

Aging as a Risk Factor for Disease and Disability: The National Institutes of Health
GeroScience Interest Group

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Senator Nelson, Senator Collins and Members of the Committee:

Good afternoon. I am Dr. Richard Hodes, Director of the National Institute on Aging (NIA) at the National Institutes of Health (NIH). It is a pleasure to be here today to talk about some of the remarkable scientific advances we've made recently regarding the basic biology of aging, as well as the initiatives we support to generate and maintain momentum in this increasingly important area.

The extraordinary increase in life expectancy for both men and women represents one of the great public health triumphs of the twentieth and early twenty-first centuries. In 1900, life expectancy at birth was just over 47 years; today, it is almost 79. The number of Americans over age 65 is also continuing to increase at a rapid rate. In 2010, there were approximately 40 million Americans over age 65; by 2030, demographers estimate that this number will jump to 70 million. The number of "oldest old" – people age 85 or older – is expected to more than triple between 2010 and 2050. Globally, most nations are experiencing a similarly significant increase in the over-65 population.

However, after about age 65, people become increasingly susceptible to progressive declines in physical and mental abilities. Age is well established as a primary risk factor for many disabling diseases and conditions, and even today, recent demographic studies are beginning to show increases in activity limitations among members of the enormous baby boom cohort. For this reason, the development of new interventions to improve and maintain health into old age – to improve *healthspan* – is an increasingly urgent frontier for modern medicine.

Since its inception in 1974, the NIA has supported groundbreaking research on the basic biology of aging in research laboratories around the country and within our own Intramural Research Program. Exciting findings from NIH's ongoing support of studies in the basic biology are suggesting new avenues for the development of interventions for age-related diseases and conditions, some of which are described in this summary. Some of the latest findings are described here. Until recently, the study of

the fundamental processes that underlie aging has often been dissociated from clinical work on aging-related disease and disability. In an attempt to bridge this gap, researchers have established the emerging field of geroscience, which is focused on the mechanisms by which the basic biology of aging drives chronic disease.

As you have heard, NIH's GeroScience Interest Group (GSIG) promotes innovative approaches to increase our understanding of the relationships between the biological processes of aging and age-related chronic diseases and disabilities. Established in 2011, the GSIG currently includes members from over 20 NIH Institutes and Centers and is one of the fastest growing Interest Groups at NIH – a testament to both the high level of cross-disciplinary interest in the topic and its critical importance with respect to public health.

Tomorrow, the GSIG and its partners, the Gerontological Society of America and the Alliance for Aging Research, will present a historic summit on “Advances in Geroscience: Impact on Healthspan and Chronic Disease.” Over 50 leading geroscientists will participate, and more than 500 attendees have registered to join. Discussion and deliberation at the Summit are expected to generate research recommendations that will advance this critical area of science.

The Summit will focus on seven broad areas of research in which the basic biology of aging is believed to inform multiple disease processes. These include:

Inflammation. A pervasive feature of aging – and most, if not all, age-related diseases – is chronic inflammation. Several epidemiological studies indicate that high blood levels of inflammatory biomarkers are the most significant risk factor for both morbidity and mortality in the elderly. However, many unanswered questions remain about the etiology of age-associated inflammation, whether inflammation is a cause or consequence (or both) of disease and the extent to which inflammation might also be beneficial.

Adaptation to stress. The ability to properly respond to chronic stress appears to be necessary for healthy aging, and an enhanced ability to adapt and adequately respond to stress has often been observed in long-lived organisms. In fact, mild stress appears to be protective (via a mechanism called hormesis, by which the organism's internal defenses against stress are activated). The point at which hormetic stress becomes damaging is not well understood. However, this remains an active area of study.

Metabolism. Scientists believe that many aspects of metabolism are implicated in basic aging processes, and a number of interventions to slow aging by altering metabolism have been tested in animal models. The most startling results have been seen with caloric restriction – sharply reducing caloric intake while ensuring optimal nutrition. Dietary manipulation has been found to extend the lifespans of several species under certain conditions. Although evidence of lifespan benefit in higher-order primates has been equivocal, most studies have shown beneficial effects of dietary restriction on health, and this remains a vibrant area of study.

One recent development has been the identification of the immunosuppressant drug rapamycin as a means to extend lifespan in mice. Working through the mTOR cellular pathway, rapamycin acts by interfering with nutrient sensing machineries, thus affecting the way cells respond to metabolic changes. Researchers are working to discover agents that may provide the positive effects of rapamycin without accompanying side effects. More recently, investigators in the NIA Intramural Research Program found that the drug metformin, commonly prescribed as a treatment for diabetes, also extends health and longevity in male mice by mimicking caloric restriction's beneficial effects.

Epigenetics. Aging and susceptibility to disease are driven by both genetic and environmental factors. While considerable success in basic aging research over the past few decades has revolved around genetic variants associated with extended lifespan, the focus has more recently shifted to

epigenetics, or heritable chemical “switches” that attach to the DNA and can activate or inactivate genes. Epigenetic activity is influenced by the environment and for this reason offers unprecedented opportunities for intervention. Recent advances in this field include the work of NIA-supported scientists who found that in worms, certain epigenetic changes that positively affect longevity can actually be passed on to future generations, so that the “grandchildren” of affected worms still had increased longevity. In another study, investigators found a strong correlation between a particular epigenetic mark and chronological age in humans, suggesting that this “molecular clock” could be used as a potential biomarker for physiological aging.

Macromolecular damage. Aging is accompanied by dramatic increases in damage to proteins, lipids and DNA. The extent to which this damage – or which specific types of damage – is related to aging and susceptibility to disease remains the subject of intense scientific scrutiny. While recent work has shifted attention away from the classical free radical theory of aging – that atoms or molecules with a single unpaired electron rattling around can cause cellular injury, which accumulates over time – a provocative alternative explanation for the role of free radicals in aging is that they may in fact serve as an intracellular signal that alerts the cell and the organism of potential danger.

Proteostasis. Scientists have recently identified proteostasis, the intra-and extracellular networks that serve to maintain the quality of cellular proteins, as a set of processes that may profoundly affect both aging and susceptibility to disease. Optimal function of the proteins within the cell is essential to the cell’s ability to respond and adapt to the changing environment, but the efficiency of the proteostasis network decreases with age. Current advances in the understanding of proteostasis and its changes during aging have opened opportunities to investigate potential therapeutic approaches. Researchers are currently pursuing interventions that will preserve the proteostasis network into older ages, thus paving the way to preventing a number of degenerative diseases.

Stem cells and regeneration. Much recent work has focused on characterizing the states of stem cells and their activities during aging. Investigators have found that stem cells are often still present in the tissues of older individuals, but the “niches” in which they reside have been altered. If we can understand the underlying causes for the reduction in function, rejuvenation of adult stem cells in older tissues may be possible. For example, NIA-supported investigators have found that the protein GDF-11, present in young mice, reversed aging-related heart disease in older mice – the first time a circulating factor has demonstrated the potential to reverse aging-related organ dysfunction. Stem cell/niche interactions, as well as mechanisms involved in preserving genomic and macromolecular quality of stem cells during aging, are topics of intense study.

These seven topics represent only a slice of the broad and rich field of geroscience. We anticipate that the discussions at the Summit will foster a better appreciation of the multiple levels at which all of these variables interact with each other, and will energize the field to develop the studies that will lead to a “systems level” understanding of the relationship between aging biology and susceptibility to disease. In turn, this may facilitate the identification of new interventions that prevent or treat multiple diseases and disorders by addressing aging as a single underlying risk factor, thereby increasing both lifespan and healthspan in humans.

Thank you, and I look forward to answering your questions.