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HEALTHY AGING: ADDING LIFE TO YEARS AND YEARS TO LIFE

Sonya Norris
Tim Williams
Science and Technology Division

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INTRODUCTION

In 1999, 12.4% of the Canadian population was 65 years of age or older. In 2026, this age group is expected to represent 21.4% of the population. During this time, the total population of people over 90 years of age is expected to more than triple while the number of people below age 44 is expected to drop by over one million people. These demographic changes will have a profound impact on society, ranging from our view of retirement to changing demands on the medical system. The extent of this impact will depend on the health of our aging society. This in turn will be heavily influenced by our scientific understanding of the aging process and the causes of ill health, through which we may improve the health of the elderly. New research into the longevity of laboratory animals has also raised the prospect of extending lifespan, the possibility of which has many ethical and practical implications. This paper describes the state of our knowledge of the aging processes, with a particular emphasis on the distinction between normal aging and age-associated disease.

LIFESPAN AND LIFE EXPECTANCY

Lifespan is the maximum length of life of an organism. For humans, the longest recorded lives have been in the vicinity of 120 years, and so this has been taken, somewhat arbitrarily, to be the lifespan of a human. Life expectancy is the average length of time a person would live based on current rates of death (mortality). Currently, the life expectancy from birth for a male in Canada is 75.7 years; for females, it is 81.4 years. The actual average number of years lived by a population depends on changes to mortality that occur over their lifetimes. Interpreting published life expectancies between countries may also be difficult given that

reporting and calculation differences exist. For example, there is some variation between countries concerning the criteria for reportable live births.

Life expectancy can be calculated for people at different ages. For instance, life expectancy at age 65 for males is 16.2 years while for women it is 20 years. Comparing this with the life expectancy from birth it is evident that, if one reaches the age of 65, the average age of death is higher (81.2 vs. 75.7 for males, 85.0 vs. 81.4 for females). This is because life expectancy at birth takes into account infant and young adult death, which brings the average down.

HISTORICAL TRENDS IN LIFE EXPECTANCY

Life expectancy from birth has increased dramatically since 1900 in Canada. Then, a male had a life expectancy of 47 years and a female had one of 50 years. Today, these expectancies have increased by more than 60%. The rate of increase in life expectancy at birth was great for the first 50 years of the 1900s but has slowed down since the 1960s. The increase in life expectancy at the beginning of the 20th century was the result of medical discoveries, such as vaccinations, and the implementation of such public health measures as water chlorination. Many infectious diseases that were common in Canada are now virtually eradicated. With lower death rates due to infectious diseases of younger people, life expectancy increases greatly because the death of a young person has a large impact on the average age of death.

In the past 30 years, the impact on life expectancy has been largely due to a decrease in unintentional injuries leading to death as well as through a reduction in cardiovascular disease.

Trends in life expectancy at greater ages have also increased but not nearly to the extent of life expectancy at birth. In the United States, life expectancy at age 85 was 4.6 years in 1960, rose to 6.2 years by 1975 and has not changed since. Thus while great strides have been made in increasing life expectancy at birth, largely through combating disease, lifespan has risen only minimally.

Medical advances against disease will almost certainly continue to increase life expectancy but the lack of any great increase in maximum lifespan suggests that there may be limits to how old people can get. The question then arises as to why, in the absence of disease, people age. The process of aging in the absence of disease is often referred to as normal aging.

NORMAL AGING

There are many misconceptions about what normal aging processes are and, as we learn more about aging, it is becoming clear that many of the negative images people have of the process of growing old are largely a function of disease and changes in lifestyle, rather than inevitabilities of age. Many of the inconsistencies regarding aging have arisen because the focus of research on aging has been on elderly people with disease. Findings from longitudinal studies of healthy individuals, such as the Baltimore Longitudinal Study on Aging, are beginning to give a clearer picture of physiological changes associated with normal aging.

A. Heart and Lungs

Although there are some changes in cardiovascular function with age, the changes are not nearly as significant as one might expect. Increases in arterial stiffness can lead to increased resistance to blood flow and consequent hypertension as well as some thickening of the walls of the heart. However, the heart pumps more efficiently. As well, generalized stiffness in the chest cavity can lead to progressive loss of pulmonary function including a decrease in the effective volume of air that can be forcibly exhaled from maximum inhalation. The lungs also lose some capability of clearing foreign particles and infection. In effect, the capacity to supply oxygen to the body is not greatly reduced by age alone but can be more easily compromised by disease.

B. Kidneys

The flow of blood in the kidneys (renal blood flow) drops by 10% per decade after age 20 so that an 80-year-old might expect to have half the renal blood flow of a young adult. The number of filtration structures known as the glomeruli decreases by 30% to 40% by age 80, and the efficiency of the remaining ones also declines. Despite this, the kidneys, under unstressed circumstances, retain the ability to maintain fluid and electrolyte balance. Once again, however, kidney function is more easily compromised by disease, and its ability to function under increased loads of some salts is decreased.

C. Immune System

Another common observation of aging is that infections that would have been tolerable in earlier years can prove fatal in the later years. Older persons who do not succumb to diseases such as cancer or cardiovascular disease often die from the flu or pneumonia. This is a result of the immune system no longer being capable of fighting a "routine" invasion.

White blood cells (lymphocytes) fight infections such as bacteria. There are two types of lymphocytes: B-cell and T-cell lymphocytes. T-cells are produced in the thymus, which is known to shrink with age. Predictably the level of functioning T-cells also declines with age. Some T-cells (called helper T-cells) produce substances called lymphokines which in turn mobilize other immune system components. Interleukin-2 is one of the lymphokines and is known to decrease with age. Current research is analyzing the anti-aging effects associated with interleukin-2 supplementation.

D. Hormones

It has been known for some time that the levels of the sex hormones estrogen and testosterone fall considerably over time. In addition, other hormones such as growth hormone (GH), melatonin and dehydroepiandrosterone (DHEA) may also decrease with age. These and other decreases help to explain much of the observed deterioration of old age. Older women are at increased risk of osteoporosis and breast cancer for example, as a result of the fall in estrogen levels. Growth hormone is also linked to bone strength, as well as muscle mass, and as its level goes down with age, frailty increases. Injections of growth hormone have been found to reverse some of the signs of aging but may in fact reduce overall lifespan. Related to GH, researchers are also studying the effects of growth hormone releasing hormone that results in higher levels of GH, and of insulin-like growth factor-1 (IGF-1) which is secreted in response to higher GH levels. Melatonin appears to regulate some seasonal changes in the body and may be associated also with sleep disturbances that are common among the elderly. The adrenal hormone DHEA is a precursor to testosterone and has been proposed as a means to enhance the immune system of the elderly and to protect against cardiovascular disease, multiple sclerosis and cancers. DHEA – which boosts levels of interleukin-2 (see Immune System above) – may be needed for the function and proliferation of immune cells.

E. Brain

Recent studies have shown that there is some localized age-related loss of neurons, but that many neuronal pathways are able to compensate by increasing the number of connections between cells and by regrowing extensions of the nerve cells such as the dendrites. As a result, many cognitive functions such as sustained attention, most linguistic abilities and sensory memory do not change greatly with age.

Although many functions of the brain remain uncompromised, neural loss in a region of the brain known as the suprachiasmatic nucleus is associated with disturbances in the circadian clock. Older people tend to want to sleep earlier and rise earlier than do younger people.

F. Eyes and Ears

There is frequently a reduction in the ability to focus close up and on moving targets, as well as an increased sensitivity to glare and difficulty seeing at low light. Higher frequency sounds are more difficult to hear with increasing age.

AGING AND LIFESTYLE: USE IT OR LOSE IT

The image of debilitating old age is not necessarily real. If diseases such as atherosclerosis and other cardiovascular maladies can be avoided, the body continues to function relatively normally as it ages. Many health problems commonly associated with aging can, therefore, be avoided through the control of disease. It is also becoming clear that lifestyle and diet play significant roles in the creation and avoidance of health problems. As we age, we tend to become more sedentary and eat less well. This in turn can have significant health consequences that can be improved by reintroducing activity and a nourishing diet.

Muscle loss, bone strength, blood glucose levels and cardiovascular capacity are all common ailments that are generally associated with old age. They may have little to do, however, with the processes of biological aging and can be reduced by remaining active and maintaining good eating habits. When adults, who have previously led sedentary lives, have an exercise program, it causes remarkable improvements in, for instance, their ability to ventilate the lungs and the functioning of blood vessels. Equally, high blood glucose levels, which are

frequently found in the elderly, are commonly the result of bad nutrition and lack of exercise. Exercise programs for elderly, glucose-intolerant individuals greatly improve glucose metabolism and decrease blood insulin levels. Osteoporosis has been shown to have links to smoking, inadequate calcium and lack of exercise. Exercise can also help to reset the circadian clock, located in the brain, which dictates when the body wants to sleep.

In addition to the benefits of physical exercise, there is now some evidence to suggest that keeping the mind active can help mitigate against some forms of mental decline. This idea is supported by studies in which rats that were kept in stimulating environments had larger cerebral cortexes, larger neurons and more connections among neurons than did rats kept in non-stimulating environments.

Our understanding of disease processes and lifestyle influences has greatly improved our capacity to alleviate some of the physiological problems that we commonly associate with aging. Medical improvements to fight disease and changes in lifestyle have thereby increased, and will continue to increase, life expectancy and the quality of life as we age. Lifespan, however, has been little affected by these advances. Further improvements in life expectancy, and the possibility of extending lifespan, may come from improving our understanding of the more fundamental biochemical and molecular processes behind normal aging.

MOLECULAR AND BIOCHEMICAL RESEARCH INTO AGING

Throughout the life of an organism, it faces a constant assault from environmental factors such as radiation and chemicals that can react with and damage important biological molecules and processes. Equally, the more times cells reproduce their genetic material, the more likely that mistakes may be made. Thus over time, the fundamental structure of cells and the day-to-day activities of cells can be compromised. The ability to repair structural and metabolic damage is key to reducing many age-associated effects.

It is also known that the activity of a variety of genes changes with age. Of particular interest are a number of genes involved in cell division that are down regulated with age. Apparent aging rates can also be associated with specific genes. Diseases such as Werner's Syndrome and Hutchinson-Guilford progeria are associated with single genes, and cause patients to prematurely undergo genetic and physiologic changes similar to aging. Werner's Syndrome

causes death usually by age 50 while the Hutchinson-Guilford disorder results in death before age 15.

In addition to damage accumulation, aging appears also to be the result of programmed processes. This specifically refers to senescence, the state into which cells enter after a pre-determined number of cell divisions. Finally, calorie-reduced diets are associated with increased lifespans and involve the interaction of many of the facets of aging.

A. Damage With Age

1. Free Radical Damage

Free radicals are the normal by-product of the metabolism of fats, proteins and carbohydrates into energy; in most cases, they are properly disposed of by the cells' own defences. Free radicals are atoms, molecules or compounds with an extra-unpaired electron. In this unstable state, the compound is highly reactive and needs to take an electron from somewhere else in order to become stable. The electron source can be any compound, which is in turn left unstable and in need of an electron. This sets off a chain reaction resulting in the formation of some harmful compounds, particularly a class called reactive oxygen species (ROS), capable of damaging proteins, membranes and DNA.

2. Glucose Crosslinking

Some gerontologists(1) have used diabetes as a model for aging after observing that diabetics exhibit some signs of premature aging. Diabetics have faster rates of glucose crosslinking than do normal individuals.

Glucose crosslinking begins when glucose and proteins combine to produce "glycoproteins," a process called glycosylation. These glycoproteins then link together, or crosslink, to form advanced glycosylation end products (or AGEs). AGEs appear to toughen tissues and may be involved in the deterioration associated with aging, such as stiffening of the connective tissue, hardened arteries, clouded eyes (cataracts), loss of nerve function, and less-efficient kidneys. All of these changes are common in old age and are observed to occur prematurely in diabetics.

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(1) Gerontologists are scientists who study aging.

3. DNA Damage

DNA damage can occur as a result of radiation, including UV, chemicals or as the result of mistakes made in the DNA replication process. Replication mistakes in particularly sensitive areas of the yeast genome, for instance, yield small circles of DNA. The accumulation of these is directly related to cell age. Daughter cells, which inherit some of these circles, have shorter lifespans.

Radiation and chemicals can lead to mutations, the placement of a wrong letter of the DNA alphabet in the genome. These point mutations accumulate in older cells. It is theorized that the accumulated genetic damage leads to malfunctioning proteins and cells and ultimately tissues and organs. Such accumulated damage could explain increased frequencies of cancer and the decline in immune function in the elderly.

DNA is not exclusively confined to the nucleus. A very small proportion of our genetic material is contained within intracellular organelles called mitochondria. These structures are the energy generators for the cell. The mitochondria contain the DNA for only a few dozen genes, as compared to tens of thousands of genes encoded in the nuclear DNA. There is, however, a much higher rate of genetic mutation in the mitochondria due to the abundant supply of free radicals, in the form of reactive oxygen species, in these structures. Free radicals are a by-product of the energy metabolism performed by the mitochondria. Although higher rates of mutation have been identified in mitochondrial DNA, the specific mutations that occur may not be entirely random. Recent studies suggest that specific mutations occur with age. It has also been suggested that mitochondria may also be the site of a "longevity gene." Studies have shown that a large proportion of people over 100 years old possess a specific mitochondrial gene.

B. Minimizing the Damage

Left unchecked, the damage created over time would lead to severe problems in the functioning of cells and organs. Healthy organisms have, therefore, mechanisms that both prevent and repair damage. To some extent, the aging process is not so much related to the production of damage but to the increasing inability to repair damage once it has occurred.

1. Neutralizing Free Radicals

Three enzymes exist within the cell to "disarm" these harmful compounds. These are superoxide dismutase (SOD), glutathione peroxidase and catalase. Recently it was shown that anti-oxidant enzyme activity is deficient in some diseases of premature aging. Conversely, studies using laboratory invertebrates have shown that increasing the activity of these enzymes may extend lifespan. Nutrients known as anti-oxidants, such as vitamins C and E as well as beta-carotene, are also capable of neutralizing free radicals. However, these defences are not usually able to prevent all the damage that can be done by free radicals; little by little, the damage accumulates, which produces some of the tissue and organ deterioration associated with advancing age.

Diabetics have been observed to show some signs of premature aging. The increased production of free radicals through glucose metabolism is one possible reason for this observation. Free radicals have also been implicated in age-associated disorders such as cancer, atherosclerosis, cataracts and neurodegeneration. Recent work suggests that a buildup of nerve cell damage by free radicals triggers a hormonal response that initiates deterioration and aging. Research has suggested that boosting anti-oxidant levels may help to slow the aging process.

2. Heat Shock Proteins

Scientists have discovered that as cells approach senescence, they produce less of a class of protein called "heat shock proteins" (HSPs). Initially they were discovered after analyzing the contents of cells that had been subjected to higher temperatures than normal. In fact, it has been found that these HSPs are normally produced in cells but that their levels are increased in response to many stressors including heat, cold, trauma and toxins as part of a defence system to protect the cell. The ability to produce these surges in HSPs in response to stress is lost with age. This observation may help to explain why younger people respond better to stresses than do older people.

Although the exact role played by HSPs in the aging process is unclear, scientists do know that they play a part in breaking down and disposing of damaged proteins, while also assisting in the production and transportation of new cellular proteins. These "chaperones" are HSPs that bind and stabilize proteins at intermediate stages of folding, assembly, translocation across membranes, and degradation.

HSPs have been linked to disease via their involvement with the immune system, including presenting antigens to the immune system for antibody production. They are also capable of initiating and propagating auto-immune disease. In addition, the HSPs appear to have a role in innate immunity. Other recent research suggests that HSPs may be involved in protection against cancer and cardiac failure.

3. DNA Protection and Repair

The lifespan of an organism has been shown to be related to its ability to prevent and repair certain types of DNA damage. Many DNA repair mechanisms are designed to find the errors, remove the segment containing the error, and re-constitute the DNA from the complementary strand.

Another aspect of DNA damage involves the enzyme DNA helicase. This enzyme is responsible for "unwinding" the double helix of the DNA strand during replication. Improperly functioning helicases have been implicated in some hereditary diseases of premature aging. This research is in its early stages and it has not yet been shown that the same mechanism is at work in normal individuals as they age.

Many of the errors of DNA replication occur in areas of the genome that are read frequently, or that have highly repetitive sequences, such as those which encode the ribosomes, the machinery for assembling proteins. Silent information regulator (SIR) proteins reduce the frequency with which stretches of the genome are expressed and, in yeast, are associated with increased lifespan.

4. Minimizing Glycosylation

The body has its own defences against AGE (advanced glycosylation end products) formation, as it does against DNA damage and free radical formation. Macrophages (immune cells that are capable of engulfing and destroying certain foreign structures) can attach themselves to AGEs. They then engulf the complex, break it down, and eject the remnants into the bloodstream for excretion via the kidneys. This system cannot prevent AGE accumulation completely, however, and AGEs accumulate with age.

Research is currently pursuing a means to artificially prevent AGE formation as well as destroy existing AGEs. A compound called aminogaunidine is being studied for its ability to prevent AGE formation. This substance has been shown to boost cardiovascular and

kidney function in laboratory animals. Another pharmaceutical agent called ALT-711 is being investigated for its ability to break apart existing AGEs and reverse the signs of aging such as reduced lung elasticity.

A decreasing ability to prevent or repair damage results in its accumulation. This can lead to the inability of cells and organs to perform their functions properly. In turn, this can lead to a weakened ability to maintain homeostasis and to fight off disease.

C. Telomeres and Programmed Senescence

Human cells, as well as many other organisms, have finite lifespans. In fact, until recently, it was believed that immortal cells, with infinite lifespans, were cancerous. After a certain number of divisions, normal cells enter a state of senescence. In this state, cells do not divide or proliferate and there is no DNA synthesis. Scientists have found links between senescence and human lifespans.

One aspect of senescence research is the discovery of a physical barrier that results in a finite number of cell divisions. Every chromosome has a long non-coding genetic tail called a telomere, which protects the unstable ends of coding DNA. Each time the DNA strand is copied (i.e., the cell divides), the telomere becomes shorter. Once the entire telomere is lost, the cell is no longer capable of dividing because further divisions would produce chromosomes that lack some information.

Human cells cultured in the laboratory have been notoriously difficult to work with because they die after a certain number of divisions. However, human cells genetically transformed to contain the enzyme telomerase do not die, as this enzyme maintains telomere length. Telomerase has also been found in some cancerous cells, which has led to a great deal of research on the possibility of controlling cancer growth by interfering with telomerase activity. It is unlikely, however, that telomeres will be the silver bullet against cancer. The immortal human telomerase-transformed cells have been shown not to be cancerous and some mice without telomerase activity have still developed cancer, so factors other than the existence of telomerase are involved in cancer cells' immortality.

The exact relationship between cell senescence and the aging process is not well defined and is an area of intense focus. Scientists have observed that the cells of cloned animals can have the telomere length of the genetic donor. The telomeres on the chromosomes of Dolly,

the first cloned animal, were shorter than anticipated for her chronological age, leading to speculation that cloned animals would age prematurely. Clones are produced using cells from adult animals, thus the cloned animal can begin life with telomeres considerably shorter than in a conventional embryo. Recently, a cloning procedure was developed that resulted in lengthened telomere size in clones. It is too early to conclude whether the lifespan of any of these clones has been significantly altered.

D. Increased Longevity through Caloric Restriction

Caloric restriction (CR), without malnutrition, is the focus of a considerable amount of current research. In both single-celled organisms such as yeast and in mammals such as rodents, CR has been shown to consistently extend life expectancy. The manner by which CR may increase life expectancy is proving to be somewhat complex. It appears as though CR may have an influence on DNA repair rates, free radical levels, hormonal balance and cell senescence as well as possibly other mechanisms. Another phenomenon associated with CR is the observation in laboratory rodents that the development of disease and tumours is prevented or slowed down. Research into CR may provide further insight into the mechanisms responsible for age-associated disease.

One of the manners by which CR may slow the aging process is by causing a reduction in the accumulation of free radicals. This is because free radicals are by-products of metabolism, the rate of which is reduced when calories are restricted. This, in turn, would result in less protein and tissue damage caused by these compounds and less DNA damage.

A connection has also been made between CR and genetic stability in yeast, a model organism from which much has been learned about fundamental aging processes. CR reduces the level of free radicals – molecules that can damage the cell's energy-producing machinery. Cells with undamaged machinery have more active SIR proteins, which in turn slow down the aging process through changes in gene expression.

A third proposed means of reducing DNA damage is based on the observation that CR lowers core body temperature. This could result in less DNA damage, and better DNA repair than at normal body temperatures. Some age-associated diseases such as cancer and cardiovascular disease have been linked to free radical and DNA damage, which may help to account for CR's observed effect on disease progression. A possible mechanism for CR's

anticarcinogenic effects is the observation that the level of insulin-like growth factor-1 (IGF-1) affects tumour growth. CR inhibits production of IGF-1, and this may be how CR prevents or slows the progression of cancer.

In addition, CR appears to somehow moderate the decline in growth hormone. This could have the effect of postponing the frailty associated with old age. Researchers have noted that CR appears to have an effect on the immune system by postponing the decline normally observed in aging. The means by which CR accomplishes this is not yet known but may also be linked back to the reduction in damage accumulation. Free radical damage results in the loss of function of some proteins and could include those produced in the immune response. Finally, CR results in reduced consumption of glucose and so it may be reasonable to theorize that CR may result in less AGE formation. This could therefore delay disease progression and other changes associated with normal aging.

It is not practical to carry out human studies in this area. Instead, scientists are studying the effects of CR on primates. Even so, these studies will take several decades and are far from being complete. Preliminary observations of these monkeys suggest that CR does delay aging in primates. Research into caloric restriction does not promote the aim of severely restricting the caloric intake of humans in order to extend life. What is hoped is that clarification of the mechanisms involved will help to provide a means of improving health in later years.

CONCLUSION

Life expectancy has increased by more than 50% in the past 100 years, and the health of the elderly has also improved as the result of disease treatment and prevention. Further improvements in life expectancy and health will inevitably arise out of research into the fundamental understanding of aging in the absence of disease. It is also possible that an increase in human lifespan may result from this research. Such an increase may involve many practical and ethical questions. The possibility of greatly increased human lifespan, however, will not occur for a long time. That time should be used to carefully address the socio-economic implications of an older, healthier population.

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