Age as a Modifiable Risk Factor for Chronic Disease

Jeffrey S. Bland, PhD, FACN, FACB, Associate Editor

Abstract

Pieces of the puzzle that is the age-disease interrelationship are starting to come together to form a more complete picture of the processes that power this complex dynamic. It will be very exciting to watch the field move forward and to see the power of this concept—that age is a modifiable risk factor—take root and thrive.

Jeffrey S. Bland, ***PhD, FACN, FACB,*** *is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book* The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life.

In 2003, Brian Alexander, a writer whose work appeared in many notable newspapers and magazines, including *Wired*, where he was a contributing editor for biotechnology, wrote a book with a compelling title: *Rapture: A Raucous Tour of Cloning, Transhumanism, and the New Era of Immortality.*[1] It's an entertaining read that provides an early look inside the corporate world of "antiaging," which—as we all know—can be an industry filled with exaggeration and exploitation of the "fountain of youth" concept. But the book also introduced readers to research in a number of emerging biotechnology fields, including stem-cell science, genetic engineering, and the manipulation of the aging process via the use of pharmacological drugs.

Although an exploitative reputation has come to be associated with many areas of inquiry related to aging, the field itself emerged as a result of very interesting progress in the study of molecular gerontology.[2] For several decades, serious and respected researchers from all around the globe have been inspired by an objective with far-reaching implications for human health: to determine why age is the number one independent risk factor for all chronic diseases, including heart disease, dementia, arthritis, diabetes, and cancer. The reason for this age-disease connection has never been obvious. Aging is not linked to a single, standalone gene, and there is no single cellular process that can explain the origin of all chronic diseases. Simply put, the association between age and chronic disease has always been something of a biological enigma. For the past 10 years, however, significant progress has been made in the search for answers. Among the many discoveries during this period, one stands out as truly remarkable and that is the understanding that age is very likely a *modifiable* risk factor for disease. The solution to the mystery, in my opinion, may—to a great extent—lie in the application of personalized lifestyle medicine.

My argument begins here. It has been well known for some time that there is an association between chronological age and the incidence of chronic diseases, but only recently has it become evident that this is not directly a cause-and-effect relationship. There are, in fact, many examples of young people with certain chronic diseases, and—conversely—there are many people of advanced age who are free of disease. The age-disease trajectory is highly variable, and a concept that is now being given careful consideration is the recognition that biological age—as opposed to chronological age—is the factor most closely associated with increased disease incidence.[3] In an article published only this year with the title "Age is Just a Number," Caleb Finch, PhD, a professor at the Leonard Davis School of Gerontology at the University of Southern California, points out this age-related factoid: naked mole-rats (rodents that are technically not a mole or rat) show no sign of increased disease as they become older, a phenomenon that has attracted much interest among longevity researchers.[4] Circling back to my focus—human aging—the question to address next is this: What is biological aging and how is it measured?

Defining *Biological Aging*

Biological age is connected to 4 categories of individual function: physical, metabolic, cognitive, and emotional.

Key metrics from each of these areas are measurable, and from this composite analysis, a biological (or functional) age can be determined. My work in this area began the 1980s. I was involved in the development of the Body Total Research Center, which was a facility where a team that I led measured functional biological age in a large group of people during a 3-year period. We used a system developed by Richard Hochschild called the H-Scan, which measured 12 principles of functional age: auditory reaction time, highest audible pitch, vibrotactile sensitivity, visual reaction time, muscle movement time, forced expiratory volume, lung vital capacity, decision reaction time, decision movement time, memory, alternative button tapping, and visual accommodation.[5,6,7] We added a number of metabolic biomarkers associated with disease risk and functional age to this panel to correlate an individual's function with their chronological age. Our experience in collecting this data was revealing. Some people who were chronologically age 45 years performed like an average 65-year-old, whereas others who had reached age 70 years performed like a person 2 decades younger. This work convinced me there was an underlying biological explanation that would account for a difference between biological and chronological age.

My thinking was influenced by research I was introduced to during my time on sabbatical at the Linus Pauling Institute for Science and Medicine. I had had the opportunity to meet Denham Harman, MD, PhD, a professor of pathology at the University of Nebraska Medical School, who has come to be known as the father of the free-radical theory of aging. In 1954, Dr Harman postulated that biological aging is the progressive accumulation of diverse, deleterious changes in cellular function with time that increase the chance of disease.[8] He believed the basic process underlying these changes was the chemical reaction of active free radicals in association with cellular metabolism, lifestyle, and environmental factors.[9] Dr Harman was a remarkable man and we had many conversations about his ideas and research—and perhaps you'll find it interesting to note that he lived to be 98 years old.

The Immunometabolic Regulation of Biological Aging

With credit owed and given to Dr Harman, the free-radical theory of aging opened the door to a new area of research: evaluating the impact of free radicals on cellular function and biological aging. Free radicals can reduce genomic stability. Damage to the DNA of the genome from exposure to free radicals could result in altered cellular function. This effect would be expected to be seen in tissues associated with increased turnover, such as cells of the immune system. In a 2017 article published in the *Journal of Cellular Biology*, a Swedish researcher—Nelson O. Gekara, PhD—indicated that DNA damage of immune cells results in a breakdown in genomic integrity and the production of micronuclei in the cells.[10] Another key researcher in this field is Michael Fenech, PhD, who is director and founder of the Genome Health Foundation (Adelaide, Australia). In 1985, Dr Fenech developed the micronucleus test for evaluating alterations in genomic stability.[11] In the more than 30 years that followed, he authored more than 300 articles that demonstrate the clinical utility of this assay and describe how it can be used to monitor alterations in genomic stability of immune cells in relation to age, diet, and lifestyle factors.[12] This assay, in essence, provides a window into a process related to biological aging.

It is now understood that many factors can influence genomic stability, including free-radical injury, epigenetic variations, telomere shortening, and lifestyle and dietary factors that affect metabolic regulation of immune system function.[13] It is also now recognized that cellular senescence—a process that is associated with exposure to various cellular stressors—can turn on or off various cellular processes that regulate DNA-damage repair and genomic stability.[14] The important takeaway from all of this work is that our understanding of diet, lifestyle, and environment as important contributors to the modification of cellular stress and—mechanistically—to cellular aging is also advancing our knowledge of the biological aging processes.[15]

Where do things stand today? A major step forward has recently taken place. A phenomenon has been identified that is highly significant to those who are seeking to explain why age is an independent risk factor to all chronic diseases. It is called *clonal hematopoiesis of indeterminate potential* (CHIP). CHIP is defined as the presence of an expanded immune-cell clone in persons without other blood cell disorders. It is common among older people and is associated with an increased risk to both atherosclerosis and cancer. Siddhartha Jaiswal, MD, PhD, is a leading researcher who is studying CHIP and its implications. In 2017, he and colleagues at the Brigham and Women's Hospital and Massachusetts General Hospital published data indicating that increased levels of CHIP in peripheral immune cells was associated with nearly a doubling in the risk of coronary heart disease in humans.[16] This team reported that formation of CHIP in the immune cells was principally related to mutations in 4 genes: *DNMT3A*, *TET2*, *ASXL1*, and *JAK2*. They found that individuals with immune cell mutations in these 4 genes had significantly greater coronary artery calcification than age-matched control subjects.

Mutations in the 4 genes that are associated with the development of CHIP may be related to exposure to factors that decrease genomic stability and result in damage to immune cell function. Development of CHIP could be seen as a fundamental process associated with biological aging, and therefore it is a key consideration in explaining why chronic diseases are associated with age. An important aspect of this observation is that variability in the formation of CHIP and chronological age has been reported. It has been observed that younger people with

high levels of CHIP have a higher incidence of age-related diseases than older individuals with lower levels of CHIP.[17]

How Lifestyle and Diet Can Influence Biological Aging

The next question is obvious: Is there any therapy that can reduce CHIP, improve genomic stability, and modify biological age? In an analysis published in the *Journal of the American Medical Association* in 2018, writer Rebecca Voelker, MSJ, profiles a number of clinical trials that have demonstrated that adhering to a Mediterranean diet can reduce the loss of function associated with age—what she describes as a "fight against frailty."[18] Although questions about the specific cellular mechanism behind the Mediterranean diet's effect on biological aging remain, a large-scale study—the Nurses' Health Study—demonstrated an association between the Mediterranean diet and increased telomere length.[19] It is known that telomere length in immune cells is a surrogate marker for genomic stability and protection of the immune system against mutational injury. I have explored this connection between biological age and the Mediterranean diet in my own research efforts. Deanna Minich, PhD, and I proposed—in an article we published together in 2008—that the combination of specific macro- and micronutrients and phytochemicals found in the Mediterranean diet, coupled with the favorable impact of the diet on the microbiome (which, in turn, improves immune function and prevents an increase in immune-activated inflammation), are associated with the successful management of a significant number of the age-related chronic diseases.[20,21] Later that same year, our full MetaProteomics research team published the results of a randomized trial that demonstrated—for the first time in a trial of this type—that supplementation of the Mediterranean diet with specific phytochemicals that are known to favorably influence immune, inflammatory-signaling processes increased the clinical effectiveness of a low glycemic load Mediterranean diet in patients with metabolic syndrome and hypercholesterolemia.[22]

Another recent and important area of research that connects to this discussion is the influence of specific diets and various phytonutrients on autophagy in senescent immune cells.[23] Autophagy is a process in which parts of eukaryotic cells are self-digested to recycle damaged cellular material. Elimination of damaged immune cells is fundamental to the regulation of immunity and inflammation in the body. In 2016, Yoshinori Ohsumi, PhD, was awarded the Nobel Prize in Physiology or Medicine for his discoveries related to the genetic regulation of autophagy.[24] Autophagy may play an important role in stem cell renewal and differentiation, as well as CHIP regulation.[25,26,27] In animal models, it has been shown that a calorie-restricted dietary program increases telomerase activity and enhances autophagy, suggesting that specific dietary interventions may be of value in improving immune cell function and its relationship to biological aging.[28] It has also recently been reported that a ketogenic diet can extend longevity and reduce chronic disease in a rodent model.[29] An increase in β-hydroxybutyrate, a ketone body that has been found to reduce the immune cell inflammatory process associated with chronic diseases of aging, can result when a ketogenic diet is consumed.[30]

Valter Longo, PhD, is director of the Longevity Institute at the University of Southern California (USC). With his colleagues at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Professor Longo has demonstrated that a fasting-mimicking diet can influence the generation, survival, and function of immune cells and reduce immunosenescence.[31] This remarkable work has shown that the fasting mimicking diet regime promotes β-cell renewal and reverses diabetes in an animal model by enhancing stem cell renewal and immune system regulation.[32,33] Furthermore, it suggests that the periodic application of the fasting mimicking diet program may promote multisystem regeneration, enhance cognitive function, and reduce the incidence of many age-related chronic diseases.[34]

There is evidence that many factors can stimulate autophagy through activation of the lysosome, the cellular organelle that controls the process, and that this can have a positive impact on reducing stem cell senescence.[35] It has been shown that the phytochemical resveratrol can activate autophagy in a variety of cell types.[36] It has also been demonstrated recently that ascorbate (vitamin C) is important in the regulation of hematopoietic stem-cell function through its impact on Tet2-dependent and independent mechanisms. The hematopoietic stem cell requires a very high level of ascorbate for proper function; reduced levels can have an adverse influence on the activity of these cells.[37]

In Summary: The Case for Categorizing Age as a Modifiable Risk Factor

Taken as a whole, we are witnessing the emergence of a new understanding of the biology of aging and the mechanism by which diet, lifestyle, and environment may influence this process in highly personalized ways. We are starting to develop a methodology for determining biological—or functional—age by measuring various physical, metabolic, cognitive, and emotional functions. New diagnostic tools for assessing processes that are associated with increased biological age such as Dr Fenech's micronucleus assay and also methods for determining telomere length have been key advancements. In addition, therapeutic dietary programs that result in stem cell renewal and rejuvenation, as well as a reduction in inflammation and mitochondrial dysfunction, open new doors for managing conditions associated with increased biological aging.[38] It is very exciting to see the field of nutrition research move beyond a focus on the calorie to recognize that various dietary components can

have a significant influence on cellular signaling processes that regulate biological age-related functions.[39] And last, there are the exciting discoveries surrounding CHIP and immune cell analysis—these represent an opportunity to identify age-related disease risk, and even more important, they are biometric tools that can be used to monitor the success of personalized lifestyle intervention in the reduction of age-related chronic diseases.

Pieces of the puzzle that is the age-disease interrelationship are starting to come together to form a more complete picture of the processes that power this complex dynamic. It will be very exciting to watch the field move forward and to see the power of this concept—that age is a modifiable risk factor—take root and thrive.

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