Thoughts on the Process of Aging

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In the past, dermatologists treated aging locally, without addressing much beyond the dermal layer or even at the cellular level. However, some systemic protocols have been illuminated in literature to significantly slow certain aging responses to external, internal, and emotional stressors. Accordingly, there are some data to justify changes to diet, stress level, and sleep habits, but researchers have yet to find a single theory that can collect the data and provide one systematic equation that produces universally predictable results locally and systemically, until now. This article will discuss the theories and scientific discoveries on aging, including current thoughts on therapeutic modalities, to offer a greater understanding of where future reseach on aging will be heading.

The mystery of aging has undoubtedly been studied and debated, but our comparatively modern studies of aging take us to Ancient Greece, where Hippocrates, the father of scientific medicine, developed theories to explain health and aging from an empirical prospective. Hippocrates developed an analytic framework that held sway in Europe until the Renaissance, in which he posited that the essential condition of the human body could be explained in terms of 4 main categories that mirrored the outside world: humid, dry, warm, and cold. He suggested that when we are young, we are humid and warm, and when we age, these 2 factors no longer prevail because the body moves into the dry and cold categories, which eventually dominate.[1]

In Hippocratic terms, more Americans will be approaching and moving into the dry and cold category as the population of individuals who are older than 65 in the United States increases. According to the Federal Interagency Forum on Aging-Related Statistics, in 2006 there were an estimated 37 million people who were 65 years or older in the United States, accounting for just over 12% of the total population.[2] The population of individuals who are older than 65 in 2030 is expected to be twice as large as in 2000, growing from 35 million to 71.5 million and representing nearly 20% of the total US population.[2] Because of this population increase, it stands to reason that the demand and funding for research on aging will likewise experience tremendous growth. This article will discuss modern theories and scientific discoveries on aging, including current thoughts on therapeutic modalities, in order to offer a greater understanding of where future research on aging will be headed.

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AGING THEORIES

Aging is currently inescapable, and it is a marker that reflects biological changes as well as cultural and social conventions.[3,4] Looking at human aging as a biological phenomenon, we can see its adaptive characteristics, such as the wisdom and mature judgment we gain over time, but we can also see the detrimental characteristics, such as physical and mental limitations, as well as a decline in the function of our senses, organs, and immune functions.[5-7]

To explain why all of this may occur, approximately 300 theories have been suggested on aging. These theories diverge considerably. Many are outdated and are only useful in a historical perspective. Others completely overlap, and still more have no experimental data to support or refute them. However, an examination of these hypotheses of aging is useful in understanding current scientific thought on the subject. The bulk of aging theories falls into 2 categories: biological and societal. Famous biological aging theories include the somatic mutation theory of aging, error accumulation theory, cross-linking theory, accumulation theory, program theory, theory of autoimmunization, and membrane hypothesis/cellular theory. Societal theories of aging include hypotheses that acknowledge the extrabiological forces that have an impact on the process of aging.

Various authors such as Strehler, Platt, Esposito, Harrison, and Hayflick have tried to create logical systematic overviews.[4,8,9] But their theories, for various reasons, have been criticized. Esposito[9] did, however, create a classification system in 1983 that has done much to help sort and categorize the theories. His classification of aging theories employs analysis that divides theories of aging into 3 groups: causal, systemic, and evolutionary.[8-10] The foundation for causal explanations of aging is the assumption that the effects of sporadic, random physicochemical changes may accumulate in complex biological systems and cause the appearance of aging. Some of the well-recognized causal theories include the theory of somatic mutations, the theory of genetic mutations, the wear-and-tear theory, the cross-linking theory (ie, glycation), and the accumulation theory. The basis for systemic theories is that aging is a consequence of interactions between various systems (organs) of vital importance to an organism. A few of the many systemic explanations include the program theory of aging, the theory of expired programs, the theory of autoimmunization, and organic explanations of aging.[8,9] Lastly, evolutionary theories consider aging as an adaptive process. For the most part, these theories favor the idea that pleiotropic genes exist, and these genes are thought to determine the specific aging rate for each species. Thus far, interpretations are highly speculative.[4,8]

Causal Theories of Aging

Cellular Damage—Regardless of the category into which the hypothesis falls, a plausible aging theory and process have eluded scientists until now. The most compelling current theory is the water principle, which states that cells and connective tissue lose their ability to reproduce because of accumulated damage and resultant water loss. The water principle, which builds on Nagy's membrane hypothesis of aging theory, acknowledges that therapeutic modalities must address cell and connective tissue damage through prevention and repair, which will assist in maintaining adequate hydration for optimal regenerative functions.[7]

Nagy's membrane hypothesis of aging theory interprets the cellular changes characteristic of senescence as structural and functional alterations occurring throughout life to every cell's plasma membrane because of free-radical–induced cross-linking of proteins and lipids, molecular damage, and residual heat formed during each discharge of the resting potential (although the system is probably more complex than that). Damaged plasma membrane is continually renewed through de novo synthesis, but certain accumulations of residual damage are inevitable. The implication is that there are functional changes within the cells, such as a gradual decrease in potassium permeability, with an increase in intracellular potassium content and a consequent colloid condensation. It also implies that there is a loss of intracellular water and an increase in dry mass content, which inhibits enzyme activity, decreases rates of RNA, and decreases the activity of the gene for protein synthesis. In addition, it suggests that there is an accumulation of waste products in cells (lipofuscin).[8,11,12]

Reactive oxygen species (ROS) are one of the factors that have been documented to contribute to cellular damage and aging. Microbes, inflammation, and neuropeptides may also play a role. As such, addressing ROS is just one part of the larger picture. There may be many other factors, sometimes overlapping, that cause cell membrane damage, which may lead to intrinsic, extrinsic, and hormonal aging. For example, with the aging process, the skin develops an ability to create a disproportionate immune response, one that goes beyond what is needed to repair the environmental insult or stress-induced damage. More specifically, the immune response produces an overaccumulation of ROS and matrix metalloproteinases, enzymes that degrade the skin matrix and enhance the external symptoms of aging.[13] Although the scientific inclination is to reduce or prevent ROS formation, there is still no evidence in human studies that removing ROS before they cause too much damage will actually extend life. Nonetheless, many experiments have shown that curtailing their unruly behavior can slow age-related changes, including those on the skin.[14,15]

Stress and Telomere Shortening—Along the same lines, much literature has been devoted to stress and aging because studies have shown that stress impairs longevity.[16] Internal, external, and emotional triggers age skin as they create microinflammatory pathways; additionally, cutaneous aging can be linked to systemic stress.[17]

Reports indicate that many Americans are currently experiencing higher levels of stress than at any other time in recorded history. Whereas stress is categorized in

3 ways (acute stress, episodic acute stress, and chronic stress), because of technological advancements, global events, and the rapid rate of communication, it has become necessary to add another category, termed *cultural stress*, to accurately reflect the changing events in human history.

Cultural stress is a new type of stress that is superimposed on the normal stresses of everyday life because of digital technology, increased population and affluence, and world-changing events such as those that occurred on September 11, 2001. Cultural stress is pervasive and constant.[18] Within the constraints of aging, stress has been shown to stimulate the release of hormones and neurotransmitters, which can cause systemic inflammation, and inflammation can lead to connective tissue and cellular damage.[19] However, further research linking cultural stress and cutaneous aging is needed to definitively understand the causative relationship and whether the rate of stress-induced aging is increasing.

With regard to the rate of aging, one provocative finding has linked stress and telomere shortening and has illuminated a causative relationship that produces aging.[17] Telomeres form the ends of chromosomes, and, as an organism ages, they naturally shorten with each cell division. Growing evidence shows that telomere shortening may be indicative of increased cellular damage and risk for diseases such as cancer.[20] In addition, it has been theorized that telomere length could be useful as a biomarker of aging.

THE WATER HYPOTHESIS

In the final analysis, regardless of what causes the damage or initiates aging, the common pathway is water loss, not only in the cell and plasma membrane, but also in the connective tissue.[7] By supporting and regulating cellular hydration and volume, we maintain optimal cell functions.[21] Simply put, when cells are not fully hydrated, they cannot function at optimal levels and this leads to aging. When cells deteriorate, disorders, diseases, and death occur. One study illustrates this process clearly as it shows that the elderly, especially if diseased, display reduced intracellular water.[22]

Because water is essential to life, as all metabolic processes occur in a water vehicle, life has been described as a process during which a highly hydrated state of fertilized oocytes, embryos, and newborns is transformed into a gradually more and more dehydrated state.[8] This process is useful until an organism reaches its optimum performance, requiring a given amount of enzymes, muscle fibers, collagen, and neurofilaments, among others. Unfortunately, the tendency for cellular dehydration continues with age progression. This dehydration helps accumulate intracellular dry mass, which has serious consequences. First, it slows down and stops an organism's growth. Second, further increase in the physical density of cell colloids compromises basic cellular functions and this increases free-radical efficiency and damage. Lastly, the in situ enzyme catalytic rate constants are all strongly dependent on the density of their microenvironment.[11,12]

In sum, reducing and repairing oxidative stress and its resultant cellular damage may help stave off cellular aging as cells and connective tissue maintain optimal hydration.[14] Additionally, it is plausible that water, life's most natural and valuable element, may offer a solution to the aging process as it formulates the basis for the water principle, which addresses cellular aging changes both topically and internally.

THERAPEUTIC MODALITIES

There are many internal and external catalysts for oxidative stress that lead to aging, including but not limited to photodamage, chronic inflammation, microbial invasion, emotional or life stress, sleeplessness, hormonal imbalance, neuropeptide imbalance, and matrix metalloproteinases. Moreover, oxidative stress is involved in several diseases, such as cancer and cardiovascular, Parkinson, and Alzheimer diseases.

Systematic Modalities

Nature has provided us with antioxidants, which neutralize ROS and even prevent them.[23] Antioxidants, in general, are well known for their health benefits as protectants against the deleterious effects of aging and inflammation.[24] Internal recommendations, such as supplements, fruits, vegetables, good fats, and minerals, are necessary to treat aging and age-associated disease.[25,26] Omega-3 essential fatty acids, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to inhibit the production of inflammatory mediators that begin the inflammation cascade. Omega-3 essential fatty acids reduce inflammation caused by prostaglandins and by exposure to UV radiation.[27,28] Also, B vitamins have been shown to provide many cell-protective benefits, specifically, vitamin B_{12}, which can be found in fish, poultry, low-fat and nonfat dairy products, fortified soy milk, eggs, and brewer's yeast, may combat age-related brain degeneration.[29]

Beyond reducing cell damage, certain foods and dietary supplements are known to encourage cell membrane strengthening. Specifically, foods that contain lecithin help rebuild tissues and help build strong cell membrane walls.[19] Lecithin is composed mainly of phosphatidylcholine, which is a major component of cellular membranes. Essential fatty acids, in addition to being necessary for normal cellular function, have also been indicated to assist in promoting cell wall integrity and may slow neurodegenerative brain diseases associated with aging.[30]

From an emotional perspective, stress and anxiety can trigger cellular water loss through perspiration. In addition, acne and eczema are known to flare in response to elevated stress hormone release, compromising tissues.[18,31] Stress has been shown to accelerate the aging process because it encourages poor health and immune function.[32] Stress modulates the rate of cellular aging because it is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity.[32] Stress is also known to cause sleep disorders, which interrupt the body's immune response and natural restorative processes such as wound healing.[18,33] Hypertension is a side effect of lack of sleep, as well as confusion, memory loss, and depression.[34-36] The body requires sleep to metabolize glucose, and as such, sleep loss can lead to diabetes.[37]

Cutaneous Modalities

To reduce oxidative cell damage topically, photodamage must be reduced. Countless studies have addressed cutaneous aging, and some of the most important research involves the protective properties of antioxidants, not only externally but also internally. Moreover, because the skin barrier is a crucial part of the immunity response, a topical regimen must address cutaneous integrity and maintenance. As structural changes occur in the skin because of aging and excessive sun exposure, cutaneous functions, such as protection, secretion, absorption, and thermoregulation, are detrimentally affected by as much as 60%.[14]

Numerous experiments and vast amounts of research have been devoted to topical therapies that strengthen and fortify the skin's barrier function. Although not an exhaustive list, the methods include different forms of exfoliation, lipid preservation, cosmeceutical use, and sun protection. Generally, topical treatment may include any combination of synthetic or botanical ingredients, such as as α- and β-hydroxy acids, enzymes, retinoids, humectants, topical antioxidants like vitamin C, and inflammation abators.[15]

Going further, to explain how some topical aging changes may occur, research has explored the mind-skin-body relationship and has found an elaborate interrelationship that has been termed the *neuro-immuno-cutaneous-endocrine* network.[38] The data show that the network involves the central nervous system and the skin and reveals specific communication molecules originating in both systems that link mind and body in wellness and disease. Through the use of this network, certain external stress-reduction techniques and treatments, such as massage and mind/body exercises (eg, tai chi, yoga, qi gong) may provide immune system benefits, thus improving cutaneous inflammation responses.[39]

In sum, it may be possible to slow aging through topical interventions that address cutaneous aging, such as photodamage, internal protocols to adjust diet and nutrition, and emotional support programs, which reduce stress and minimize its effects on hormones and sleep.

CONCLUSION

Various theories have been put forth in an attempt to explain the process of aging. Many theories may contain some truths and have provided some insights. It is likely that aging has a genetic component in addition to other components. Science understands some of the mechanics of aging, but the complete process has yet to be uncovered. What has been elucidated through scientific research is that there are indeed connections between cellular decline and water loss in all systems, and this offers more support for the water principle as an all-embracing aging theory.

Current scientific discoveries, cellular research, and established therapeutic modalities for addressing aging have led the field of cosmetic dermatology to look to the water principle as a more comprehensive theory on aging that addresses both local and systemic symptoms. The future lies in the creation/use of a more comprehensive approach that addresses water loss and simultaneously reduces cell and connective tissue damage, whatever the cause. It is possible to accomplish these goals with topical care to prevent environmental assaults, internal solutions to flood the body with essential nutrients, stress reduction to keep hormone levels in balance, and programs that encourage restorative sleep.

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