disease, and cancer. In humans, caloric restriction is associated with increased lifespan and healthspan. This is most convincingly demonstrated in Okinawa, Japan, where one of the most long-lived human populations resides. In comparison to the rest of the Japanese population, Okinawan people usually combine an above-average amount of daily exercise with a below-average food intake. However, when Okinawan families move to Brazil, they adopt a Western lifestyle that affects both exercise and nutrition, causing a rise in weight and a reduction in life expectancy by nearly two decades. In the Biosphere II project, where volunteers lived together for 24 months undergoing an unforeseen severe caloric restriction, there were improvements in insulin, blood sugar, glycated hemoglobin, cholesterol levels, and blood pressure—all outcomes that would be expected to benefit lifespan. Caloric restriction changes many aspects of human aging that might influence lifespan such as the transcriptome, hormonal status (especially IGF-I and thyroid hormones), oxidative stress, inflammation, mitochondrial function, glucose homeostasis, and cardiometabolic risk factors. Epigenetic modifications are an emerging target for caloric restriction.

It must be noted that maintaining caloric restriction and avoiding malnutrition is not only arduous in humans but is also linked with substantial side effects. For instance, prolonged reduction of calorie intake may decrease fertility and libido, impair wound healing, reduce the potential to combat infections, and lead to amenorrhea and osteoporosis.

Although extreme obesity (body mass index [BMI] >35) leads to a 29% increased risk of dying, people with BMI in the overweight range seem to have reduced mortality, at least in population studies of middle-aged and older subjects. People with a BMI in the overweight range seem more able to counteract and respond to disease, trauma, and infection, whereas caloric restriction impairs healing and immune responses. On the other hand, BMI is an insufficient denominator of body and body fat composition. A well-trained athlete may have a similar BMI as an overweight person because of the higher muscle mass density. The waist-to-hip ratio is a much better indicator for body fat and an excellent and stringent predictor of the risk of dying from cardiovascular disease: the lower the waist-to-hip ratio, the lower is the risk.

PERIODIC FASTING How can caloric restriction be translated to humans in a socially and medically feasible way? A whole series of periodic fasting regimens are asserting themselves as suitable strategies, among them the alternate-day fasting diet, the "five:two" intermittent fasting diet, and a 48-h fast once or twice each month. Periodic fasting is psychologically more viable, lacks some of the negative side effects, and is only accompanied by minimal weight loss.

It is striking that many cultures implement periodic fasting rituals, for example Buddhists, Christians, Hindus, Jews, Muslims, and some African animistic religions. It could be speculated that a selective advantage of fasting versus nonfasting populations is conferred by health-promoting attributes of religious routines that periodically limit caloric intake. Indeed, several lines of evidence indicate that intermittent fasting regimens exert antiaging effects. For example improved morbidity and longevity were observed among Spanish home nursing residents who underwent alternate-day fasting. Even rats subjected to alternate-day fasting live up to 83% longer than normally fed control animals, and one 24-h fasting period every 4 days is sufficient to generate lifespan extension

Repeated fasting and eating cycles may circumvent the negative side effects of sustained caloric restriction. This strategy may even yield effects despite extreme overeating during the nonfasting periods. In a spectacular experiment, mice fed a high-fat diet in a time-restricted manner, i.e., with regular fasting breaks, showed reduced inflammation markers and no fatty liver and were slim in comparison to mice with equivalent total calorie consumption but ad libitum. From an evolutionary point of view, this kind of feeding pattern may reflect mammalian adaptation to food availability: overeating in times of nutrient availability (e.g., after a hunting success) and starvation in between. This is how some indigenous peoples who have avoided Western lifestyles live today; those who have been investigated show limited signs of age-induced diseases such as cancer, neurodegeneration, diabetes, cardiovascular disease, and hypertension.

Fasting exerts beneficial effects on healthspan by minimizing the risk of developing age- related diseases including hypertension, neurodegeneration, cancer, and cardiovascular diseases. The most effective and rapid repercussion of fasting is reduction in hypertension. Two weeks of water-only fasting resulted in a blood pressure below 120/80 mmHg in 82% of subjects with borderline hypertension. Ten days of fasting cured all hypertensive patients who had been taking antihypertensive medication previously.

Periodic fasting dampens the consequences of many age-related neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, and frontotemporal dementia, but not amyotrophic lateral sclerosis in mouse models). Fasting cycles are as effective as chemotherapy against certain tumors in mice. In combination with chemotherapy, fasting protected mice against the negative side effects of chemotherapeutic drugs, while it enhanced their efficacy against tumors. Combining fasting and chemotherapy rendered 20–60% of mice cancer-free when inoculated with highly aggressive tumors like glioblastoma or pancreatic tumors, which have 100% mortality even with chemotherapy. This approach has been attempted in people with some indication that toxicities of chemotherapy are reduced.

Pharmacologic Interventions to Delay Aging and Increase Lifespan

Virtually all obese people know that stable weight reduction will reduce their elevated risk of cardiometabolic disease and enhance their overall survival, yet only 20% of overweight individuals are able to lose 10% of their weight for a period of at least 1 year. Even in the most motivated people (such as the "Cronies" who deliberately attempt long-term caloric restriction in order to extend their lives), long-term caloric restriction is extremely difficult. Thus, focus has been directed at the possibility of developing medicines that replicate the beneficial effects of caloric restriction without the need for reducing food intake ("CR-mimetics," Fig. 94e-5):

- *Resveratrol*. Resveratrol, an agonist of SIRT1, is a polyphenol that is found in grapes and in red wine. The potential of resveratrol to promote lifespan was first identified in yeast, and it has gathered fame since, at least in part because it might be responsible for the so-called French paradox whereby wine reduces some of the cardiometabolic risks of a high-fat diet. Resveratrol has been reported to increase lifespan in many lower order species such as yeast, fruit flies, worms, and mice on high-fat diets. In monkeys fed a diet high in sugar and fat, resveratrol had beneficial outcomes related to inflammation and cardiometabolic parameters. Some studies in humans have also shown improvements in cardiometabolic function, whereas

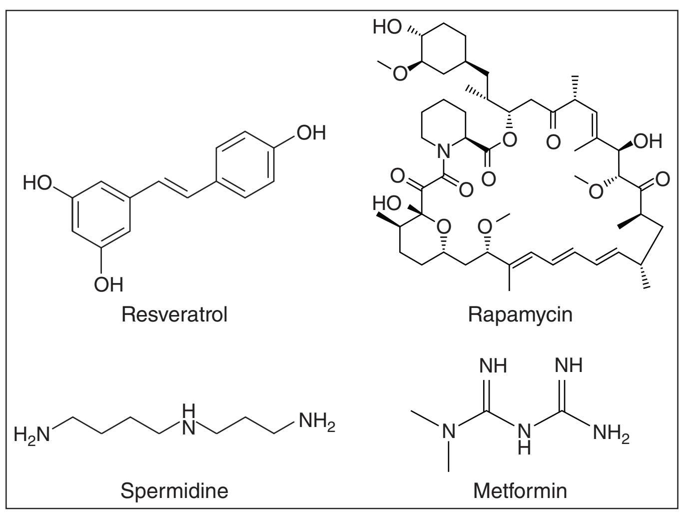

FIGURE 94e-5 Chemical structures of four agents (resveratrol, rapamycin, spermidine, and metformin) that have been shown to delay aging in experimental animal models.