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Can aging be slowed down?

Aila Malik[a,*], **Leonard J. Hoenig, MD**[b]

[a]*CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan*
[b]*Pembroke Pines, Florida, USA*

Abstract Aging is a complex process, with genetic and environmental influences, that unfolds over time. The rate at which skin aging proceeds is predictable, although many persons appear older or younger than their chronologic age. This is especially evident in rare genetic disorders such as Hutchinson-Gilford progeria syndrome in which persons suffer from a premature aged appearance and in neotenic complex syndrome in which children appear to be "frozen in time," remaining physically and cognitively similar to an infant or toddler despite increasing age. Ideally, it would be desirable to slow down the aging process with the hope of looking younger longer and improving good health and longevity. Evidence that this is possible comes from data showing increases in average human life expectancy over the past century and recognition of the photoaging effects of sun exposure, with the development of protective strategies, including the routine use of clothing, hats, sunglasses, and sunscreen while avoiding the sun during its peak hours of 10 AM to 4 PM. Other strategies for maintaining younger-looking skin include the adoption of a healthy lifestyle and use of antiaging skin preparations. Stem cell therapy may also play a role in aging therapy. Current research is clarifying the genetic basis of skin youthfulness and may help to direct future therapies to target key biologic pathways of aging.
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Introduction

Can aging be slowed down? The answer depends on what "slowing down" the aging process means. One definition is that slowing down aging means reducing damage to cell components that occurs over time and improving tissue maintenance.[1] Accomplishing these welcome goals hopefully would then translate into an extended healthy human life span. Perhaps we are already seeing this happen as evidenced by improved average human life expectancy and better strategies for preserving a youthful appearance, especially for the skin. On average, Americans can now be expected to live 78.6 years (men 76.1 years, women 81.1 years).[2] This is a marked improvement from 1900 CE, when the average life expectancy for men was 46.3 years and for women was 48.3 years.[3] Health advances that are believed to have contributed to this rise in average life expectancy include decline in infant mortality, control of infectious diseases, safer foods, and recognition of the dangers of cigarette smoking[4]; but inroads have also been made in the reduction of aging-associated diseases. The dramatic decline in cardiovascular disease over the past 50 years is but one example.[4,5] Concerning the preservation of youthfulness, a major advance has been the recognition of photoaging as a cause of premature skin aging. Proper protection from the sun and limited sun exposure during peak daytime hours may assist in keeping the skin looking younger longer. Preventing, such extrinsic causes of premature skin aging as photoaging, is just another side of the "slowing down aging" coin. Can intrinsic aging in humans also be slowed down? To explore this question further, consider aging as a function of time and how aging can clinically appear to speed up and slow down in very rare human genetic disorders.

* Corresponding author.
E-mail address: ailamalik@yahoo.com (A. Malik).

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Aging as a time-dependent process

Aging is time dependent; it unfolds over time. It appears to be governed by two separate clocks: a mechanical clock that determines our chronologic age and a biologic clock that determines our biologic age.[6] Chronologic age is simply how old we are; that is, two people who are 70 years old share the same chronologic age. By contrast, biologic age denotes how old and healthy we clinically appear to be compared with other persons of the same chronologic age. A 70-year-old who suffers from multiple medical problems may appear to be biologically older than a healthy 70-year-old. A way of measuring biologic age is the epigenetic clock that uses DNA methylation levels to estimate molecular age.[7] For the most part, chronologic age seems to correlate with biologic age, although some people look much younger than expected or live much longer than average. In Hutchinson-Gilford progeria syndrome, just the opposite happens, and children afflicted with this disorder suffer from severe premature aging.

Hutchinson-Gilford progeria syndrome

Progeria (Figure 1) is a rare, autosomal-dominant genetic disorder characterized by failure to thrive, a premature aged appearance, alopecia, progressive atherosclerosis, lipodystrophy, and bone dysplasia. Myocardial infarction and stroke usually cause death at an average age of 14.6 years.[8,9]

The premature aging in progeria does not reproduce all of the features of normal aging, sparing the development of malignancies or the neurodegenerative diseases associated with old age. There is a recurrent, single base substitution in the *LMNA* gene, resulting in the accumulation of the abnormal protein known as progerin. A recent clinical trial that used farnesyltransferase inhibitor lonafarnib, showed a lower mortality in treated patients.[9] This study illustrates a successful effort to alter the lethal effects of an intrinsic genetic disorder of premature aging and may provide insights into treating normal aging, especially preventing cardiovascular diseases. Contrasting with progeria is a newly described rare disorder, known as the neotenic complex syndrome in which children appear to remain physically and cognitively similar to an infant or toddler despite increasing age. They are termed children "frozen in time."

Neotenic complex syndrome

The neotenic complex syndrome has been described in eight girls, ranging in age from 4 to 23 years.[1] They presented with a biologically younger phenotype than that corresponding to their chronologic age and retained a striking infant or toddler appearance. These children were well below the fifth percentile in height and weight, failed to develop sexually, and lacked the use of language.

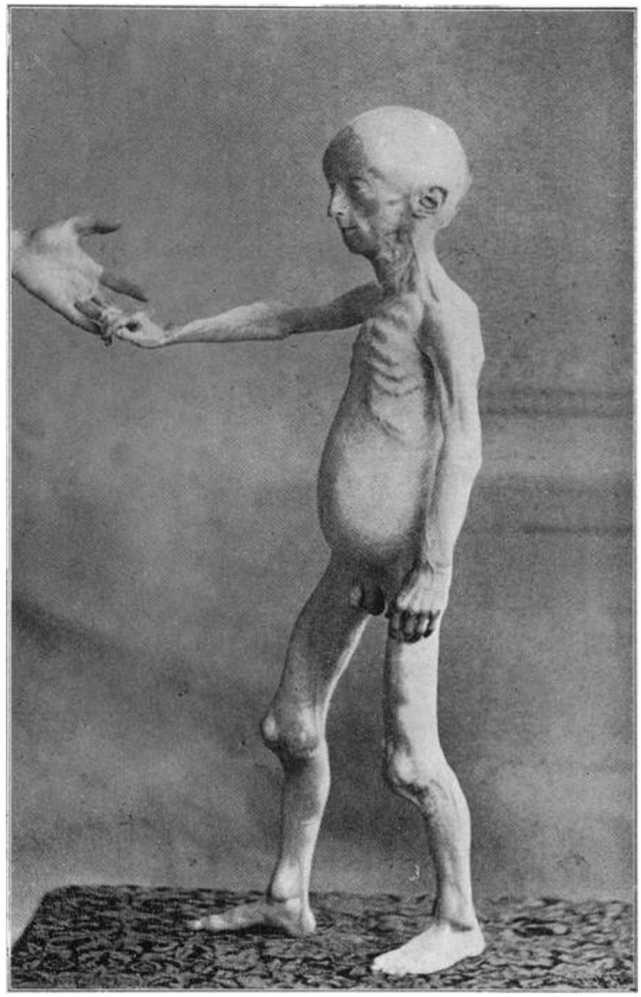

Fig. 1 Photograph of Jonathan Hutchinson's patient S.B. with progeria at age 15½. Published by Hastings Gilford (*Med Chir Trans* 1897;80:17-46.25). The patient is seen in a side view with a normal hand introduced to show relative size. The patient has the typical clinical features of progeria: premature aging, alopecia, slowed growth, loss of body fat, narrow face, small lower jaw, beaked nose, sclerodermalike skin, and head disproportionately large for face. Myocardial infarction and strokes are the usual causes of death at an average age of 14.6 years.

In five of these children, coding *de novo* mutations were found in five different genes, but it was not clear if these abnormalities contributed to the neotenic complex syndrome. At first, it was thought that these children had an abnormally slow rate of aging, but now the neotenic complex syndrome is believed to represent an extreme form of developmental delay.

The genetic basis for skin youthfulness

Hereditary influences on skin aging have caught the public's attention with the suggestion that there may be "Peter Pan" genes that are associated with a younger appearance, just as the fictional character who never grew up. The skin of persons

carrying "Peter Pan" genes could be aging more slowly. By contrast, persons carrying less-favorable genes would look older. One study found that persons who were homozygote carriers for variants in *MC1 R*, a pigmentary gene, looked 2 years older than noncarriers.[10]

Further evidence that certain genes may play a key role in skin youthfulness comes from a recent examination of 158 white women, aged 20 to 74 years, which included women who appeared younger than their chronologic age.[11] Skin samples were collected from sun-exposed (face and forearm) and sun-protected (buttock) areas and evaluated at the molecular, cellular, and tissue levels.

The analysis, which looked at patterns of gene expression, revealed progressive changes from the subjects' ages of 20s to 70s in pathways related to oxidative stress, energy metabolism, senescence, and skin barrier function. These changes were accelerated in the 60s and 70s. Certain genetic changes were likely due to photoaging.

A striking finding was that younger-looking women had similar gene expression patterns compared with those women who were actually younger in age, suggesting that their skin not only looked younger but also behaved younger. Future therapies could target these biologic pathways, which involve fundamental cellular repair and metabolic processes, as well as functional properties such as skin barrier, to help slow down skin aging.

Maintaining a youthful skin appearance

According to the United Nations, a youth is someone between 15 and 24 years of age. Many of us would welcome having the youthful skin appearance of a 20- or even a 30-year-old. The following are some strategies that can promote skin youthfulness and may delay skin aging. Most of these are well known to dermatologists and are discussed in further detail elsewhere in this issue. See Table 1 for a summary of senile changes in skin structure.

Sun protection

Sun exposure is the main driving factor of extrinsic aging and causes the appearance of wrinkles and uneven pigmentation via damage to DNA.[12] This makes crucial the daily use of sun protection, taking into account that even on cloudy days UV rays can reach the skin. Sun protection strategies include avoiding sun exposure during the peak sun hours of 10 AM to 4 PM, and wearing clothing, hats, and sunglasses that block UV radiation. Daily sunscreen should be used in addition to these sun protection strategies. Obviously, indoor tanning beds should be avoided.

Cessation of smoking

The aging effects of smoking can appear in as little as 10 years after one begins smoking.[13] Nicotine narrows blood vessels, causing less oxygen and nutrients to be delivered to the skin. The postischemic reperfusion injury, as well as other smoke compounds, generates damaging free radicals.[14] Youthful skin is just another addition to the long list of incentives to quit smoking.

Adoption of a healthy lifestyle

Eating a healthy, well-balanced diet along with antioxidant supplements, such as vitamins C and E, may help prevent skin damage that leads to premature aging. These vitamins have antioxidant properties that neutralize damage by free radicals. Foods with high glycemic index cause production of advanced glycation end products (AGEs), which damage collagen and lead to saggy skin.[15] Alcohol consumption can dehydrate the skin and may, over time, cause skin damage, and so reducing it is also beneficial. Exercise can improve circulation, boost the immune system, and improve mitochondrial functionality.[16] Appropriate sun protection should be taken during outdoor exercise. Proper sleep helps to refresh the body and may give

Table 1 Senile changes in skin structure

Histologic changes	Visible signs of aging
Epidermis	
Decreased epidermal turnover rate with accumulation of old, thin skin with dull appearance and rough corneocytes	Thin skin with dull appearance and rough texture, delayed re-epithelization post injury
Flattening of dermo-epidermal junction with decreased interdigitation	Decreased transfer of oxygen and nutrients decreased resistance to shearing forces, wrinkle formation
Decreased enzymatically active melanocytes	Uneven pigmentation
Dermis	
Decreased production of collagen	Decreased skin elasticity, wrinkle formation
Increased calcification and degradation of elastin	Decreased skin elasticity, wrinkle formation
Hypodermis	
Changes in subcutaneous fat distribution with reduction in overall volume	Pronounced nasolabial folds, appearance of marionette lines and jowls
Displacement of malar fat pad	Pronounced nasolabial folds

the skin a more youthful look. Recent evidence suggests that the Mediterranean diet may be helpful to prevent and treat frailty in older adults.[17] Frailty has been defined as a clinical syndrome in which older adults have at least three of the following five criteria: (1) unintentional weight loss of about 10 pounds in the past year; (2) exhaustion; (3) weakness as measured by grip strength; (4) slow walking speed; and (5) low physical activity.[17]

Antiaging skin creams

Many antiaging creams contain derivatives of vitamin A, that is, tretinoin, which increases production of the integral components of collagen and hyaluronic acid.[18] Persons using these products must ensure use of sunscreen because these compounds make the skin sun sensitive. See Table 2 for a list on skin rejuvenation.

Esthetic procedures

With the increased popularity of esthetic procedures to help make the skin appear more youthful, many more people seek chemical peels, fillers, and Botox injections.

Hormone replacement therapy

An acceleration of the skin aging process is observed in the postmenopausal period.[19] As such, signs of premature aging appear earlier in women compared with their male counterparts.[19] Notable changes in the skin include increased dryness as well as increased wrinkling secondary to thinning of the skin and reduction in the collagen content.[20] Skin thickness decreases by 1.13% per year and the amount of collagen decreases by 2% per year after menopause.[21] These detrimental changes can be mitigated with estrogen replacement therapy, which leads to increased epidermal hydration, increased skin elasticity, and improved vascularization.[22,23] An increase in epidermal thickness and keratinocyte proliferation is seen with the application of topical estrogen on aged skin in as little as 2 weeks.[24] A randomized, double-blind, placebo-controlled study has shown that dermal thickness increases by 30% after administration of oral estrogen for 1 year.[25] Although estrogen replacement therapy has shown positive effects on tissues such as the skin, concerns have been raised regarding increased medical risks with its use. The US Preventive Services Task Force recommends against the use of hormone therapy in postmenopausal women for the primary prevention of chronic conditions.[26]

Future treatment options

Stem cell therapy may play a role in aging therapy. A recent early stage clinical trial found that elderly patients breathed easier and walked longer distances after receiving a single infusion of stem cells from young and healthy donors.[27]

Table 2

	Proposed mechanism of action	Desired effects
Topical		
Retinoids (vitamin A derivatives)	Increased production of procollagen, decreased expression of MMPs, proliferation of dermal fibroblasts	Improved appearance of rhytides and dyschromia
Adapalene (synthetic naphthoic acid with retinoid activity)	Binds nuclear retinoic acid receptor leading to increased keratinocyte turnover rate	Exfoliation, reduced microcomedone formation
Vitamins C and E (synergistic action)	Antioxidant properties, vitamin C also increases procollagen and elastic fiber production	Protective and reparative effects
Alpha hydroxyl acids, eg, salicylic acid	Weakening of intercellular bonds between keratinocytes, leading to increased turnover rate	Exfoliation, improved appearance of rhytides, and dyschromia
Co-enzyme Q_{10}	Decreased expression of MMPs, antioxidant properties, proliferation of dermal fibroblasts	Protective and reparative effects
Energy-based		
Nonablative lasers	Stimulate production of collagen via induction of fractional thermolysis	Improved appearance of rhytides and dyschromia
Ablative lasers	Induce thermal necrosis, leading to increased collagen production	Improved appearance of deep rhytides
Injectable		
Soft tissue fillers (hyaluronic acid, synthetic, autologous fat)	Replace lost soft tissue volume	Restoration of youthful facial contours
Botulinum toxin	Paralyzing agent	Reduces formation of dynamic rhytides

MMPs, matrix metalloproteinases.

The connection between longevity and skin youthfulness

A recent study suggests that there might be a connection between longevity and skin youthfulness.[28] It compared the amount of skin wrinkling at a sun-protected site (upper portion of the inner aspect of the arm) and the facial appearance of 261 offspring (mean age, 63.2 years) of nonagenarian siblings with 253 age-matched controls (mean age, 62.7 years). It found that individuals from long-lived families had less skin wrinkling than age-matched controls. In addition, perceived facial age was a marker of familial longevity in men and cardiovascular risk in women. Male offspring looked 1.4 years younger than controls. Women in the lowest quartile of cardiovascular risk looked more than 2 years younger for their age than those in higher risk quartiles. This study suggests that skin aging and a perceived youthful facial appearance may offer insights into longevity and cardiovascular risk in human populations.

Fig. 2 Painting entitled *Vanitas (The Old Coquette)*, ca 1637 CE by the Italian artist Bernardo Strozzi (Pushkin Museum of Fine Art). The work shows an aging woman, assisted by two servants, sprucing herself up in front of a mirror, trying to look beautiful and young with the help of her cosmetics, perfume, abundant pearl jewelry, expensive fabrics, and a feather accessory. The Latin term *vanitas* means emptiness, and the painting serves as a symbolic reminder of the transience of life.

Conclusions

The quest for immortality and endless youth belongs more to the realm of science fiction than to today's medical science (Figure 2). More realistically, it is likely that the average American life expectancy will continue to grow. According to one estimate, by the year 2050 CE, American women would live, on average, 89 to 94 years, and men would live 83 to 86 years.[29] It is also likely that continued progress in the understanding, prevention, and treatment of skin aging will better enable physicians to keep patients' skin looking younger, longer. A variety of approaches to this goal appear in this special issue on skin aging. Perhaps the single most important step is to prevent photoaging. Protection of the skin from the sun should be a routine strategy for all persons beginning in infancy. Finally, it is worth noting that "staying young" is also a state of mind, as suggested by the Bohemian, Jewish novelist Franz Kafka (1883-1924) in the following quote: "anyone who keeps the ability to see beauty never grows old."[30] By continuing to learn, to help others, to dream, and to never stop reaching from the stars, one always can be young at heart.

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