Beyond the Absence of Disease: In Pursuit of Healthspan

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In the bustling coastal city of Kochi, nestled in the southern Indian state of Kerala, a quiet revolution is taking place. As the first city in Southeast Asia to join the World Health Organization's Global Network for Age-Friendly Cities and Communities (WHO-GNAFCC), Kochi is pioneering a new approach to urban development that puts the needs of older individuals at the forefront.

The emerging field of geroscience is helping us better understand the biological changes that drive aging. In the not-too-distant future, this research could lead to entirely new ways of maintaining good health as we age.

A persistent challenge in making this shift is the conventional way we define and measure health. The traditional "disease model" regards health as the absence of disease. In this model, diseases are typically studied in isolation, with a focus on their specific causes in a linear fashion. For example, it's well-established that high cholesterol and high blood pressure increase the risk of cardiovascular disease, which has led to initiatives focused on screening for these risk factors and preventing progression to overt disease.

This disease-centered approach has served modern medicine well and is a major contributor to the increase in global life expectancy over the past century. However, medical and public health leaders have long argued that a more holistic approach — one that also addresses the underlying social determinants of health — might be more effective. In fact, the traditional disease model now stands in contrast to recent advances in geroscience — which emerged from the observation that age is the single greatest risk factor for nearly all chronic diseases. Rather than targeting individual diseases, geroscience therefore seeks to understand why and how age-related biological changes increase disease risk in general.

Age-Related Changes and Chronic Disease

The biological processes of aging are complex. Some result from environmental exposures, while others stem from the natural wear and tear of life. These changes can trigger biological responses that further accelerate deterioration. Over time, these accumulating changes reduce an individual's resilience to future stressors. What were once minor issues or temporary concerns become more significant, and the risk of a range of chronic diseases increases.

One area of focus has been the immune system. As we age, a range of changes naturally occur within our immune system, leading to decreased production of cells that help us develop immunity when we are exposed to new challenges. In itself, this trend does not generally cause major problems, and it probably arose for a good reason we don't yet fully understand, although it does tend to make vaccines less effective in older adults.

When chronic immune stressors are superimposed on these normal age-related changes, the sustained inflammation that results can lead to a maladaptive process. This can happen when people experience major ongoing infections, for example with HIV, or even following chronic minor viral infections that initially appear to present no major problems to the individual. These chronic infections exhaust immune cells which can then no longer perform the task they were designed for. Nor can the body easily dispose of them.

Instead, these cells become senescent, or dormant, and are sometimes called zombie cells. Rather than combatting infections, these senescent cells can secrete a range of pro-inflammatory mediators in a complex progression known as inflammaging. The cells that were designed to protect against outside threats now start to stimulate an unwanted inflammatory response. They shift from being the defender to becoming the aggressor.

Inflammaging is likely a key driver of many age-related chronic diseases, including cardiovascular disease, dementia, osteoarthritis, chronic kidney disease, diabetes, cancer, Parkinson's, disease, and other conditions, such as frailty. And while we have traditionally thought of these conditions as having independent causes, in the new world of geroscience they might better be thought of as different manifestations of a common underlying process.

This is a critical breakthrough in scientific thinking. If we can understand these underlying mechanisms, we may be able to develop interventions to delay or avoid not just one, but multiple chronic conditions at the same time.

The Challenge

The way forward will require research and clinical approaches that are very different to those we currently use. So far, much of geroscience has focused on linking age-related processes to lifespan — how long people live. But the outcome

of greater importance to most people is the quality of these years. The National Academy of Medicine therefore recently called for a concerted effort to also extend the proportion of peoples' lives spent in good health — their healthspan.

There has been limited focus on the relationship of age-related processes and healthspan. Traditional funding and research models tend to be disease specific, and as a result, much of the research has centered on individual conditions. Biological aging, however, is associated with multiple conditions, and most individuals will experience age-related declines even in the absence of disease. A ninety-year-old, does not look or function like a 20-year-old, even if they are disease free. Research linked to a single disease outcome will, by design, miss potential impacts on this broader array of health outcomes. For geroscience to advance it will therefore need to challenge established research paradigms and methods.

Rethinking Interventions and Outcomes

How can we tell if interventions targeting age-related biological change actually improve healthspan? Scientists are already working on ways to remove senescent cells or block the inflammatory mediators they secrete. While they may be able to show that these interventions are successful in a laboratory setting, the real challenge will be to determine whether they make a tangible difference in people's lives. Traditional approaches would require long follow-up periods to demonstrate if these interventions reduced the incidence of specific diseases. But what if they don't reduce the disease incidence, but they do reduce disease severity? And which diseases should scientists follow?

To provide more immediate answers, scientists are turning to biomarkers of aging — biological tests that can detect physiologic changes that might signify improvements. If interventions are successful, they should be able to quickly demonstrate an impact on these biological measures. However, these measures face the same challenge: how will we know if they signify real improvements in people's day-to-day lives?

One solution could be found in an alternative way of framing health in older adults that was recently proposed by the World Health Organization. In this strengths-based model, healthy aging is considered not through the presence or absence of disease but based on an individual's ability to be and do the things they value. This ability is understood to be determined by individual-level attributes — a person's "intrinsic capacity," as well as the environments they inhabit and the interaction between the individual and these environments.

Some researchers now think that intrinsic capacity might provide a more appropriate outcome for geroscience research. Intrinsic capacity is directly relevant to the things that matter in people's lives. Recent studies have suggested it is easily measurable and comprises logical subdomains including cognitive, locomotor, sensory and psychological capacity, and a further subdomain labelled vitality. Data on many of these are already routinely collected by devices such as mobile phones and new techniques of machine learning may help us better understand it.

If this information could be brought together in a meaningful way it could tell us how we are doing on a day-to-day basis. This would allow us to compare people's health to others of similar ages and track whether they are following the usual life trajectory. By monitoring capacity across the lifecourse, we might be able to better understand the characteristics that help someone reach the highest possible peak and experience the slowest possible declines. For geroscience this is also a logical, clinically meaningful endpoint that is likely to be much more manageable than waiting for a disease not to appear.

This is an exciting time for research on biological aging. It will require new ways of thinking and methods that are radically different from traditional medical research. As a first step, it might be time to apply the well-known phrase from the constitution of the World Health Organization: that health is more than the absence of disease. •

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