others have been negative. Gene expression studies in animals and humans reveal that resveratrol mimics some of the metabolic and gene expression changes of caloric restriction.

- *Rapamycin.* Rapamycin, an inhibitor of mTOR, was originally discovered on Easter Island (Rapa Nui; hence its name) as a bacterial secretion with antibiotic properties. Before its immersion in the antiaging field, rapamycin already had a longstanding career as an immunosuppressant and cancer chemotherapeutic in humans. Rapamycin extends lifespan in all organisms tested so far, including yeast, flies, worms, and mice. However, the potential utility of rapamycin for human lifespan extension is likely to be limited by adverse effects related to immunosuppression, wound healing, proteinuria, and hypercholesterolemia, among others. An alternative strategy may be intermittent rapamycin feeding, which was found to increase mouse lifespan.
- *Spermidine.* Spermidine is a physiologic polyamine that induces autophagy-mediated lifespan extension in yeast, flies, and worms. Spermidine levels decrease during the life of virtually all organisms including humans, with the stunning exception of centenarians. Oral administration of spermidine and upregulation of bacterial polyamine production in the gut both lead to lifespan extension in short-lived mouse models. Spermidine has also been found to have beneficial effects on neurodegeneration probably by increasing transcription of genes involved in autophagy.
- *Metformin.* Metformin, an activator of AMPK, is a biguanide first isolated from the French lilac that is widely used for the treatment of type 2 diabetes mellitus. Metformin decreases hepatic gluconeogenesis and increases insulin sensitivity. Metformin has other actions including inhibition of mTOR and mitochondrial complex I and activation of the transcription factor SKN-1/Nrf2. Metformin increases lifespan in different mouse strains including female mouse strains predisposed to high incidence of mammary tumors. At a biochemical level, metformin supplementation is associated with reduced oxidative damage and inflammation and mimics some of the gene expression changes seen with caloric restriction.

Exercise and Physical Activity In humans and animals, regular exercise reduces the risk of morbidity and mortality. Given that cardiovascular diseases are the dominant cause of aging in humans but not in mice, the effects on human health may be even stronger than those seen in mouse experiments. An increase in aerobic exercise capacity, which declines during aging, is associated with favorable effects on blood pressure, lipids, glucose tolerance, bone density, and depression in older people. Likewise, exercise training protects against aging disorders such as cardiovascular diseases, diabetes mellitus, and osteoporosis. Exercise is the only treatment that can prevent or even reverse sarcopenia (age-related muscle wasting). Even moderate or low levels of exercise (30 min walking per day) have significant protective effects in obese subjects. In older people, regular physical activity has been found to increase the duration of independent living.

While clearly promoting health and thus quality of life, regular exercise does not extend lifespan. Furthermore, the combination of exercise with caloric restriction has no additive effect on maximal lifespan in rodents. On the other hand, alternate-day fasting with exercise is more beneficial for the muscle mass than single treatments alone. In nonobese humans, exercise combined with caloric restriction has synergistic effects on insulin sensitivity and inflammation. From the evolutionary perspective, the responses to hunger and exercise are linked: when food is scarce, increased activity is required to hunt and gather.

Hormesis The term *hormesis* describes the, at first sight paradoxic, protective effects conferred by the exposure to low doses of stressors or toxins (or as Nietzsche stated, "What does not kill him makes him stronger"). Adaptive stress responses elicited by noxious agents (chemical, thermal, or radioactive) precondition an organism, rendering it resistant to subsequent higher and otherwise lethal doses of the same trigger. Hormetic stressors have been found to influence aging and lifespan, presumably by increasing cellular resilience to factors that might contribute to aging such as oxidative stress.

Yeast cells that have been exposed to low doses of oxidative stress exhibit a marked antistress response that inhibits death following exposure to lethal doses of oxidants. During ischemic preconditioning in humans, short periods of ischemia protect the brain and the heart against a more severe deprivation of oxygen and subsequent reperfusion-induced oxidative stress. Similarly, the lifelong and periodic exposure to various stressors can inhibit or retard the aging process. Consistent with this concept, heat or mild doses of oxidative stress can lead to lifespan extension in *C. elegans*. Caloric restriction can also be considered to be a type of hormetic stress that results in the activation of antistress transcription factors (Rim15, Gis1, and Msn2/Msn4 in yeast and FOXO in mammals) that enhance the expression of free radical–scavenging factors and heat shock proteins.

CONCLUSIONS

Clinicians need to understand aging biology in order to better manage people who are elderly now. Moreover there is an urgent need to develop strategies based on aging biology that delay aging, reduce or postpone the onset of age-related disorders, and increase functional life and healthspan for future generations. Interventions related to nutritional interventions and drugs that act on nutrient-sensing pathways are being developed and, in some cases, are already being studied in humans. Whether these interventions are universally effective or species/individual specific needs to be determined.