

01 - 488 Biology of Aging

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Biology of Aging The increase in older people over the past few decades is one of the most significant changes in human history. For the first time, people over the age of 65 years now exceed children under the age of 5 years (Fig. 488-1). Aging is associated with an exponential increase in the incidence of many chronic diseases (Fig. 488-2). This has significant implications for the delivery of health services and aged care in all nations. Older people are living even longer due to advances in medical care but at the cost of longer periods of frailty and disability and of iatrogenic burdens associated with intensive medical care of multiple diseases, such as polypharmacy. Establishing the relationship between aging and disease, particularly noncommunicable disease, is one of the most important goals for biomedical research. Studies in animal models confirm that aging is malleable. The “longevity dividend” refers to the concept whereby an intervention that slows the aging process is likely to delay the onset of a wide range of age-related diseases and syndromes, as well as potentially increasing years of healthy lifespan (“health span”).

DEFINITIONS OF AGING Aging is a progressive process associated with deterioration in structure and function, leading to increased susceptibility to disease and mortality, and often associated with impaired reproductive capacity. There are statistical, biological, and phenotypic components to most definitions of aging (Fig. 488-3).

THEORIES OF AGING ■

■ MUTATION ACCUMULATION AND

ANTAGONISTIC PLEIOTROPY Evolutionary theories of aging attempt to explain why aging, which impairs health and survival, has evolved, and why there is so much variability in lifespan across taxa. Aging is generally considered to be nonadaptive. This means aging has not been shaped by evolution or genetically programmed. However, many genes influence the aging process, and the initiating process of aging is most likely to involve stochastic, nonprogrammed changes in nuclear maintenance that influence gene expression and repair. Many theories of aging are based on the concept that, in the wild, mortality is secondary to extrinsic causes, such as predation, injury, and infection, and evolutionary selection

65 years and older Percentage of world population

Less than 5 years

Year **FIGURE 488-1** Globally, people over the age of 65 years now exceed children under the age of 5 years.

Aging PART 18 pressure is generated by early life survival and reproductive success. There is minimal selection pressure to maintain health and extend life beyond early reproductive years and inevitable death from extrinsic causes. In fact, traits may evolve that are beneficial in early life and for reproduction but become harmful if the animal lives to an older age. These theories were set out by the classic “mutation accumulation” (John B.S. Haldane) and “antagonistic pleiotropy” (George C. Williams) theories of aging. ■ ■DISPOSABLE SOMA THEORY There is often a trade-off between aging and reproduction. Animals with high extrinsic mortality tend to have short lives, small bodies, and greater reproductive output, while animals with low extrinsic mortality, such as humans and other primates, tend to have longer lives, larger bodies, and fewer offspring. The disposable soma theory of aging (Thomas Kirkwood) explicitly hypothesizes that evolution selects strategies that prioritize utilization of finite resources to maintain germ cells necessary for reproduction rather than for maintenance of the soma (nongerm cells), hence leading to age-related accumulation of damage to the soma. ■ ■INFORMATION THEORY OF AGING This theory has its foundations in studies of aging biology and the role of DNA methylation in aging and as an “aging clock.” With aging, there are marked changes in the epigenome (an analog information system), which have profound effects of gene expression (an information retrieval system). By contrast, the DNA code (a digital information system) is relatively stable with aging. COMPARATIVE AGING ACROSS SPECIES ■ ■NEGLIGIBLE SENESCENCE AND

PROGRAMMED AGING There are some animals that undergo “negligible senescence,” meaning that there are no obvious biological changes of aging and the rate of mortality does not increase with time. These include some strains and species of clams, sharks, hydra, and worms. The longest living vertebrate is the Greenland shark, which may live up to nearly 400 years of age. On the other hand, there are a few animals that undergo programmed aging and death. These are the semelparous animals such as Pacific salmon and marsupial mice (Fig. 488-4). ■ ■GRANDMOTHER EFFECT There are species, including humans, where evolution could influence late-life survival through what is called the grandmother effect. In these species, survival of offspring depends on the care provided by their long-lived grandmothers. This also explains the development of extended postreproductive survival in humans. BIOLOGICAL HALLMARKS OF AGING Aging is associated with a range of molecular processes that are remarkably similar between species. These “hallmarks of aging” are the mechanistic pathways that cause aging. The processes are highly interconnected, and impairment of one process will impact the others. The hallmarks include those that act at the various biological strata and together erode various pillars of health (Fig. 488-5). Interventions that alter the behavior of each of these pathways (via genetic manipulation, pharmacologic treatments, or nutritional interventions) influence aging and lifespan of laboratory animals such as mice, fruit flies (*Drosophila melanogaster*) or worms (*Caenorhabditis elegans*). Each of the hallmarks is a potential target for pharmacotherapies that might delay aging and the onset of age-related morbidity and increase both health span and lifespan. ■ ■GENOMIC INSTABILITY The integrity of DNA is vulnerable to many exogenous (e.g., irradiation, chemicals, transposons) and endogenous (e.g., oxidative stress)

Alzheimer’s dementia Chronic obstructive pulmonary disease Stroke

Incidence

Ischemic heart disease Non-Hodgkin lymphoma

PART 18 Aging

FIGURE 488-2 Many noncommunicable diseases have an exponential increase in incidence with age. Aging biology is likely to be an integral part of the mechanisms for these diseases. stresses that generate largely random DNA lesions such as point mutations, translocations, and chromosomal anomalies. Mitochondrial DNA is especially susceptible to damage with aging because of its proximity to free radicals produced during oxidative phosphorylation and lack of histones and repair mechanisms. Genetic manipulation of nuclear and mitochondrial DNA repair mechanisms shortens lifespan in mice, while human premature aging syndromes are associated with deficiencies in genes necessary for nuclear maintenance. For example, Werner's syndrome is caused by mutations in a recQ helicase gene (WRN) required for repair of double-stranded breaks, and Hutchinson-Guilford progeria syndrome is caused by mutations in the lamin A gene (LMNA) required for structural support of the nucleus. ■ ■TELOMERE ATTRITION Telomeres are repeat sequences at the ends of linear chromosomes that counter the inability of DNA polymerase to replicate the tips of chromosomes. In humans, telomeres consist of a redundant TTAGGG sequence repeated several thousand times. Some cells (e.g., germ cells, tumor cells) contain telomerase, which can reform telomeres that are shortened during replication. In most cells, after multiple divisions, the telomeres are truncated to a point where cell division cannot continue. In cell culture, this number of divisions is called the Hayflick limit, and cells that cannot undergo further division are said to have Dementia Cataracts Delirium Cancer Incontinence Sarcopenia C B A Age

FIGURE 488-3 Definitions of aging often include (A) a biological component encapsulated by the 12 hallmarks of aging, (B) a phenotypic component that includes many chronic diseases and syndromes of aging, and (C) a statistical component that in most species involves an exponential (Gompertz) increase in the risk of mortality with age.

Colon and rectum cancer

Age entered a phase of "replicative cellular senescence." Some studies in humans have found that telomere length in blood cells decreases with age, while mice that have been genetically manipulated to have short or long telomeres have decreased and increased lifespans, respectively. In humans, telomerase deficiency is associated with pulmonary fibrosis and aplastic anemia. ■ ■EPIGENETIC ALTERATIONS Gene expression is regulated by DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs. These all change with age, leading to altered transcription of genes, especially those involved with inflammation, mitochondrial function, and autophagy pathways. There are consistent age-related changes in the pattern of DNA methylation in human blood samples that have been called "epigenetic clocks" (e.g., "Horvath epigenetic clock") because they reflect chronologic age. Histones are proteins that package DNA into nucleosomes, thus influencing DNA available for transcription. The sirtuins are a family of NAD-dependent proteins that regulate histones through deacetylation and have significant effects on aging and lifespan. For example, overexpression of sirtuins and activation by drugs such as resveratrol increase lifespan in model organisms. De-repression of retrotransposons has been implicated in aging, and nonreverse transcriptase inhibitors decrease this and delay aging in mice.

1.0	1.0	Risk of death	Survival	0.8	0.8	Risk of death	0.6	0.6	Vascular disease	Survival	Falls	0.4	0.4
Osteoporosis	0.2	0.2	Frailty	0.0	0.0								

Ocean quahog clam Greenland shark Negligible senescence Antechinus Pacific salmon Semelparous animals Asian elephant Humans Grandmother effect FIGURE 488-4 Some animals undergo negligible senescence, while others such as the semelparous animals undergo programmed aging and death. In some long-lived species, including humans, there is a prolonged postreproductive period that can evolve because of the beneficial effects of grandmothers on survival of infants. ■ ■LOSS OF PROTEOSTASIS Damaged proteins in cells are removed by the autophagy-lysosomal system and ubiquitin-proteasome system. These processes are impaired with aging, which can lead to intracellular and extracellular aggregates of damaged proteins and other cellular components such as lipofuscin, Lewy bodies, neurofibrillary tangles, and amylin (Fig. 488-6). ■ ■DISABLED MACROAUTOPHAGY Autophagy refers to the sequestration and digestion of proteins (i.e., proteostasis), nonprotein macromolecules (e.g., glycogen), and organelles (e.g., mitochondria, “mitophagy”). Autophagy and the expression of autophagy-related genes decline with old age. Autophagy is activated by caloric restriction (CR), spermidine, and inhibition of mechanistic target of rapamycin (mTOR) that all are associated with delayed aging. Loss of function of genes that are associated with autophagy in humans is associated with increased susceptibility to a range of age-related diseases. ■ ■DEREGULATED NUTRIENT SENSING Nutrition has a profound effect on aging in all species. One of the most important nutritional interventions that influences aging is CR. CR involves providing animals with less food (usually ~30–50% less than eaten by ad libitum fed controls). When this is maintained over a lifetime, lifespan is increased, and many age-related pathologies and diseases are delayed. There are several interconnected pathways that mediate the effects of nutrition and CR on aging and age-related health through a wide range of downstream effects (Fig. 488-7). Drugs that act on these pathways to replicate CR are called CR-mimetics

and increase lifespan regardless of calorie intake. These key pathways include the following:

1. Insulin and insulin-like growth factor (IGF)-1 signaling pathway (IIS), including growth hormone (GH). Animals with genetic downregulation of this pathway have longer lifespans, including the very long-living Methuselah mice with knock out of the receptor for GH. Humans with GH receptor deficiency (Laron syndrome) have less incidence of cancer and diabetes. Many of the downstream effects on aging pathways are mediated by FOXO (forkhead box O) transcription factors. Genetic variation in some FOXO genes is associated with longevity in humans.
2. mTOR pathway. This pathway is activated by amino acids via tRNA and the IIS and therefore can be manipulated by dietary protein intake. Inactivation of mTOR by dietary restriction or rapamycin is associated with reduced protein synthesis and increased autophagy, leading to increased lifespan.
3. Sirtuins. The sirtuins are a class of seven proteins that respond to CHAPTER 488 dietary energy via the cofactor NAD. Sirtuins regulate gene expression via deacetylation of histone and nonhistone proteins and have been shown to impact many processes related to aging, including apoptosis, inflammation, DNA damage/repair, and mitochondrial biogenesis. Increased sirtuin activity induced by genetic manipulation, resveratrol, or NAD supplementation has been associated with increased lifespan.
4. AMP-activated protein kinase (AMPK) responds to dietary energy Biology of Aging restriction via cellular levels of AMP. Activation of AMPK with metformin increases lifespan in animals, and observational studies in humans suggest that metformin impacts age-

related conditions. Human clinical trials of metformin are underway to determine its effects on aging.

5. Fibroblast growth factor 21 (FGF21) responds to dietary protein, with protein restriction leading to increased production and release into the blood. FGF21 promotes AMPK signaling and insulin sensitivity, and overexpression in mice increases lifespan. ■
- **MITOCHONDRIAL DYSFUNCTION** Age-related changes in mitochondria include increased electron leak and decreased ATP production, primarily due to impaired complex IV activity. Mitochondrial DNA damage accumulates with age, and mitochondria may become swollen with disrupted cristae. Impaired mitochondrial function leads to increased generation of superoxide radicals and hydrogen peroxide, which are potent oxidants. Consequently, aging is associated with the accumulation of oxidative damage to fat, proteins, and DNA. This forms the basis of the free radical theory of aging. Antioxidants have been investigated as a method to delay age-related oxidative stress but have been ineffective in delaying aging. On the other hand, many of the nutritional and pharmacologic interventions that delay aging are associated with increased mitochondrial biogenesis, usually via their effect on the PGC1 α transcription factor. ■
- **CELLULAR SENESENCE** Senescent cells have stopped dividing because of either telomere shortening or other damage mediated by the INK4/ARF system. Senescent cells (sometimes called zombie cells) accumulate in various tissues with increasing age. They produce a range of inflammatory cytokines including interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α), collectively called the senescence-associated secretory phenotype (SASP), which contributes to systemic inflammation. Elimination of senescent cells that express INK4 and several drugs that eradicate senescent cells called senolytics (e.g., dasatinib, quercetin, fisetin) delay the progression of age-related pathologies. ■
- **STEM CELL EXHAUSTION** The numbers of stem cells decline with aging, probably secondary to replicative senescence and telomere shortening. Transplantation of pluripotent stem cells from young donors to old recipients extends lifespan in mice and may improve frailty in humans. Another strategy involves induction of genes that regulate stem cells (Yamanaka OSKM factors:

GENE Genomic instability Epigenetic alterations Telomere attrition METAORGANISM MAINTENANCE OF HOMEOSTASIS Dysbiosis Integrity of cellular barriers Recycling and turnover Circadian rhythm PART 18 Aging Hormesis Cellular resilience Repair and regeneration SYSTEM Inflammation CELL Altered cellular communication Cellular senescence Deregulated nutrient sensing pathways Stem cell depletion FIGURE 488-5 The hallmarks of aging include 12 processes that form the foundations of the biological changes of aging and age-related diseases and syndromes. OCT4, SOX2, KLF4, MYC), which delays aging in progeria mouse models. After bone marrow transplantation, no evidence suggests that the recipient runs out of donor stem cells even though the stem cell population could be compromised numerically and due to the age of the donor. Can the stem cells renew themselves in the new host? Lipofuscin Lewy bodies Neurofibrillary tangles Amylin FIGURE 488-6 Impaired proteostasis with old age contributes to the accumulation of aggregates often associated with disease (lipofuscin in the liver, Lewy bodies in the substantia nigra, neurofibrillary tangles in neurons, and amylin in pancreatic islets).

■ **ALTERED INTRACELLULAR COMMUNICATION** Many signaling pathways undergo changes with old age including insulin/IGF-1, dopaminergic, sex hormones, growth differentiation factor 11 (GDF11), and the renin-angiotensin system. These and other bloodborne factors might explain

some of the antiaging effects of blood transfusions. Age-related changes are also noted in the extracellular matrix, including increased fibrosis, that impact cell-to-cell communication.

ORGANELLE ■ ■ CHRONIC INFLAMMATION Aging is associated with low-grade activation of the innate immune system, leading to elevated levels of IL-6 and TNF- α and often elevated C-reactive protein and erythrocyte sedimentation rate (ESR) with a lower lymphocyte-to-neutrophil

ratio. This has been called “inflammaging.” This may be secondary to several factors including the SASP, chronic infection with cytomegalovirus, obesity, leaky gut, and activation of the nuclear factor κ B (NF- κ B) pathway. Inflammation is a key factor in the pathogenesis of many chronic diseases and, in particular, frailty. Mitochondrial dysfunction Disabled macroautophagy Loss of proteostasis ■ ■ **DYSBIOSIS** Complex changes occur in the gut microbiome with old age in humans. The degree of microbial heterogeneity declines, and changes are seen in some species and phyla (e.g., Bacteroidetes, Akkermansia). Fecal microbiome transplantation and various probiotics have some effects on aging in mice. **GEROSCIENCE** Old age is the major risk factor for many chronic diseases. The nature of the relationship has been the source of debate for millennia. On one hand, it has been argued that aging is similar to any other disease and, therefore, is amenable to therapeutic interventions. On the other hand, it has been argued that aging is an inevitable and untreatable process that increases the risk for other diseases. Regardless, there is a marked and often exponential increase in the prevalence and incidence of most chronic diseases with age (Fig. 488-2), and there are several conditions that are generally considered to be primarily age-related disorders, including dementia, sarcopenia, frailty, and osteoporosis. These conditions are very rare below the age of 50 years. Geroscience refers to the study of the relationship between aging biology and disease. Aging leads to impairment of many physiologic systems that will increase susceptibility to disease. For example, aging is associated with marked changes in immune function. Immunosenescence refers to age-related deterioration of the responsiveness of the immune system to infection and other antigenic challenges, caused by thymic involution with reduced naïve T cells and impaired memory T cells, a reduction in hematopoietic stem cells, and impaired antigenpresenting cell function. Aging is associated with many endocrine changes, most notably a reduction in sex steroids and GH, which contributes to sarcopenia and osteoporosis. Vascular changes including increased arterial stiffness leading to high peripheral vascular resistance and microvascular pathology have an obvious link with cardiovascular disease, but also probably contribute to other conditions such as dementia, osteoarthritis, and sarcopenia. Although the usual dogma is that aging is a process that increases susceptibility to diseases, the relationship between chronic disease and aging may be much more fundamental. The pathogenesis of most chronic diseases includes one or more of the hallmarks of aging, and differences between disease and normal aging are defined by a quantitative difference in the expression of these hallmarks and the tissues that are affected. Likewise, the difference between aging and

Dietary energy Dietary calories Nutrient-sensing pathways AMPK SIRT1 mTOR Insulin/IGF-1 FGF21 Key downstream proteins ATG FOXO PGC1A S6K Fundamental cellular functions influenced by diet and aging Autophagosome autophagy proteostasis Nucleus regulation transcription **FIGURE 488-7** Nutrient sensing pathways. The main molecular switches that respond to changes in dietary intake (blue boxes: insulin/IGF-1, mTOR, AMPK, SIRT1, FGF21) influence a range of downstream intermediaries (some of these are shown in the gray boxes). These regulate key cellular processes (white boxes) including metabolism, autophagy, mitochondria, and protein synthesis. disease in terms of the clinical features is often based on quantitative differences. Therefore, there is a

continuum between aging and many chronic diseases. These are often separated by so-called “prediseases” or “subclinical diseases,” which are evidence for this continuum. Then, chronic disease can be considered a manifestation of aging that is predominant in a particular tissue. The presence of several chronic diseases, termed multimorbidity, represents aging changes that are more advanced in several tissues. Frailty can be defined as a multisystem aging syndrome where aging changes are present in most tissues, leading to multiple deficits and impaired function.

STRATEGIES THAT INCREASE HEALTH SPAN AND DELAY AGING Aging is an intrinsic feature of human life whose manipulation has fascinated humans ever since becoming conscious of their existence. Several long-term experimental interventions (e.g., resveratrol, rapamycin, spermidine, and metformin) may open doors for pharmacologic strategies. Surprisingly, most of the effective aging interventions proposed to date converge on only a few molecular pathways: nutrient signaling, mitochondrial proteostasis, and the autophagic machinery. Lifespan is inevitably accompanied by a gradual functional decline, steady increase of several chronic diseases, and ultimately death. For millennia, it has been a dream of mankind to prolong both lifespan and health span. Developed countries have profited from advances in medical care and technology, improvements in their public health care systems, and better living conditions derived from their socioeconomic power—to achieve remarkable increases in life expectancy during the past century. In the United States, the percentage of the population aged ≥ 65 is projected to increase from 13% in 2010 to 19.3% in 2030. However, old age remains the leading risk factor for major life-threatening disorders. The number of people suffering from age-related diseases is anticipated to almost double over the next two decades. The prevalence of age-related pathologies represents a major threat and an economic burden that urgently needs effective interventions. Molecules, drugs, and other interventions that might decelerate aging processes continue to be a major focus among the general public and scientists of all biological and medical fields. Over the past three decades, this interest has taken root because many of the molecular mechanisms underlying aging are interconnected and linked with pathways that cause diseases, including cancer and cardiovascular and neurodegenerative disorders. Unfortunately, results often lack reproducibility because of the unavoidable problem of the time needed to assess the effectiveness of antiaging interventions in mammals. Experiments lasting the lifetime of animal models are prone to develop

CHAPTER 488 Endoplasmic reticulum protein synthesis Cytoplasm metabolism of fats and carbohydrates Mitochondria ATP synthesis Biology of Aging artifacts, increasing the possibilities and time windows for experimental discrepancies. Some inconsistencies in the field arise from over interpreting the results of animal models with shortened lifespan and scenarios of accelerated aging. Molecules, drugs, and other interventions have been proposed to have antiaging properties throughout history and into the present. In the following sections, interventions will be restricted to those that meet the following highly selective criteria: (1) promotion of lifespan and/or health span, (2) validation in at least three model organisms, and (3) confirmation by at least three different laboratories. These include CR and intermittent fasting regimens, some pharmacotherapies (resveratrol, rapamycin, spermidine, and metformin), and exercise. ■ ■ **CALORIC RESTRICTION** One of the most important and robust interventions that delays aging is CR. This outcome has been recorded in rodents, dogs, worms, flies, yeasts, monkeys, and prokaryotes. CR is defined as a reduction in the total caloric intake, usually of $\sim 30\%$, and without malnutrition. CR reduces the nutrient-mediated release of growth factors, such as GH, insulin, and IGF-1, which have been shown to accelerate aging and enhance the probability for mortality in many organisms. Yet, the effects of CR on aging were first discovered by McCay in 1935, long before the discovery of these

hormones and growth factors and signaling properties. Some of the pathways that mediate this remarkable response of CR have been elucidated in experimental models. These include the nutrient-sensing pathways (mTOR, AMPK, insulin/IGF-1, and sirtuins) and the family of FOXO transcription factors (orthologs are found in *D. melanogaster* and *C. elegans*). The transcription factor Nrf2 appears to confer most of the anticancer properties of CR in mice, even though it is dispensable for lifespan extension. The effects of CR in monkeys have been assessed in two studies with different outcomes: one study observed prolonged life, while the other did not. In these monkey studies, there were key differences in the onset of the intervention, diet composition, feeding protocols, and genetic background that may explain this discordance. However, both studies confirmed that CR increases health span by reducing the risk for diabetes, cardiovascular disease, and cancer. In humans, CR is associated with extended lifespan and increased health span. 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 moved to Brazil, they adopted a Western lifestyle that affected both exercise and nutrition,

causing a rise in weight and a reduction in life expectancy by nearly two decades. In the Biosphere II project, volunteers lived together for 24 months undergoing an unforeseen severe CR that led to improvements in insulin, blood sugar, glycated hemoglobin, cholesterol levels, and blood pressure—all outcomes that would be expected to benefit lifespan. CR changes many aspects of human aging that might influence lifespan such as the transcriptome, hormonal status (especially IGF-1 and thyroid hormones), oxidative stress, inflammation, mitochondrial function, glucose homeostasis, and cardiometabolic risk factors. Epigenetic modifications are also an emerging target for CR. The first clinical trial of CR in people at average weight (a body mass index between 20 and 25) started in 2007. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) included 143 adults between the ages of 21 and 50 years intending to reduce their caloric intake by 25% of their typical intake for 2 years; also included was a group of 75 people who remained on their normal diets and caloric intake. CALERIE has provided evidence for improvements to the quality of life, immune health, cardiometabolic integrity, liver function, and skeletal muscle quality, even though the participants only reached a moderate level of CR ($11.9 \pm 0.7\%$) over the 2-year span. CR in this clinical trial also led to a reduction in the rate of biological aging measured by a series of common clinical biomarkers of preservation of physiologic and functional integrity (e.g., liver enzymes, albumin, fasting blood glucose, insulin, and blood pressure). At the molecular level, gene expression analyses in a subset of CALERIE participants indicate that CR induces the regulation of core longevity pathways linked to the preservation of mitochondrial function and stability, lowering chronic inflammation and reducing oxidative stress.

PART 18 Aging ■ ■ PERIODIC FASTING It must be noted that maintaining CR while avoiding malnutrition over a long period of time is not only arduous in humans but 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. How can CR be translated to humans in a socially and medically acceptable way? A whole series of periodic fasting regimens are asserting themselves as suitable strategies, among them (1) the alternate-day fasting diet, (2) the “5:2” intermittent fasting diet, (3) a 48-h fast once or twice each month, and (4) daily time-restricted feeding (TRF). Periodic fasting is

psychologically more viable, lacks some of the negative side effects of CR, and is only accompanied by minimal weight loss. All these dietary interventions involve a substantial reduction of caloric intake for a defined period and typically lead to an elevation of circulating ketone bodies during those low-calorie intake periods, illustrating the metabolic switch from the utilization of glucose as a fuel source to the use of fatty acids and ketone bodies. This metabolic shift results in a reduction in the respiratory exchange ratio (the ratio of carbon dioxide produced to oxygen consumed), indicating greater metabolic flexibility and energy production efficiency from use of fatty acids and ketone bodies. It is striking that many cultures implement periodic fasting rituals, for example, some Buddhists, Christians, Hindus, Jews, Muslims, and practitioners of 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 nursing home residents who underwent alternate-day fasting. Rats subjected to alternate-day fasting live up to 83% longer than control animals fed ad libitum, and even 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 CR. This strategy may even yield health benefits despite overeating behavior during the nonfasting periods. In a landmark experiment, mice fed a high-fat diet in a time-restricted manner, i.e., with regular fasting breaks, showed reduced inflammation markers, did not develop fatty liver, and were slim in comparison

to mice fed ad libitum despite equivalent total calories consumed. 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 times of food scarcity. 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 health span by minimizing the risk of developing age-related diseases, including hypertension, neurodegeneration, cancer, and cardiovascular disease. The most effective and rapid repercussion of fasting is a reduction in hypertension. Two weeks of water-only fasting resulted in blood pressure <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 also dampens the consequences of many age-related neurodegenerative diseases in mouse models of Alzheimer's disease, Parkinson's disease, Huntington's disease, and frontotemporal dementia, but not amyotrophic lateral sclerosis. Fasting cycles are as effective as chemotherapy against certain tumors in mice. When combined with chemotherapy, fasting protects mice against the negative side effects of chemotherapeutic drugs, while enhancing efficacy against tumors. Combining fasting and chemotherapy rendered 20–60% mice cancer-free when inoculated with highly aggressive tumors like glioblastoma or pancreatic tumors, which have 100% mortality even with chemotherapy. ■ ■ PHARMACOLOGIC

INTERVENTIONS TO

DELAY AGING AND INCREASE LIFESPAN Virtually all obese people know that stable weight reduction will lower their risk of cardiometabolic disease and enhance their overall survival, and yet only 20% of overweight individuals are able to lose 10% weight for a period of at least 1 year. Even in the most motivated people (e.g., the “Cronies” who deliberately attempt long-term CR to extend their

lives), long-term CR is extremely difficult to adhere to. Thus, much focus has been directed at the possibility of developing medicines that replicate the beneficial effects of CR but without the need for reducing food intake ("CR-mimetics," Fig. 488-8).

- **Resveratrol.** Resveratrol, an agonist of SIRT1, is a polyphenol that is found in grapes and 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 has been suggested to 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 fish, as well as mice on high-fat diets. In monkeys fed a diet high in sugar and fat, resveratrol had beneficial effects.
- **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 emergence in the antiaging arena, rapamycin was known 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 in lifespan extension in humans is likely to be limited by adverse effects related to immunosuppression, impaired wound healing, proteinuria, and hypercholesterolemia, among others. An alternative strategy may be the implementation of intermittent rapamycin treatment, which was found to increase mouse lifespan.
- **Spermidine.** Spermidine is a physiologic polyamine that induces autophagy-mediated lifespan extension in yeast, flies, and worms. Endogenous spermidine levels decrease during life in virtually all organisms including humans, with the remarkable exception of centenarians. Oral administration of spermidine or upregulation of bacterial polyamine production in the gut leads to lifespan extension in short-lived mouse models. The lifespan effects of spermidine are mediated through the inhibition of histone acetylases and the activation of autophagy genes, such as atg7, atg11, and atg15 (Morselli et al., 2009). Spermidine has also been found to have beneficial effects on neurodegeneration and cardioprotection through activation of autophagy. Spermidine supplementation is safe in humans and has been associated with positive effects on cognitive function of older adults and on blood pressure maintenance.
- **Metformin.** Metformin, a biguanide first isolated from the French lilac, is widely used for the treatment of type 2 diabetes. Metformin decreases hepatic gluconeogenesis and increases insulin sensitivity. Other actions of metformin include AMPK activation, leading to mTOR inhibition and lower mitochondrial complex I activity, and activation of the transcription factor SKN-1/Nrf2. Metformin increases lifespan in different mouse strains including female mice 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 CR. Based on experimental data on the positive outcomes in model organisms and the evidence emerging from epidemiologic studies, a clinical

outcomes related to inflammation and cardiometabolic parameters. Some studies in humans have also shown improvements in cardiometabolic function, while others have not. Studies in animals and humans reveal that resveratrol mimics some of the metabolic and gene expression changes of CR. In most experimental models, resveratrol induces beneficial health effects by suppressing inflammation, oxidative damage, tumorigenesis, and immunomodulatory activities. Resveratrol also leads to improvements in mitochondrial function and protection against obesity, cancer, and cardiovascular dysfunction.

FIGURE 488-8 Chemical structure of four agents (resveratrol, rapamycin, spermidine, and metformin) that have been shown to delay aging in experimental animal models.

trial known as TAME (Tar getting Aging with Metformin) has been initiated to assess whether metformin can delay the onset of age-related diseases beyond its effects on glucose metabolism. TAME is planning to enroll 3000 subjects, ages 65–79, in a multicenter trial in the United States. ■

■ **EXERCISE AND PHYSICAL ACTIVITY** In humans and animals, regular exercise reduces the risk of morbidity and mortality. Given the marked increase in cardiovascular disease in the elderly, the effects of exercise on human health may be even stronger than those seen in laboratory mice, as mice do not develop atherosclerosis and have a far lower incidence of age-related cardiovascular disease. 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 disease, diabetes mellitus, and osteoporosis. Exercise

is the only intervention 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 length of stay in independent living.

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

■ **HORMESIS** Paradoxically, the term hormesis describes the protective effects conferred by the exposure to low doses of stressors or toxins (or as Nietzsche stated, “What does not kill me makes me 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. CHAPTER 488 Biology of Aging Yeast cells that have been exposed to low doses oxidative stress exhibit a marked anti-stress-like 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*. CR can also be considered as a type of hormetic stress that results in the activation of antistress transcription factors (e.g., Rim15, Gis1, and Msn2/Msn4 in yeast, Nrf2 and FOXO in mammals) that enhance the expression of free radical-scavenging factors and heat shock proteins. CONCLUSIONS Clinicians need to understand aging biology to better manage and care for the elderly. Moreover, strategies based on aging biology are needed that delay aging, reduce the onset of age-related disorders, and increase health span for future generations. Dietary interventions and drugs that act on nutrient-sensing pathways are being developed and, in some cases, are already being tested in humans. Well-controlled human clinical trials have started to recapitulate the preclinical evidence of intermittent fasting on obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. While most animal studies show that intermittent fasting improves health throughout the lifespan, most human studies are focused on relatively short-term interventions over a few days or months. While

intriguing, it remains to be seen whether people will be willing to maintain strict intermittent fasting regimens over long periods of time or if short-term clinical benefits can be obtained in combination with other therapeutic approaches. ■ ■ FURTHER READING Ferrucci L et al: Measuring biological aging in humans: A quest. *Aging Cell* 19:e13080, 2020. Le Couteur DG, Thillainadesan J: What is an aging-related disease? An epidemiological perspective. *J Gerontol A Biol Sci Med Sci* 77:2168, 2022. López-Otín C et al: Hallmarks of aging: An expanding universe. *Cell* 186:243278, 2023. Morselli L et al: Autophagy mediates pharmacological life extension of spermidine and resveratrol. *Aging* 1:961, 2009.

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