eating *ad libitum* (normal strategy). In circumstances of undernourishment, the animals can survive by using an “emergency strategy” until living conditions improve.
an emergency strategy that allows them to wait until living conditions become favorable again. The best strategy may be to temporarily sacrifice reproduction in order to improve resistance to stress and to live longer. We would then expect longevity to increase in all species subjected to undernourishment, as is the case in rodents. However, this is not what we observe in *Drosophila melanogaster*[^1], *Ceratitis capitata*[^2], or in the *Speyeria mormonia* butterfly[^3].

**Increased Longevity is Species-Specific**
Masoro and Austad[^4] hypothesized that species living in environments where undernourishment occurs only rarely, such as tropical forests, lose the ability to react to environments where undernourishment occurs only rarely, such as tropical forests, lose the ability to react to undernourishment during the course of evolution. That is, unlike rodents, for example, such species would not live longer when undernourished. Let us add another consideration. Species that can leave a temporarily inhospitable biotope because food has become scarce do not need to react to undernourishment by living longer: they can simply leave. This should be the case for birds that can fly, especially migratory birds, flying insects, and all the species capable of fleeing when necessary. Unfortunately, we cannot verify this hypothesis because it does not appear that studies of undernourishment have been conducted in these species, except for some winged insects (see above). If undernourishment increases longevity only in species incapable of moving quickly and far, it is not surprising that rodents live longer undernourished, because it is difficult for them to move long distances.

**Is Flight the Best Response for the Human Species?**
How does this apply to humans? Are they incapable of fleeing their environment if it becomes unfavorable, or can they escape swiftly? History has clearly shown that they can flee: humans colonized the entire planet after leaving their birthplace in Africa. During famines, populations move, en masse if necessary, to other places, whether these are already inhabited (the Roman empire at the time of the barbarian invasions) or largely empty (the United States after the famine in Ireland in the 19th century): those who do not move have a substantially greater risk of dying than of becoming centenarians. Thus it is improbable that calorie restriction in the human species will increase its longevity. This is my opinion, of course, and others hypothesize the contrary: de Jaeger[^7] believes that we can attain a life expectancy of 140 years by restricting calorie intake in adulthood, which would imply a maximum longevity approaching 240 years[^8]. Other authors, more prudent, think that calorie restriction may be effective in humans, but do not put a figure on their predictions[^9]. Even if we accept that calorie restriction does not increase longevity in humans, it could be argued that it may have positive effects that contribute to healthier aging and would thus be worthwhile to put into practice.

**Daily Calorie Restriction — a Recipe for Illness**

Beyond the positive effects hoped for in humans, calorie restriction has proven negative effects. Prolonged undernourishment is known to increase the risk of amenorrhea, weaken resistance to cold and infection[^10], reduce the possibility of physical activity, and accelerate the onset of osteoporosis[^11]. In the Biosphere-2 study, none of the 4 women had amenorrhea and all the participants practiced intense physical activity[^12], but it is unlikely that the same results would be observed in a more representative sample of the general population. In particular, it is doubtful whether continuing to work is compatible with permanent calorie restriction in adulthood. It might be argued that these disadvantages would not exist in practice because, of course, no one would plan to follow such a diet without medical advice, for only a physician could supervise such a diet. De Jaeger[^7] writes that entering “a calorie restriction program cannot be imagined without strict medical surveillance”. Several pages earlier, however, he says that “calorie restriction is not dangerous if one uses common sense”, that the person must not “lose more than 20-25% of their initial weight in the case of “moderate obesity”, and indicates the “signs of poor tolerance for this diet” (amenorrhea, hypersomnia, fatigue, or concentration problems). He adds, “If you lose too much weight or lose it too rapidly, or if you do not lose any or not enough, then adjust the number of calories accordingly”; a physician’s intervention thus does not appear absolutely essential since everything seems to rely on the decision of the person following the diet. Other authors go still further: André Klarsfeld and Frédéric Revah[^12] write that “we can all test for ourselves the efficacy of calorie restriction, as long as we take every possible precaution to avoid any deficiencies”. This illustrates the danger of these calorie-restricted diets, for few people other than nutritionists are capable of developing such a balanced diet. Under these circumstances, the emphasis on “every possible precaution” amounts to saying that those playing Russian roulette must be careful to not hurt themselves! The risk posed by the books by de Jaeger[^7] and Klarsfeld and Revah[^12] is that some readers will conclude that they can follow a regimen of calorie restriction on their own. The consequences in terms of hospitalizations for malnutrition are all too easy to imagine. Should calorie restriction diets therefore be pros-
described for adults? I certainly think so. It is clear that adopting a calorie-restricted diet is different from eating a moderate and balanced diet that helps prevent obesity, among other things. A regimen of caloric restriction is a permanent near-famine for life, as a glance at figure 2 clearly shows.

The solution

Does this mean that no diet can improve the aging process? Certainly not. It is hardly necessary to dwell on the advantages of a moderate and balanced diet now that obesity has become a public health problem: the harmful effects of obesity on health are well established and overweight, too, has negative consequences on mortality (review in reference 45). What is less apparent to the general public is the value of following a diet rich in fruits and vegetables for the most successful aging possible. While the advantages of caloric restriction throughout adulthood remain hypothetical, those of eating large quantities of fruits and vegetables seem clearly established. Eating well is not only eating little. Accordingly, Greeks aged 70 years and older following a Mediterranean diet rich in fruits and vegetables but with relatively little meat had a lower mortality rate after 5 years of follow-up (relative risk: 0.83) 46. The Mediterranean diet does not require sunshine to work, since Danes aged 65-70 years also had a lower mortality rate (relative risk: 0.79) after 6 years of follow-up 37. In Sweden, mortality was lower in the subjects (aged 54 years at the beginning of the study and followed for 16 years) who ate a lot of fruit 48, but vegetable consumption was not linked to mortality. Eating fruits and vegetables also seemed to diminish cardiovascular mortality (relative risk: 0.54) in persons 66 years and older who were followed for 5 years 49. Better cognitive performance also seems to be associated with higher consumption of fruits and vegetables 50, although these results might also be explained by the likelihood that those in good cognitive condition have the best eating habits. These results (reviewed in reference 51) clearly indicate the advantages that the elderly, in particular, can expect from a diet rich in fruits and vegetables. The population as a whole does not apparently (yet?) share this opinion, given what people actually eat.

Conclusion

Physicians are probably much more likely to help their patients live for a long time in good health by encouraging them to follow a fairly healthy diet, rather than allowing them or, worse, advising them to follow a calorie-restricted diet. These diets are a laboratory tool but not in any sense a treatment against aging. The negative effects of calorie restriction in humans are known, while its positive effects are hypothetical. Calorie restriction must not be confused with a moderate and balanced diet to avoid obesity. While such a balanced diet can only have positive consequences for the patient, caloric restriction will very likely have negative effects. Recommending such a diet to patients amounts to offering them a pill that has not been approved because of its numerous and dangerous side effects: few of us would be willing to take that chance.

Acknowledgments

The author thanks Prof. Luc Passera, of the University Paul-Sabatier in Toulouse (Toulouse 3), and Dr Roland Sastre, of the Henry Dunant medical group in Ramonville Saint-Agne (31), who graciously consented to spend time reading this article.

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