Older Adults

Anti-aging Therapies and Cosmeceuticals: An Evidence-Based Update

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Learning Objectives

1. Distinguish among genetic, biologic, and environmental influences on the overall aging process as well as the aging of skin.
2. Using an evidence-based approach, evaluate potential anti-aging interventions in humans.
3. Assess patient risk factors that lead to aging of the skin to determine potentially reversible extrinsic and intrinsic causes that contribute to premature aging of the skin.
4. Given a patient's risk factors, recommend appropriate cosmeceuticals to prevent and reverse aging of skin.
5. Distinguish among common anti-aging ingredients in topical skin care products to help consumers make informed purchases.

Introduction

Overview of Aging in the United States and Implications

Between 1946 and 1964, 77.7 million Americans were born into what is known as the "baby boomer" generation. The aging of this large cohort of people, coupled with an increase in life span of the population, is causing a dramatic change in the age demographics in the United States. By 2030, 70 million Americans will be older than 65 years, accounting for 20% of the U.S. population. Life expectancy for those born in 2003 is projected to be 77.4 years; however, people who were 65 years old in 2003 will live an average of 18.5 additional years, and those who were 85 years old can expect to live an additional 6.6 years. This increase in life expectancy is the result of decreases in death from heart disease, malignant neoplasm, and cerebrovascular disease for both men and women.

The baby boomers are better educated, have higher household incomes, and live in households that are smaller than any previous generation. Their poverty rate of 7.3% is lower than any other segment of the U.S. population. This large group of aging Americans has the desire and means to live "younger" for longer periods. Pharmacists with knowledge of the evidence supporting pharmaceutical interventions that purport to extend life or reduce the effects of aging on the skin will be able to meet the educational needs of this group of people.

Definitions Used to Describe Aging in the Literature

Aging is generally considered a natural process for most species and not a disease or condition that can be treated per se. Age is usually defined in chronologic years, but most geriatricians and other clinicians argue that this measurement is not sensitive or descriptive in functional ways, given the wide heterogeneity in individuals who are "old." For instance, we all know people in their 90s who live independently and function at a high level and also individuals in their 60s with high disease burdens who are dependent on others for their care. The *maximal life span* is the greatest number of years a member of a group or species has been observed to survive. For humans, that is about 115–120 years. Jeanne Calment of France lived to be 122.5 years based on documentation consistent with modern record-keeping methods. The *mean life span*, or life expectancy, is the amount of time most humans can expect to live (currently, about 78 years). The maximal life span has remained remarkably constant throughout history despite significant gains in life expectancy.

Aging is more than the simple passage of time, and most people want to be highly functional and healthy in their older years. Thus, additional aging terms such as *healthy life span,* appear in the literature. Some people advocate that a compression of morbidity should be an aging goal; this implies that people live at a high functional level for most of their life expectancy and that the age-associated diseases that might cause death are compressed into as short a time as possible. This goal clearly is not reached by the many older people who suffer from chronic diseases that affect function for years, such as those with complications secondary to diabetes, cerebrovascular and cardiac disease, bone and joint disease, and neurodegenerative diseases such as Parkinson's and Alzheimer's.

Abbreviations in This Chapter

DHEA	Dehydroepiandrosterone
FDA	U.S. Food and Drug Administration
SIR	*Saccharomyces cerevisiae* silent information regulator (gene family)
SIRT1	*SIR2* homolog 1 (mammalian gene)
SPF	Sun protection factor; sunburn protection factor
UVA	Ultraviolet A
UVB	Ultraviolet B

An Update on the Biology of Aging

Wear and Tear Theory

Aging is the accumulation of slow and progressive decline throughout cells and tissues in humans that results in a loss of function, an increase in susceptibility to disease, and eventually death. This deterioration in cellular and human function is biologically based and can respond to changes in the cellular environment. One of the most-investigated hypotheses of aging is the wear and tear theory. Aging of the cells and eventually the whole person is believed to be caused by a lack of repair processes from the accumulating damage from free radicals. Most free radicals are a by-product of the biochemical process of adenosine triphosphate synthesis in cells. As we age, more free radicals are formed and are more likely to leak out of the mitochondria, gaining exposure to and damaging DNA. Many of the present anti-aging strategies are proposed to limit free radical damage to cells at the various steps of the aging process.

The series of free radical changes occurs as we age because the pattern of gene expression changes between an old and young cell. As cells divide, the long piece of DNA on the end of the chromosome (i.e., the telomere) shortens, leading to slight changes in gene expression. In different cellular lines, when the telomere is prevented from shortening, cells do not age as they divide. Using animals with skin grafts of "old" skin, the gene expression can be reset with telomerase so that the graft produces "young" skin. Investigations are now under way to evaluate the best method for resetting human telomerase gene expression in diseases such as Hutchinson-Gilford progeria in children. Conditions associated with aging, such as osteoarthritis, atherosclerosis, and skin wrinkling, may become future opportunities to target telomerase gene expression.

Endocrine Theory

Many hormones and nutrients decline with aging at a time during the human life span that coincides with the onset of degenerative changes, some chronic diseases, and functional loss. In women, loss of estrogen and progesterone during menopause is an important example of hormone loss that occurs with aging and may lead to osteoporosis and fractures. In older men, testosterone concentrations are substantially lower than those observed in younger men and may be related to decreases in lean muscle mass and other changes in body composition. Growth hormone falls by about 12% per decade beginning in midlife. Recently, investigators hypothesized that frailty syndrome in older people (sometimes referred to as *failure to thrive*), which leads to anemia, sarcopenia, weight loss, and loss of physical function, is partly the result of low vitamin D_2 concentrations and that some of these changes are reversible with replacement therapy. Other compounds with a biologic function that is not well understood also decline with age, such as dehydroepiandrosterone (DHEA), the largest component of adrenal gland secretions and hormones. One approach or theory to prevent aging is to replace hormones (or other substances) that decline as we get older to prevent loss of function or delay the onset of age-associated disease.

Genetic Theory

Genetic explanations for aging generally began with a theory referred to as programmed aging. This theory implied that a genome, programmed to activate at a certain point, leads to self-destructive cellular actions. This could mean that the activation of a gene or family of genes somehow leads to senescence. It could also imply that some genes that are essential for early development (reproduction) are detrimental to the life cycle during a long period. Several gene families are under investigation; however, the *Saccharomyces cerevisiae* silent information regulator (*SIR*) family has been most extensively investigated. One member of the *SIR* family of genes in yeast, the *SIR2* gene, encodes an enzyme called Sir2 that prevents the deacetylation of DNA. In yeast cells, the addition of an extra copy of *SIR2* results in cells that remain healthy and divide longer. Calorie restriction increases the expression of the *SIR* family of mammalian genes known as *SIR2* homolog 1 (*SIRT1*). The *SIRT1* gene is the mammalian equivalent of the yeast gene; it encodes a similar enzyme (called Sirt1) that deacetylates several proteins that control apoptosis and cellular function. In mammals, when Sirt1 is released, cells are capable of surviving stress that normally leads to programmed cell death. The Sirt1 enzyme influences additional biologic processes related to aging and chronic disease, such as (1) insulin and fat storage and (2) DNA repair and survival. There is also overlap among different families of genes linked to aging that might reflect a cascade of actions. For instance, the family of genes known as the mammalian target of rapamycin regulates upstream of *SIRT1*, and the forkhead box O family has complex and interrelated actions on longevity in mammals. Some of these genes are influenced by pharmaceutical agents with theoretical anti-aging effects. Metformin activates an enzymatic pathway that inhibits the mammalian target of rapamycin. Resveratrol activates *SIRT1* and suppresses the phosphorylation of enzymes that decrease the mammalian target of rapamycin. Sirolimus (rapamycin) inhibits the mammalian target of rapamycin in a pleiotropic fashion, meaning that it inhibits both yeast growth and yeast senescence.

The three theories presented are not the only theories under investigation to explain aging, but they are the theories with the most support. It is unlikely that any single theory explains aging. It is more likely that several complex

overlapping processes contribute to aging. As we learn more of the genetic, biologic, and environmental causes of age-associated disease, in addition to the information from nonhuman models of aging research, we may uncover mechanisms that can be used to treat many of the chronic diseases linked with aging as well as extend the functional human life span.

Anti-aging Interventions

Calorie Restriction

Restricting caloric intake while maintaining good nutrition is a proven method of extending life in a variety of species such as yeast, worms, flies, rodents, and dogs as well as, perhaps, nonhuman primates. If caloric intake is reduced by 30% to 40% of the normal amount for that species, the animal lives longer and does not develop as many age-associated diseases as expected for that species. In most nonmammalian species studied, both maximal life span and maximal life expectancy have increased. Originally, scientists believed that limiting calories reduced the formation of free radicals by decreasing cellular activity. An additional mechanism supported by recent research is that calorie reduction in nonhuman species causes a recurring mild stress to cells that improves both protective and repair processes. In the literature, this adaptive response of species or cells to low levels of stress is sometimes referred to as hormesis.

The protective and repair processes are highly regulated through genetic mechanisms, and the genes identified are conserved through evolutionary processes from many different species to human systems. Much of what has been proved recently about the genetic control of aging is from calorie restriction research in yeast, fruit flies, and earthworms using families of genes that are preserved in the evolutionary tree and expressed in mammals and humans. For instance, in yeast models, caloric restriction improves *SIR* enzymatic activity, which leads to improved DNA stability, increased cellular repair, and prolonged cell survival, extending life span by about 30%. The enzymes from the *SIR* family are known as the sirtuins, and sirtuin-activating compounds are an active area of new drug investigation. Recently, two sirtuin transcription factor proteins that regulate the expression of many genes in the nematode were shown to be responsible for the increased longevity of that species.

An understanding of the biologic mechanisms that underlie an association between caloric restriction and increase in life span will likely lead to pharmaceutical compounds to prevent some of the steps of aging. Human experimental data that support calorie reduction as an anti-aging intervention are limited to one small study. On September 26, 1991, eight individuals entered Biosphere 2, a 3.2-acre closed ecologic system outside Tucson, Arizona, as part of a 2-year experiment to see whether people could live in a closed ecologic system with all of their air and water recycled and food created. The volunteers consumed a diet that was nutrient dense and low in fat. The calorie deficit was not intentional but was related to the availability of food in the Biosphere 2 ecosystem. These nonobese individuals lost an average of 17% plus or minus 5% of their preentry body weight. Many physiologic parameters were monitored during and after the 2-year period; significant changes are summarized in Table 1-1.

Many of the biologic changes that occurred with caloric restriction and weight loss in the subjects of the Biosphere project were expected to lower the incidence of cardiovascular and metabolic diseases linked with aging. However, there are no data to show that people live longer with caloric restriction as an anti-aging intervention. Because there is insufficient evidence in humans, recommendations for calorie restriction as an intervention to increase longevity are not advisable. However, maintaining one's weight at a lean value by eating a diet rich in vegetables, whole grains, and low-fat sources of protein is clearly consistent with health promotion guidelines for disease prevention from many organizations. Although there is no evidence in humans that this type of diet results in a longer life, this diet lowers the incidence of many diseases that are associated with aging, such as coronary, cerebral, and peripheral artery disease; diabetes; and some types of cancer. There are other health concerns to consider with the caloric restriction intervention. In men, testosterone and other hormone concentrations decline, which may place men at risk of osteoporosis and bone fractures. There are also concerns about the emotional effects of this intervention, which can include obsessive thoughts about food and lead to food fantasies. Finally, the focus of caloric restriction is on limiting calories consumed and not weight reduction (which could be viewed as an adverse effect of this intervention). Individuals at risk of anorexia syndromes should be strongly discouraged from following this unproven intervention.

Antioxidants

Many substances, particularly nutritional supplements, have antioxidant properties. As an anti-aging strategy, antioxidants are expected to lessen cellular damage that occurs from the formation of free radicals in the mitochondria. Antioxidants have been evaluated in the treatment of many diseases linked with aging, such as the

Table 1-1. Biologic Changes Seen During Unintended Calorie Restriction in Biosphere 2[a]

Biologic Variable	Preentry Values	After 2 years	After 4 years[b]
Body mass index (kg/m^2)	23	21.5	24
Systolic blood pressure (mm Hg)	108	91	111
Diastolic blood pressure (mm Hg)	77	60	73
Total cholesterol (mg/dL)	188	135	172
High-density lipoprotein (mg/dL)	60	51	57
Low-density lipoprotein (mg/dL)	105	71	80
Triglycerides (mg/dL)	115	65	140
Androstenedione	105	176	140

[a]Values presented are the mean of the eight crew members; values were significantly different after 2 years compared with preentry values. The eight crew members resided in the Biosphere for 2 years, with long-term follow-up data 4 years after entry.
[b]Values at 4 years were obtained after Biosphere participants had been living outside the sphere for 2 years after study completion and while consuming their normal unrestricted diet.

prevention of coronary artery disease, the treatment of degenerative neurologic diseases, and the reduction in the risk of stroke. Several prospective randomized, controlled clinical trials have evaluated antioxidants (vitamin E, vitamin C, and carotenoids) on cardiovascular and cerebrovascular diseases with negative results. In particular, vitamins E and C do not reduce the risk of cardiovascular mortality or stroke, whereas carotenoids may increase mortality. There is inconsistent evidence that vitamins E and C decrease serum cholesterol and low-density lipoprotein concentrations, but no evidence for an improvement in mortality has been demonstrated.

Vitamin E

Vitamin E, or α-tocopherol, has been evaluated for the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's. A review of vitamin E for the treatment of Alzheimer's disease and mild cognitive impairment found only two studies that were double-blind randomized trials. There are no data to support the role of α-tocopherol in the treatment of mild cognitive impairment, and only one trial shows lack of decline for patients with advanced Alzheimer's disease receiving 2000 IU of α-tocopherol per day. With compounds that occur naturally in food, it is often not known exactly which form of a vitamin or other ingredient is responsible for positive effects. With vitamin E, γ-tocopherol may be an important ingredient in addition to α-tocopherol.

Coenzyme Q10

Coenzyme Q10, or ubiquinone, is a lipid-soluble benzoquinone available as a nutritional supplement. Coenzyme Q10 is an essential cofactor in the mitochondrial electron transport for adenosine triphosphate synthesis. Coenzyme Q10 is a potent antioxidant because it is present in all cellular membranes and removes oxygen free radicals in the mitochondria. Coenzyme Q10 is under evaluation for the treatment of heart disease and degenerative neurologic diseases. Recently, a pilot study was published suggesting coenzyme Q10 is beneficial in the treatment of early untreated Parkinson's disease. A follow-up randomized double-blind futility trial suggests that coenzyme Q10 merits further study, although the improvement in outcome measure scores was small. Dosages used in this early phase of clinical research are between 1200 mg/day and 2400 mg/day, and no adverse effects have been reported. Although the literature is enthusiastic with respect to the potency of antioxidant effects with coenzyme Q10, little evidence supports its use for neurodegenerative or ischemic diseases, and no evidence has been published with respect to an anti-aging effect.

Hormones and Nutrients

Concentrations of some hormones and nutrients decline with age; this is linked with age-associated changes and age-linked chronic diseases. This section reviews hormones commonly used as anti-aging replacements. Even though there may be strong epidemiologic evidence showing associations between lower concentrations of certain compounds and some common age-associated changes, such evidence and changes do not mean that replacement with the compound reverses or prevents aging.

DHEA and Testosterone

Concentrations of DHEA and its sulfated metabolite decline markedly in humans after about age 30. Research studies in animals suggest that decreasing concentrations of DHEA are linked to age-associated diseases such as cardiovascular disease and diabetes. Some epidemiologic data in humans suggest that DHEA concentrations are positively associated with long life; however, the function of DHEA in humans is largely unknown. In one randomized clinical trial, older individuals with low DHEA concentrations received replacement therapy with DHEA (female participants) or both DHEA and testosterone (male participants). Replacement increased testosterone and DHEA concentrations in the study participants, and a slight increase in bone mineral density was observed. Replacement of testosterone in older men with low serum concentrations may lead to unacceptable adverse effects, including prostate enlargement and perhaps prostate cancer. The Dehydroepiandrosterone and WellNess (DAWN) study, a clinical trial, is under way to evaluate the therapeutic replacement of 50 mg of DHEA for 1 year in people aged 55–85. The DAWN study intends to further explore the sex-specific differences in metabolism of oral DHEA and the subsequent effects on physiologic outcomes.

Recently, replacement of testosterone was evaluated in older men with low normal serum concentrations of testosterone. The goal of this randomized, double-blind, placebo-controlled trial was to evaluate the effect of oral testosterone on functional mobility, cognition, bone mineral density, body composition, and quality of life during a 6-month period. Individuals were, on average, 67 years old and in good health, and they received 80 mg of testosterone undecenoate twice daily. At study conclusion, significant improvements were found in body composition (a decrease in fat mass and an increase in lean body mass). Cognitive and physical function did not change. This study is consistent with other research showing minimal improvement with testosterone replacement in older men with low serum testosterone concentrations.

Human Growth Hormone

In the early 1990s, an article was published evaluating the effect of growth hormone replacement in 21 healthy elderly men for 6 months. Most of the individuals treated showed improvements in body composition, such as increased lean body mass and decreased adiposity. This article helped generate interest in growth hormone as an intervention to reverse some of the commonly seen biologic changes associated with aging.

Growth hormone is labeled for the treatment of severe short stature in children from various causes; the wasting syndrome associated with acquired immunodeficiency syndrome; and growth hormone deficiency in adults, which is defined by a lack of response to the growth hormone stimulation test. Congress enacted legislation in 1990 to limit access to anabolic steroids and growth hormone, with severe penalties for health care providers convicted of prescribing or distributing growth hormone outside these specific indications. Nonetheless, many Web sites and books advertise growth hormone in various pharmaceutical forms for the treatment of aging in normal adults. Worldwide, growth hormone sales range from $1.5 billion to $2.0 billion

annually, and it is estimated that 30% of all use in the United States is for off-label indications, including the treatment of aging. The data that support growth hormone as an anti-aging intervention are limited.

Vitamin D

Vitamin D is a nutrient with many positive biologic effects apart from its use to prevent and treat rickets. With ultraviolet B (UVB) radiation to the skin, humans convert 7-dehydrocholesterol to previtamin D_3, which is rapidly metabolized to vitamin D_3 in the body. Vitamin D can also be ingested in the diet and with supplements. Most supplements contain vitamin D_2, which is also the major circulating form of vitamin D evaluated by laboratory assay. Vitamin D_2 (calciferol or 25-hydroxyvitamin D) is activated in the kidneys to vitamin D_3 (1,25-dihydroxyvitamin D or cholecalciferol). Normal concentrations of vitamin D_2 should exceed 30 ng/mL, and it is estimated that 40% to 100% of community-dwelling adults are deficient in vitamin D. Older people may be vitamin D deficient because they lack sun exposure (for those living in institutions or at high latitudes), they use sunscreens that block UVB radiation, and they lack the compound in their skin (7-dehydrocholesterol) that is converted to vitamin D_3. In addition to the expected negative consequences on bone strength, deficiency of vitamin D may lead to muscle weakness and immune deficits. There is epidemiologic evidence linking disease state prevalence to geographic latitude. For instance, rates of some cancers (Hodgkin's disease and colon, pancreatic, breast, and prostate cancers) are higher in high-latitude areas of the United States compared with lower latitudes that have more sun exposure; and some immune-based diseases, such as type 1 diabetes in children, occur more often in higher latitudes.

The recommended daily allowance of vitamin D for adults 50–70 years old is 400 IU by mouth and, for adults older than 71 years, 600 IU of oral vitamin D. These amounts are not expected to maintain vitamin D_2 concentrations above 30 ng/mL in older individuals. Vitamin D_2 is about one-third as effective as vitamin D_3 in maintaining therapeutic serum concentrations, and it is recommended that the elderly consume between 800 IU and 1000 IU per day of vitamin D_3 to maintain serum concentrations greater than 30 ng/mL. To treat an older person with vitamin D deficiency, 50,000 IU of vitamin D_2 should be given every week for 8 weeks. Although there presently is enthusiasm in the geriatrics literature related to correcting low vitamin D concentrations in the elderly to prevent bone loss, fractures, muscle weakness, and perhaps other components of the frailty syndrome, there is no evidence that vitamin D replacement extends life per se, even though replacement may improve the functional life span of older people.

Gene Regulation, Sirtuins, and Sirtuin-Activating Compounds

Sirtuins are a class of enzymes that activate the *SIR2* and *SIRT1* genes, which regulate cellular reactions to stress. The *SIR2* gene encodes an enzyme that deacetylates histone proteins of DNA using nicotinamide adenine dinucleotide and prevents the accumulation of extra DNA particles in dividing mother yeast cells. The lack of extra DNA particles in the mother cells allows many more cell divisions, which extends the life of the cell.

Resveratrol is a molecule identified in the 1940s and is found in red grape skins, blueberries, lingonberries, and peanuts. Resveratrol in red wine is believed to improve health and increase longevity through antioxidant activity. It is now known that resveratrol is one of many plant-derived molecules that modulate stress, and it is considered a sirtuin-activating compound. Interest in resveratrol as a component of red wine increased substantially when it was hypothesized to be responsible for the "French paradox," the phrase that describes the low risk of heart disease in France despite a diet high in saturated fats. There is a large body of in vivo evidence evaluating the health-protective effects of resveratrol that include cancer prevention, heart disease and stroke prevention, and life extension properties. Resveratrol has many proposed pharmacological mechanisms that are summarized in Table 1-2. With respect to life extension, resveratrol is a potent inducer of deacetylase activity in the *SIRT1* and *SIR2* family of genes. Various species (yeast, nematode, fruit fly, and fish) have shown an extension of life span of between 15% and 70% when treated with resveratrol.

Many difficulties are present when evaluating the literature on resveratrol to understand how to apply the information to mammalian species for further investigation. For instance, a wide dose range of resveratrol has been used in the in vivo research, and the bioavailability of resveratrol is in question. Resveratrol undergoes extensive metabolism to sulfated conjugates and has a short half-life (about 15 minutes). If all metabolites are included, the serum half-life of resveratrol in addition to its metabolites is about 9 hours. Most red wines contain about 5 mg/L of resveratrol, suggesting that a daily intake of two glasses of red wine yields a dosage of about 27 ng/kg for a 70-kg person. This amount is substantially less than the amount used in most animal investigations that show promising pharmacological and biological effects. Increasing wine consumption to reach the doses used in animal investigations would likely lead to adverse consequences from alcohol consumption. Concentrations of resveratrol in red grape juice are about 3-fold less than in red wine.

Even though there are problems with the bioavailability of this compound in mammals, a large body of in vivo evidence shows that resveratrol has preventive effects on the onset of cancer, heart disease, and some inflammatory diseases and has life-extending properties in other animal species. Another hypothesis that may explain discrepancies between pharmacokinetics and efficacy is the presence of other compounds in red wine. For instance, quercetin is a constituent in red wine that inhibits resveratrol sulfation. Clinical trials are ongoing to evaluate the effects of resveratrol on the prevention and treatment of disease, but no conclusions can be reached on the efficacy of this substance in humans.

Identifying compounds that activate *SIRT1* is an exciting focus of research because of the potential to create both anti-aging and disease therapies. Small molecules have recently been identified that are not chemically similar to resveratrol but are much more potent at activating *SIRT1*. Investigators evaluated these compounds in the treatment of obese mice and found improvements in insulin sensitivity and glucose

Table 1-2. Proposed Pharmacological Mechanisms of Resveratrol

Disease or Condition	Mechanism
Cancer	Carcinogenesis is inhibited at several steps for different forms of cancer including inhibition of both forms of cyclooxygenase, inhibition of angiogenesis, modulation of drug metabolism enzymes such as phase I cytochrome 450s, induction of cell cycle arrest and apoptosis, and antioxidant properties
Heart disease	Prevention of platelet aggregation through preferential inhibition of cyclooxygenase I over cyclooxygenase II, stimulation of calcium-activated potassium channels leading to vasodilatation, and prevention of low-density lipoprotein oxidation as an antioxidant
Inflammation	Inhibition of cyclooxygenase enzymes and a subsequent reduction in both acute and chronic inflammatory responses
Neuroprotection	Brain injury after ischemia has been prevented in animal models through anti-inflammatory effects and anti-seizure effects
Aging	Resveratrol is a potent inducer of the conserved family of genes known as *SIRT*[a] responsible for histone deacetylases

[a]*SIRT* is the SIR2 homolog 1 of the *Saccharomyces cerevisiae* silent information regulator family of genes.

metabolism. The research findings suggest the presence of an endogenous regulator of *SIRT1* with which the molecules react, leading to the benefits.

Role of the Pharmacist

Pharmacists are often approached for advice and input regarding the ever-increasing array of compounds, vitamins, minerals, and other substances purported to prevent aging or age-associated conditions. There is little to no positive evidence-based literature to guide the pharmacist when answering patient questions in this area. The most robust evidence to maintain health and prevent age-associated changes is ordinary lifestyle modifications that include consuming a diet rich in fruits and vegetables, whole grains, and low-fat sources of protein; maintenance of a healthy body weight; avoidance of cigarette smoke; participation in exercise that focuses on aerobic fitness, muscle strength, and balance; and maintenance of one's social and mental skills through interaction with people and processes that improve cognition, such as reading, playing games, playing a musical instrument, and dancing. Other reasonable health promotion advice can include taking a multivitamin that contains vitamin D and perhaps consuming red wine (no more than one or two glasses per day) for those who enjoy wine.

Cosmeceuticals

Normal Structure of the Skin

The skin is the largest organ system of the body on a weight-adjusted basis and it serves several functions, including protection from pathogens and chemicals as well as temperature and water regulation. Skin has three layers: the epidermis, dermis, and subcutaneous fat. The outermost layer of cells on the surface of the epidermis is called the stratum corneum, which can be thought of as a waterproof layer consisting of dead, flattened keratin cells interlocked with lipids. The epidermis and dermis contain melanocytes, Langerhans cells, hair follicles, oil glands, nerve cells, and veins and arteries. The fat layer underneath the dermis serves as a cushion and pad for the skin, providing a certain amount of bulk between the skin and muscle layers that both supports and provides contours for the skin.

Pathophysiology of Aging of the Skin

When skin ages, the dermal and epidermal layers flatten, and the subcutaneous layer of fat decreases. There are fewer metabolically active cells in the dermis. These changes lead to loss in elasticity of the skin and less volume under the skin, which creates skin folds and skin laxity. Texture changes also occur such as pore enlargement, roughness, and fine wrinkles. The rate of aging of skin is primarily caused by three factors that are sometimes grouped into intrinsic or extrinsic categories. Sun exposure and damage from pollutants are the two most important extrinsic factors, whereas genetics constitutes the intrinsic factor responsible for skin aging. Without extrinsic factors that contribute to aging of the skin, one would still expect to find skin texture changes such as dryness and roughness, skin laxity changes from a loss of subcutaneous fat, and wrinkling. However, most research suggests that more than two-thirds of age-related skin changes are preventable and related to ultraviolet light damage and pollutants.

Factors That Accelerate Aging of the Skin

Sun damage to the skin is profound, causing fine and coarse wrinkles, brown pigmented areas known as lentigines, roughness and thickening, sallowness, and telangiectasias. Other sun-related and age-related changes include the development of actinic keratoses, which are premalignant growths; and frown lines, which are caused by muscle hypertonicity. Individuals can assess some of these more obvious changes by comparing the quality of their own skin on a sun-exposed area such as the face to a sun-protected area such as the underside of the arm or the inner thigh. People with a high amount of skin exposure to the sun should be evaluated for actinic keratosis because it is associated with the development of squamous cell cancer of the skin. Both types of sun exposure, ultraviolet A (UVA) and UVB, are associated with the signs of aged skin mentioned, although UVB exposure is more strongly linked to actinic keratosis and nonmelanoma skin cancer.

Topical exposure to tobacco smoke is the leading cause of pollution affecting the skin. Tobacco smoke is a moderate risk factor associated with signs of aged skin and contributes to wrinkles and telangiectasias.

Table 1-3. Active Sunscreen Ingredients by UV Protection Type

Active Ingredient	Comments
UVB protection	
Para-aminobenzoic acid and derivatives	Hypersensitivity reactions are common, limiting their usefulness
Palmate-O	
Cinnamates	Popular UVB absorbers often used in combination with other agents to reach high SPF values
Ethyl hexyl methoxycinnamate	
Cinnamate	
Salicylates	Weak UVB absorbers; water insoluble with long-term safety data
2-ethylhexyl salicylate (octisalate)	
Homosalate	
Trolamine salicylate	
Others	
Octocrylene	
Phenylbenzimidazole sulfonic acid	
UVA protection	
Benzophenones	Block UV light in the low-band range of UVA
Oxybenzone	
Sulisobenzone	
Benzophenone-5	
Others	
Methyl-2-aminobenzoate	
Avobenzone	Exclusively absorbs UVA light
Ecamsule (in Anthelios-SX)	A broadband agent approved for use in 2006
Inorganic absorbers	Reflect light and scatter radiation by forming a thin layer of metal particles on the skin; products are opaque and occlusive, limiting their cosmetic appeal; cosmetic formulations of some preparations were improved with micronization of the metal particles
Titanium oxide	
Zinc oxide	

SPF = sun protection factor/sunburn protection factor; UV = ultraviolet; UVA = ultraviolet A; UVB = ultraviolet B.

Skin Care Products

The U.S. cosmetic industry was estimated to be a $13 billion industry in 2005, with many advertised skin care products claiming to reduce wrinkles, fade dark spots, and improve texture of the skin to better resemble a youthful condition. Thousands of Web pages and countless advertisements promote anti-aging types of skin care products and provide a lot of confusing and often misleading information to the consumer. *Cosmeceuticals* is a term describing a diverse array of consumer products that lie somewhere between a drug and a cosmetic. For this evaluation, cosmeceuticals are defined as skin care products that may possess a pharmaceutical property but do not have a systemic biologic effect. Drugs exert a biologic effect and are labeled in specific ways by the U.S. Food and Drug Administration (FDA). Cosmeceuticals are not subject to scientific trials to establish efficacy. Safety trials required for the marketing of cosmetics are generally performed on in vitro models that replicate the skin. The lack of regulation of cosmeceuticals, together with aggressive marketing by the cosmetic industry, often lead to confusion among both health care providers and the public. The cosmetics industry is skilled at the use of terms that are not easily quantified. For instance, claims for "improved smoothness," "youthful appearance," or "reduced fine lines" are subjective and not easily measured.

Avoiding sun exposure is the single best way to prevent and treat photoaging of the skin. Wearing protective clothing is a good method to protect skin from sun damage. Fabric that is tightly woven, thick, dark, and treated with an ultraviolet absorber increases protection. Ultraviolet B radiation can be blocked with sunscreens. When products with a sun protection factor (SPF) of 29 were used for 2 years, histologic changes seen with sun exposure were stabilized, whereas individuals on placebo showed progression. Actinic keratoses were reduced by 40% with daily use of an SPF 15 product compared with a placebo group, and individuals who used an SPF 15 product intermittently had a reduction

of 24%. The SPF is the sun radiation dose (mostly UVB) required to produce minimum erythema after application of 2 mg/cm^3 of sunscreen compared with the energy required to produce a sunburn in the absence of sunscreen. For example, an SPF of 2 absorbs 50% of the ultraviolet radiation, and an SPF of 8 absorbs 87.5%.

In August 2007, the FDA recommended changing the term *sun protection factor* to *sunburn protection factor* and added additional labeling to quantify the sunscreen products' ability to also block UVA radiation. A four-star system will be used in the product labeling, in which one star represents low UVA protection, two stars represent medium protection, three stars represent high protection, and four stars represent the highest protection possible in an over-the-counter product. Ultraviolet A radiation is substantially blocked only by opaque screens containing ingredients such as titanium dioxide, zinc oxide and the newly marketed Anthelios-SX (a combination of ecamsule, avobenzone, and octocrylene). Common sunscreens are listed in Table 1-3.

Topical retinoids are prescription drugs containing tretinoin or tazarotene that reduce the severity of damage to photoaged skin. As prescription products, they are not cosmeceuticals but are included in this section because of the literature that supports their efficacy. These products reduce fine wrinkles, hyperpigmented areas, and tactile roughness, and tazarotene is labeled for the treatment of lentigines. Continued use is necessary to maintain a benefit. Most patients experience skin irritation, even with proper application of topical retinoids. Dilute concentrations are initially applied, with an increase in concentration during the following 3–12 months. When using a topical retinoid, patients are at increased risk of sunburn from UVB radiation, so present recommendations include the use of a topical sunscreen during the day and the application of a retinoid at night. Most insurance companies do not reimburse patients for cosmetic use of topical retinoids.

Table 1-4 lists common categories of cosmeceuticals and the most common groups of ingredients. For these products to have efficacy, penetration of the active ingredient through the stratum corneum to the dermis must occur. Gentle exfoliation of cells of this outermost layer is important to aid in penetration to the dermis and to promote the formation of a new layer of collagen between the dermal and epidermal interface. Exfoliation can occur with gentle abrasion (from a facecloth, textured sponge, or scrubs that are gritty with salt, sugar, or another granular material) and with exfoliants.

Cosmeceutical preparations of exfoliants usually contain α-hydroxy acid from fruit, which is present in low concentrations (less than 10%). Products of moderate concentration (20% to 30%) are available in salons, and high concentrations can be applied by dermatologists. These products promote shedding of the surface cells by gently burning cells and may cause irritation and redness of the skin. Patients should apply the product at night, avoiding contact with skin close to the eye. During the day, a lotion with an SPF of at least 15 should be applied.

Many moisturizers are available with many ingredients purported to reduce the signs of aging. Penetration of antioxidants such as vitamin E, vitamin C, and coenzyme Q10 is improved in formulations that are fat soluble. There is limited clinical evidence quantifying the effect of antioxidants on the skin, but the hypothesis is that they neutralize the DNA damage from free radical formation caused by exposure to air pollution and sun. Moisturizers with sunscreens provide added protection against UVB radiation.

Role of the Pharmacist

To maintain a healthy and youthful appearance to skin, consumers should be advised to maintain a healthy lifestyle that includes eating a diet rich in fruits, vegetables, and whole grains; to maintain a healthy weight and to exercise for cardiovascular, strength, and balance improvements; to limit consumption of alcohol; to avoid all tobacco smoke; and to drink enough water to remain well hydrated. The face should be gently cleansed twice daily with a textured facecloth or sponge that is mildly abrasive, and the skin should be moisturized with a lotion that contains a sunscreen with an SPF of at least 15. Moisturizers that are noncomedogenic lessen the formation of clogged pores, comedones, and acne. Products that are oil free and water-based are less likely to cause comedones than oil- or fat-based products. If the consumer chooses to use a moisturizer during the day, a moisturizer that also contains antioxidants may limit cellular damage from pollutants and sun. Using a product with α-hydroxy acids at night helps promote exfoliation of the skin. Beyond these general recommendations, there is no evidence to suggest greater efficacy from any particular cosmeceutical product and certainly no evidence to establish a relationship between the cost of any particular cosmeceutical product and anti-aging effectiveness. Everyone should be advised to apply a liberal amount of sunscreen before going into the sun (and to reapply every 2 hours with prolonged exposure and after swimming) and to wear protective clothing.

Annotated Bibliography

1. Calorie Restriction.org [homepage on the Internet]. Newport, NC: The Calorie Restriction Society; c1996–2007. Available at *www.calorierestriction.org.* Accessed May 9, 2008.

   This is the Web page sponsored by the Calorie Restriction Society that follows the teachings of Roy L. Walford, M.D., who has published several books and many research articles on this topic. It provides an introduction to the concepts and research underlying calorie restriction as an anti-aging intervention with information on how to implement dietary changes that will lead to a lifestyle that incorporates this intervention. The focus of the site is on calorie restriction, not weight loss, as the goal, although weight loss is the easiest way to monitor calorie restriction. The goal weight for those following calorie restriction is generally their lean weight during their late teen years. The caloric restriction diet that is promoted is based on eating a large quantity of vegetables, fruits, and whole grains and sufficient low-fat protein while limiting the intake of calorie-dense foods. The Web page includes a useful fact sheet that describes the differences between an individual who follows a calorie restriction diet lifestyle and someone with anorexia and a fact sheet on the adverse effects of calorie restriction with some suggestions for managing adverse effects. For instance, osteoporosis/bone loss is an adverse consequence that should be monitored. There is little mention of the emotional or psychiatric consequences of caloric reduction interventions.

Table 1-4. Characteristics of Common Cosmeceutical Ingredients

Category	Comment	Pharmaceutical Effect
Antioxidants		
Vitamin A (retinol)	A member of the retinoid family with less biologic activity than tretinoin	Interferes with melanogenesis, preventing collagen breakdown; less irritating than tretinoin
Vitamin B		
Niacinamide		Improves the lipid barrier of skin by increasing ceramide and fatty acids; stimulates collagen synthesis
Panthenol	Water soluble with good skin penetration	Acts as a humectant as well as serving as a cofactor for lipid synthesis
Vitamin C (ascorbic acid)	Water-soluble antioxidant essential for collagen synthesis	May improve photodamaged skin; may lighten melasma and lentigines[a]
Vitamin E (α-tocopherol)	Combinations of vitamins C and E improve antioxidant and photoprotective effects of each compound	Decreases peroxidation; decreases sunburn after sun exposure and acts as a humectant
α-Lipoic acid	A lipoamide synthesized in plants; both water soluble and fat soluble, allowing good penetration	Prevents lipid peroxidation with anti-inflammatory and exfoliant effects; decreases skin roughness, lentigines, and fine wrinkles[a]
Idebenone	A potent synthetic version of coenzyme Q10	Decreases sun damage; may repair mitochondrial damage
Polyphenols		
Flavonoids	From grape seed, green tea, and soy	Antioxidant; anti-inflammatory[b]
Peptides		
Copper peptide	Copper enhances wound healing and angiogenesis; the peptide may stabilize delivery of copper into cells	May improve skin firmness, skin texture, and fine lines and lessen pigmentation
Amino peptides	May stimulate collagen production by fibroblasts	Improves skin roughness; decreases skin wrinkles and wrinkle depth[a]
Botanicals		
Licochalcone A	An anti-inflammatory from the licorice plant	Improves erythema in adults with rosacea
Lycopene	A carotenoid from the tomato plant	In topical forms, lycopene prevents sun damage from ultraviolet B radiation
Chamomile	An anti-inflammatory	In a cream formulation, chamomile is effective for treating sunburn[a]
Polysaccharides		
Hydroxy acids	α-Hydroxy acid, β-hydroxy acid, and polyhydroxy acids and other fruit acids are keratolytics; polyhydroxy acids such as gluconolactone do not penetrate the skin as easily as the smaller hydroxy acids	Decrease corneocytes in the stratum, causing exfoliation and improving skin tone
Pigment lightening agents		
Hydroquinone	Common product that works by inhibiting melanin synthesis through tyrosinase; use with caution in individuals with darker skin tones because irregular bleaching may occur	Available in both prescription and over-the-counter strengths

[a]Evidence is supported by randomized split-face clinical trials in humans.
[b]No differences were seen as reported by randomized split-face trials in humans.

2. Walford RL, Mock D, Verdery R, MacCallum T. Calorie restriction in Biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. J Gerontol A Biol Sci Med Sci 2002;57A:B211–24.

   Eight nonobese individuals unintentionally consumed a low-calorie nutrient-rich diet while sealed in the Biosphere 2 closed ecosystem for 2 years in the early 1990s. This publication contains extensive data on the laboratory testing that occurred at baseline, during the 2-year period of calorie restriction, and for 30 months after the end of the Biosphere experiment. The diet was low calorie because the individuals were testing their ability to live completely within an ecosystem that supported and recycled everything necessary for life and were not able to grow enough food to consume more than about 1750–2100 kcal/day. The data in this publication support what is generally expected in people consuming a low-fat, low-calorie diet for 2 years: dramatic decreases in weight, blood pressure, blood lipids, blood glucose, and other physiologic parameters. Two components of this report are noteworthy. First, the authors compared many of the measured variables from the eight humans with the variables from animal studies in which calorie restriction was being tested as an anti-aging intervention. Second, the authors measured several hormones of the participants in Biosphere 2. Calorie restriction may lead to a loss in the normal amounts of circulating sex hormones, thyroid concentrations, and cortisol concentrations, and there is concern about the long-term effects of this hormone loss.

3. Nair KS, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, et al. DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006;355:1647–59.

   This was a randomized controlled trial evaluating the effect of DHEA in women and DHEA or testosterone in men versus placebo for 2 years. Individuals selected for study inclusion were at least 60 years old with DHEA or testosterone values in the lower 15th percentile for normal young men and women. Men received 75 mg daily of DHEA plus a placebo patch or a 5-mg testosterone patch and a placebo tablet. Women received either 50 mg of DHEA or placebo. Outcome measures were related to physical performance, body composition, bone mineral density, plasma insulin and glucose concentrations, and measures of total body fat, insulin sensitivity, various hormone concentrations, and quality of life. At baseline, study participants were about 70 years of age with a body mass index of 27 kg/m^2. Baseline sulfated DHEA concentrations were 0.3 mcg/mL and 0.7 mcg/mL for women and men, respectively. Men had baseline bioavailable testosterone concentrations between 53 ng/mL and 62 ng/mL. After 2 years, men on testosterone improved their testosterone concentrations by median values of 30.4 ng/mL; men and women on DHEA improved their mean sulfated concentrations by 3.4 mcg/mL and 3.8 mcg/mL, respectively. Beyond improvement in the hormone concentrations, there were few changes in any biologic variable studied. Small improvements in bone mineral density were seen in both men and women. No changes in quality-of-life scores and no adverse effects were reported. A power analysis of this study showed that 150 older people (90 men and 60 women) were needed to be 90% certain that clinically meaningful results were found. The authors randomized 87 men and 57 women but believe they succeeded in being able to detect a clinically meaningful difference between groups. Criticisms of this study include the small sample size and randomization to drug intervention without concomitant lifestyle modification regimens.

4. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA 2008;299:39–52.

   Oral testosterone supplementation was evaluated in 237 healthy older men who had serum testosterone concentrations below the 50th percentile value of 13.7 nmol/L. Individuals were randomized to receive either 80 mg of testosterone undecenoate two times/day or placebo in a double-blind manner. Treatment duration was 6 months. A variety of outcome measures were used and included assessment of functional mobility, a health assessment questionnaire with items on activities of daily living, and isometric handgrip strength. Cognitive function was evaluated. Body composition changes were evaluated by x-ray absorptiometry for bone mineral density, weight and body mass calculation, and body fat determination through dual-energy x-ray absorptiometry and ultrasonography. In addition, subjects underwent blood pressure and metabolic change testing with appropriate serum chemistries as well as quality-of-life assessment. On average, the men were 67 years old with a body mass index of 27 kg/m^2 at study entry. At study completion, average fat mass decreased by 1.3 kg, and average lean mass increased by 1.2 kg. Total cholesterol concentrations decreased, primarily because of decreases in high-density lipoprotein. Glucose and insulin concentrations increased significantly in the placebo group, and there was a slight, but nonsignificant, increase in the metabolic syndrome in the testosterone group. No appreciable changes were seen in other outcome measures of physical or cognitive function, quality of life, or adverse effects including prostate function. The authors concluded that, in older healthy men with low serum testosterone concentrations, replacement with oral testosterone increases lean body mass without any other meaningful changes in physical or mental function.

5. Stern RS. Treatment of photoaging. N Engl J Med 2004;350:1526–34.

   This article reviews strategies to assess, prevent, and treat the consequences of photoaging of the skin. The focus of the article is on prescription therapies, office procedures, and surgical techniques and their different efficacies. In addition to evaluating hydroxy acids, retinoids, and fluorouracil cream, the authors evaluate procedures for removing signs of aging in the skin. Most of these procedures are more successful than topical therapies. Botulinum toxin A relaxes the hypertonicity of frown lines through a neurotoxic effect. Most persons (50% to 75%) experience moderate results with botulinum toxin A. Skin fillers such as hyaluronic acid and injectable bovine collagen are used to fill coarse or deep wrinkles and furrows. Other interventions that can be accomplished in a physician's office include laser treatment and cryosurgery. Laser treatment is best used for pigmented lesions such as lentigines and telangiectasias. Cryosurgery freezes the skin so that discrete lesions can be removed. This article is a useful introduction to the field of cosmetic dermatology.

6. Choi CM, Berson DS. Cosmeceuticals. Semin Cutan Med Surg 2006;25:163–8.

   This comprehensive review of the many ingredients present in cosmetic skin products is intended to educate dermatologists about the vast amount of skin care products sold over the counter in the United States. The review is well organized and includes antioxidants, growth factors, peptides,

anti-inflammatories, botanicals, polysaccharides, and agents used to lighten the skin. New areas of interest include the use of growth factors, which are proteins that regulate signaling on cell surface receptors. Some mixtures of growth factors have been evaluated for photo damaged skin for 2 months; a majority of participants showed improvement in wrinkle scores and with microscopic documentation of new collagen growth. In addition to their cosmetic benefits, these products may prove useful in efforts to improve wound healing.

7. Sinclair DA, Guarente L. Unlocking the secrets of longevity genes. Sci Am 2006;294:48–51, 54–7.

This article can be recommended as a reference source to the educated consumer who wishes to understand the role of genes in the aging process. These researchers have conducted and published research in this field. They weave together the evidence showing how calorie restriction extends the life span of certain animal species with the genetic pathways that are activated through calorie restriction. The authors also explain how calorie restriction causes a chronic low level of stress to cells, activating *Sirt1* with subsequently improved DNA stability, increased host cell repair and defense, and prolonged cell survival. A table in the article summarizes the genetic pathways that are under investigation for life span effects.

8. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007;146:104–15.

This meta-analysis was designed to assess both the efficacy and safety of growth hormone in healthy elderly people. The literature was evaluated through November 21, 2005, and identified 64 articles that met specific criteria. Studies needed to be randomized controlled trials of growth hormone versus placebo, or growth hormone with lifestyle modification versus lifestyle modification alone, to be included in the analysis. Growth hormone needed to be given for at least 2 weeks to community-dwelling people older than 50 years who had a body mass index less than 35 kg/m^2. The duration of growth hormone treatment was generally 27 weeks, and the dosage varied but was usually about 14 mcg/kg/day. The 31 studies (with 18 unique populations) yielded 220 people who received growth hormone; their average age was 68.7 years, and their body mass index was 28 kg/m^2. Quality varied among the studies with no study meeting all of the quality parameters, although two studies reached seven of eight criteria. Of the 18 studies with distinct populations, 12 were placebo controlled, and 6 were lifestyle modification controlled. Many biologic outcomes were assessed, but statistically significant differences were only found for two: a decrease in fat mass of 2.1 kg and an increase in lean mass of 2.0 kg. There was no net change in weight. Adverse effects were often reported and included soft tissue edema, joint pain, muscle pain, possible diabetes development, and carpal tunnel syndrome. The authors concluded that there was insufficient efficacy of growth hormone in healthy elderly people to offset the high rate of adverse effects.

9. Food and Drug Administration.gov. Rockville, MD: U.S. Food and Drug Administration. [July 2007]. Available at *www.fda.gov/bbs/topics/NEWS/2007/NEW01687.html*. Accessed May 9, 2008.

The FDA Web site has several useful monographs describing the change in labeling for sunscreen products. The URL above links to other sites with additional professional and consumer information about sunscreens. These sites define UVA and UVB, explain the importance of protecting skin from sun radiation, and describe the new scoring system for UVA protection that all sunscreen products will adopt in the future. The new four-star system for UVA ranking is described with an illustration to show how the proposed labeling will differ from current practice. In addition, the FDA has recommended changes with the SPF rating for UVB protection to allow an increase in the maximal sunburn protection factor from SPF 30+ to 50+.

10. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006;5:493–506.

This is a review of the evidence that supports the efficacy of resveratrol in several different biologic models that are used to screen or evaluate compounds for various diseases. The review includes an assessment of evidence from models used to evaluate anti-cancer properties and suggests that resveratrol merits further study as an anti-cancer agent because of the potential for multiple pharmacological mechanisms. An assessment of the cardiovascular and anti-inflammatory properties of resveratrol is also present in this article, suggesting possible mechanisms for cardiac and cerebral disease prevention. There is an assessment of resveratrol's effect on the cytochrome metabolic enzymes and pharmacokinetics properties. The authors provide evidence showing that the doses required for many of the positive in vivo effects of resveratrol are not likely to be achieved through dietary sources related to the low bioavailability of this compound. Other compounds present in wine and other natural sources of resveratrol, such as quercetin, may inhibit its metabolism and improve its bioavailability. Finally, there is a useful chart listing dietary and herbal sources of resveratrol with approximate amounts they contain.

11. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.

This article provides a review summarizing the epidemiology of vitamin D deficiency, the sources and metabolism of vitamin D, and the role of vitamin D in many disease processes. Some of the diseases reviewed have well-established links with vitamin D deficiency such as those associated with calcium, phosphorus, and bone metabolism and fractures. The more interesting parts of this article, however, review the relationship between vitamin D deficiency and muscle strength (which help in understanding some of the pathophysiology of the frailty syndrome in older people) and other diseases not generally linked to vitamin D deficiency. These include cancer, autoimmune diseases, diabetes, cardiovascular disease, schizophrenia, and pulmonary symptoms. The author provides extensive tables listing the dietary and pharmaceutical sources of vitamin D, causes of vitamin D deficiency, and strategies to prevent and treat vitamin D deficiency. The author also suggests that preventive doses of vitamin D, which are higher than commonly seen with the recommended dietary allowance, be recommended.

12. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007;92:2058–65.

A cross-sectional and longitudinal study of 1234 older Dutch men and women with a 3-year follow-up period assessed the relationship between vitamin D_2 concentrations and measures of physical performance. Physical performance

was evaluated through a walking test, chair stands, and tandem stand. About one-half of the study subjects had vitamin D_2 concentrations less than 20 ng/mL. The investigators showed that individuals with vitamin D_2 concentrations less than 30 ng/mL had poorer physical performance than individuals with higher concentrations. The association between poor physical performance and low vitamin D_2 concentration was adjusted for age, gender, chronic diseases, body mass index, living circumstances (urban or not), and alcohol consumption. In addition, individuals with low vitamin D_2 concentrations were more likely to decline in physical performance during the 3-year period than individuals with concentrations greater than 30 ng/mL. This article provides additional support for the practice of evaluating vitamin D_2 concentrations, although it is still not known whether physical performance decline can be prevented by treatment of the deficiency.

13. Isaac M, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2000;4:CD002854.

    This Cochrane review was first published in 2000 with a substantive amendment in 2006. The objectives in reviewing the literature were to evaluate vitamin E for both the treatment of Alzheimer's disease and the prevention of progression of mild cognitive impairment to Alzheimer's disease. One of the goals of anti-aging research is to create interventions that not only slow aging but also help treat or prevent diseases associated with aging. Alzheimer's disease is arguably the best representative of a disease associated with aging. If a compound with antioxidant properties such as vitamin E were shown either to improve the treatment or prevent progression of this disease, then researchers might have useful human data on the efficacy of antioxidants in a degenerative process. Only two studies met the search criteria of being unconfounded, double-blind, randomized trials of any dose of vitamin E versus placebo in either the treatment of Alzheimer's disease or prevention of progression to Alzheimer's disease for those with mild cognitive impairment. There is no evidence that vitamin E prevents the progression of mild cognitive impairment to Alzheimer's disease, and only one trial supports the efficacy of the treatment of Alzheimer's disease with vitamin E. Clearly, more research is required to support the use of vitamin E in the treatment of Alzheimer's disease. This article adds to the growing literature that fails to support the reversal or prevention of free radical damage to either prevent progression of or protect against human disease.

14. Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, et al. The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med 2008;168:154–8.

    Exercise is well documented as an intervention to prevent many age-associated diseases. Even though older people who exercise appear "younger" than their nonexercising peers, the role of exercise in the aging process versus a disease process is not known. Telomeres are DNA sequences on the end of chromosomes that shorten with cell division and may serve as a marker of cellular aging. The investigators in this report evaluated 2401 twins to assess both their exercise habits and leukocyte terminal fragment length. The twins were, on average, 49 years old and participants of the U.K. Adult Twin Registry. Exercise activity was measured through self-report with a questionnaire during the previous 12 months. There were 167 monozygotic twin pairs, 915 dizygotic twin pairs, and 237 unpaired twins in this study. Results showed that, overall, leukocyte telomere length decreased with age, and increasing body mass index was associated with decreased physical activity and smoking. After adjusting for confounding variables, a significant and positive association was seen between leukocyte telomere length and physical activity level. This finding was confirmed in monozygotic twins discordant for physical activity. For the most active twins, telomere length was about 200 nucleotides longer than for inactive twins, which is a difference seen after about 10 years of aging. This observational research not only suggests that exercise extends life, but also develops a laboratory tool to evaluate cell senescence.

15. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology 2007;68:20–8.

    Futility studies are phase II trials designed to compare new agents for the treatment of a disease against a specified threshold value determined from previous clinical trials using accepted outcome measures. The investigators wanted to evaluate coenzyme Q10 and a neuroimmunophilin-ligand (GPI-1485) in patients with early Parkinson's disease. Patients were randomized to either placebo, coenzyme Q10 600 mg four times/day, or GPI-1485 1000 mg four times/day. Patients were evaluated against a futility threshold determined from the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism trial. This change was defined as 30% less progression on the total United Parkinson Disease Rating Scale than the change observed in the deprenyl and tocopherol trial. After 1 year of treatment, the 71 subjects enrolled in the coenzyme Q10 arm of the study had a mean change in their United Parkinson Disease Rating Scale value that was large enough to warrant further clinical testing. However, the change in outcome measures was small and suggested that either the patient population, medical practice for Parkinson disease, or both had changed significantly since the threshold study was published. Nonetheless, a large clinical trial of coenzyme Q10 is under consideration.

16. Snowdon DA. Aging with Grace. What the Nun Study Teaches Us About Leading Longer, Healthier, and More Meaningful Lives. New York: Bantam, 2001.

    In 1991, an epidemiologist began a large longitudinal study in communities of aging Catholic sisters in Minnesota. This book describes the remarkable findings from this research. The participants in this study, 678 members of the School Sisters of Notre Dame, were at least 75 years old at entry. Data from the sisters include archival information from the essays written during their 20s, complete and extensive annual examinations of cognitive and physical function, and brain pathology information (all sisters donated their brains at death). Even though there was a strong overall correlation between memory impairment and Alzheimer's disease pathology, many participants with mild and moderate disease pathology staging showed no symptoms of memory impairment. The authors also explored the interrelationship between cerebrovascular disease, Alzheimer's disease, and memory impairment. This information helps the reader understand how some older individuals resist memory impairment and lead healthy older lives.