There are two main research questions that underpin biogerontology: What causes aging and how can we delay or prevent the harmful aspects of old age. These two questions appear to be inextricably linked: First, we must understand the cause of aging (or at least the pathways that govern it) before can we develop therapies to increase healthspan and delay death. Yet in their review of the development of aging therapies, Minor and colleagues (1) from the National Institute on Aging have shown that this is not necessarily the case. In doing so, they have provided a blueprint for the development of novel therapeutic aging targets.

In the past, it was concluded that many biological processes that accompany aging are harmful and somehow mechanistically linked to aging. For example, it is well established that old age is associated with oxidative stress and free radical damage and that this is often accompanied by diminished antioxidant defenses (2). The theory that free radicals cause aging was first postulated by Harman (3) in 1956 and has gained widespread support. Antioxidants have been investigated extensively for their possible antiaging effects, and antioxidants are taken by many people on the assumption this will delay aging. Yet as pointed out by Minor and colleagues (1), a recent meta-analysis of antioxidant clinical trials (albeit none of these were performed to delay aging) has shown that antioxidants do not improve life expectancy in humans and might even increase the risk of premature death.

Similarly, there are decreases in many hormones in old age, and the use of hormone supplements to delay aging is widely accepted by the lay community. Yet Everitt showed long ago that hormonal depletion by hypophysectomy increased life span and delayed age-related changes (4). Likewise Bartke has clearly demonstrated that growth hormone deficiency in mice is associated with remarkable increases in longevity (5,6). However, the marketing and use of hormones such as growth hormone to delay aging is widespread.

Increasingly, it seems that just because a particular biological process occurs with age, it does not mean that this process is involved in the pathogenesis of aging. More importantly, attempting to reverse individual biological processes that accompany aging does not necessarily reverse aging and can even be harmful. Although scientists have extensively itemized the changes that are associated with old age, the key cellular mechanism for aging that can be therapeutically manipulated remains elusive. This rational mechanism-based approach to the development of aging therapies has not yet yielded any dividends. Minor and colleagues (1) have shown that there is another approach to developing aging therapies that is based on understanding the effects of caloric restriction on aging. This approach has generated some very promising lead compounds. In 1935, McCay (7) reported that reducing food intake over the life span of rats paradoxically increased their life expectancy. Caloric restriction has since become a major model for the study of aging and has delayed aging and death in most species that have been studied. The mechanism was generally thought to be passive: A reduction in food intake was expected to lead to less cellular damage, for example, by reduced production of free radicals.

Holliday (8) proposed that caloric restriction might in fact be an active rather than a passive mechanism that presumably evolved to make us more resilient in times of famine. Following this lead, Guarente’s and Sinclair’s groups discovered that the sirtuin pathway was implicated in this active response to caloric restriction in yeast (9,10). As described by Minor and colleagues, this pivotal discovery...
led to the investigation of resveratrol and various sirtuin agonists for the treatment of aging. It is now known that there are many pathways that interact to increase the resilience of cells that are exposed to caloric restriction. These include the sirtuin, target of rapamycin, AMP-activated protein kinase, and insulin/insulin-like growth factor-1 pathways and undoubtedly other signaling mechanisms remain to be discovered. It seems that evolution has provided us with a variety of cellular mechanisms that allow us to survive famine and delay reproduction until food is again abundant enough for reproduction and the survival of our offspring. Harnessing these evolutionary mechanisms has provided the first real opportunity to make a pharmacotherapeutic impact on aging.

Are there any other responses that could be exploited in a similar fashion to caloric restriction? Rattan and Masoro (11,12) are strong proponents of the concept of hormesis in aging. Hormetic responses are those where there are paradoxical increases in the health and resilience of an organism exposed to a small dose of a toxic factor. Such hormetic stressors include not only caloric restriction but also others such as irradiation, heat stress, exercise, and even reactive oxygen species. Perhaps by studying the cell pathways that control each hormetic response, we will discover new targets for aging therapies. There are also various other dietary manipulations apart from caloric restriction that increase longevity, including alternate day feeding and protein restriction (13). Pathways involved in these responses also remain to be elucidated.

How will we use the study of hormetic and dietary influences on aging to create new medications that impact on aging? Using genetic screening and other high-throughput approaches, researchers have identified a network of genes that mediate the beneficial effects of caloric restriction and hormesis. Drug screens against these targets have identified agents that act on these pathways. This type of approach was successful in identifying resveratrol, a stress-induced plant compound (14). The xenohormesis theory shows how we have evolved to recognize these plant stress signals to provide advance warning of a deterioration in the environment (15). If this theory is correct, it is highly likely that natural product drug libraries will yield many other compounds that act on human hormetic and caloric restriction signaling pathways. The first drug that mimics caloric restriction is likely to be prescribed to treat a single disease of aging because aging is not usually considered to be a disease using current definitions. Eventually, assuming these drugs have low toxicity, they may be used prophylactically to slow aging. For this to occur, however, the long-term safety of the compounds needs to be determined using well-characterized aging animal colonies, including rodents and nonhuman primates. Agents that impact on aging will increase both longevity and healthspan therefore studying the effects of lead compounds on both these outcomes is critical.

In this timely and important review, Minor and colleagues (1) have shown that aging can be manipulated with pharmacotherapy, leading to improvements in both longevity and healthspan in animals. We hope that these agents prove to be useful in humans. They have also emphasized that drug development has been successful because of the focus on understanding mechanisms for caloric restriction rather than just on mechanisms for aging. We now have the proof of principle to justify a major investment in the development of therapies that influence aging. Given the aging demographic and the likelihood that drugs that act on aging will delay many diseases and increase healthspan, it is imperative that the types of drug development infrastructure available for various traditional single disease models are now made available for the study of therapies that impact on aging.

References