The goal of this Summit was to explore new ways to understand how common mechanisms governing aging might underlie the pathology associated with diverse chronic diseases. A second, equally important goal was to promote new pathways for collaboration among researchers in these varied diseases, specifically within the context of aging. To accomplish this, the meeting was organized into sessions according to distinct mechanisms known or suspected to be related to aging, without regard to specific diseases, but in a way that might highlight how aging mechanisms enable disease. Speakers were chosen based on acknowledged expertise in a broad range of chronic diseases (e.g., cancer, heart failure, sarcopenia, etc.) and/or biology of aging. The program was structured around short talks with ample time for discussions among investigators who, because of diverse interests related to specific disease areas, might not have been likely to otherwise interact. The theme of geroscience provided a large tent under which speakers focused on different chronic diseases came together in an environment that was highly conducive to cross-talk.

Goals of this Summary

1. Identify tangible outcomes
   - Set of position papers to share with the scientific community (in press at The Journals of Gerontology-Series A)
   - Advisory statement for NIH ICs (this document)
   - A white paper to be published in a high-visibility journal (in preparation)

2. Identify intangible outcomes
   - Cross-pollination among disciplines / fields, both among researchers and NIH staff
   - Increased awareness of commonalities in several chronic conditions
   - Holistic approach to addressing age-related diseases as a group, rather than individually
Scientific Recommendations

• Foster studies aimed at identifying how our current knowledge of the biology of aging can be applied to study the impact of aging on individual (and multiple) age-related diseases/conditions.

• How are the seven pillars connected with each other and with chronic diseases? The seven discussion areas were treated separately during the meeting, but may be seven sides of the same coin. Certainly they influence each other, raising questions as to whether early changes in one or more of these processes drive maladaptive changes in others. Moreover, the connections likely overlap but differ across chronic disease states. Studies that focus on the connections between different aspects of aging and their relationship to disease should be encouraged.

• Identify which aspects of aging are most amenable to preventive therapy or ameliorative interventions.

• Develop metrics to assess healthspan so that preventative therapies can be assessed for efficacy.

• Develop chronologically relevant animal models of specific chronic diseases to improve translation. One major limitation of rodent models of chronic disease states is that studies are often performed in models that develop the disease when the animals are young. The use of models that incorporate aging, although more time consuming and costly, may dramatically enhance reproducibility of therapies in human clinical trials.

• Develop paradigms and models to incorporate environmental exposure (including in early development) as etiological factors for late-life chronic disease.

• Interventions that affect lifespan need to be tested for their effect both in prevention and treatment of a wider range of chronic disease animal models, preferentially those that incorporate aging.

• Develop a systems biology approach to better integrate aging and disease, based on the 7 topics highlighted in the Summit.

• Foster mechanistic studies aimed at linking the molecular/cellular parameters that underlie aging to outcomes such as frailty and resilience, which define susceptibility to chronic disease, and may be at the crossroads of aging and disease. Particularly, much more emphasis needs to be placed on how to define, measure and maintain resilience during aging.

• Effectively address the extent to which aging and disease represent a two way process. More specifically, foster studies that measure the extent to which diseases enhance the onset of aging (e.g., through promotion of chronic inflammatory processes.)

• Increase pathology measures in multiple animal models with age so as to assess the presence of comorbidities, and the role of aging.

• Promote comparative geroscience studies of exceptional lifespan and healthspan, as a window into genetic and physiological determinants of disease susceptibility.
Administrative Recommendations

- Support and fund the activities of GSIG as a critical infrastructure to foster research in geroscience across NIH Institutes and Centers.
- Develop outreach activities to expand appreciation of the relevance of geroscience across NIH Institutes and Centers.
- Develop outreach activities to expand geroscience beyond the confines of NIH, including information dissemination at research institutions and the general public.
- Develop consortia aimed at addressing the global aspect of aging and its role in enabling chronic disease states in a more holistic manner.

SESSION-SPECIFIC RECOMMENDATIONS

A two-pronged approach was recommended for each session: First, to expand the understanding of each topic in the context of geroscience, and second, to integrate studies in two or more topics for a more complete molecular understanding of the interactions between aging and chronic disease.

Adaptation to Stress - Both physiologic and psychologic stressors are linked to aging and chronic disease states, but it has been difficult to pin down precisely how specific stressors interacts with molecular drivers of pathology and how age impacts these interactions. Despite the difficulty, this is a critical field of endeavor since many forms of stress can be modified by behavioral change, opening a potentially rapid path by which people might prevent or delay chronic diseases.

Recommendations:

- Bridge the continuum psychological stress at the organismal level to molecular and cellular impacts with an eye toward understanding how different stresses accelerate and/or offset aging and associated chronic diseases.
- Differentiate horsetic stress, (associated with resilience and healthy aging) from toxic stress (which accelerates aging and associated disease) at each of these levels (molecular, cellular and organismal). This recommendation should be executed with the goal to identify behavioral interventions that could maximize human healthspan and prevent disease onset.
- Reduce the gap between understanding stress in humans and in animal models by developing better metrics, and utilizing relevant stressors in animal models, particularly forms of low level chronic stress, more closely linked to human experiences.

Epigenetics - Widespread epigenetic changes are evident in a number of chronic diseases, including but not limited to the cancer field. Recently, epigenetic changes have been linked to the aging process directly. Described in briefest terms, age-associated changes drive developmentally organized epigenomes toward entropy, challenging the ability of cells to
Determine the extent to which changing global gene expression and chromatin signatures during the aging process are informative of integrative beneficial versus deleterious adaptation to stress, resulting in changes in susceptibility to pathology.

Assess whether the epigenetic changes that occur during aging or in response to environmental stress are reversible, and determine the consequences of reversing these changes in animal models of aging and disease.

Examine the range of recently developed small molecules that target enzymes responsible for epigenetic changes for efficacy across a wide range of chronic conditions associated with aging.

**Inflammation** - *Acute inflammation is an important adaptive response to mediate tissue repair in response to a range of insults. However, recent research led to the discovery that low grade chronic inflammation is a contributing factor to aging and chronic disease states.*

**Recommendations:**

- Efforts need to be made to define the molecular distinctions between adaptive and maladaptive inflammatory responses and how, with aging, the chronic maladaptive responses predominate. Incorporated in this approach should be studies to define strategies to promote anti-inflammatory processes during aging that could reduce the incidence or severity of chronic disease.

- The inflammatory components that cause damage across a range of age-related diseases need to be more clearly defined, in terms of whether the cytokines act in autocrine, paracrine or endocrine fashion. Furthermore, their sources of production should be established, particularly with regard to the role played by senescent cells and chronic stress.

- Direct comparisons need to be made between the inflammation associated with overnutrition and obesity to that associated with aging. This will lead to a better understanding of the interactions between metabolic dysfunction, aging and the increased risks imposed by each on chronic disease.

**Macromolecular Damage** - One of the oldest theories of aging is that cumulative damage contributes to aging phenotypes, since a wide range of molecules exhibit increasing damage during aging. However, it remains unclear which of these events promote aging and to what extent. Strong evidence has emerged for macromolecular damage as a driver of chronic diseases (e.g. DNA damage in cancer; oxidative damage in cardiovascular disease). A systematic understanding of types and levels of macromolecular damage in a wide range of chronic diseases may help to identify the common components that are associated with aging and underlie the effects of aging on disease.
Recommendations:

- Generate a systemic understanding of the relationship between multiple forms of macromolecular damage and the onset of chronic diseases associated with aging. Given that DNA damage is associated with multiple progeroid disorders, particular attention should be paid to this form of damage in chronic diseases.

- Define the role of stochastic macromolecular damage and the damage response pathways to determine how this may underlie the wide variation in life expectancy and disease susceptibility among individual organisms in a genetically identical population.

**Metabolism** - Widespread metabolic changes occur during aging that could underlie part of the increased incidence of chronic diseases, including type II diabetes, cardiovascular disease, neurodegenerative disease and cancer. However, the specific metabolic changes during aging that underlie disease are still a matter of extensive debate.

Recommendations:

- Determine how signaling pathways that regulate growth, metabolism and lifespan contribute to age-dependent chronic diseases – and not solely metabolic diseases. Are these processes directly or indirectly related to age-associated chronic pathologies such as diabetes, cardiovascular and neurodegenerative diseases? In what tissues and at what time during the aging process do these pathways intersect with other mechanisms of aging such as inflammation, stress responses, to increase susceptibility to chronic diseases?

- Increasing evidence suggests that the circadian clock becomes dysfunctional with mammalian aging (including in humans) and that this contributes to disease onset. The role of central and peripheral clocks in aging and disease onset requires elaboration.

- Explore links between metabolic dysfunction and other elements of aging such as hypothalamus dysfunction, stem cell regeneration and adipose function, and their interplay as risk factors for chronic disease onset.

**Proteostasis** - Altered proteostasis is increasingly associated with aging and interventions improving proteostatic mechanisms including autophagy, proteasome function and unfolded protein responses are all linked to longevity in animal models of aging. Increasingly, these interventions are showing promise for disease states as well. Thus, strategies to enhance proteostasis could have wide therapeutic advantages across the spectrum of chronic diseases.

Recommendations:

- With age, the task of several proteostasis machineries increases due to an elevated load of damaged proteins and the capacity of these machineries might be exceeded. Studies are encouraged to assess the extent to which reduced
activity of proteostasis pathways with age underlies onset and progression of multiple chronic diseases of aging, particularly neurodegenerative syndromes including Alzheimer’s, Parkinson’s, Huntington’s, ALS and others, but also a range of other chronic diseases particularly affecting less proliferative tissues (e.g. heart, retina, skeletal muscle).

- Increasing evidence indicates crosstalk between different proteostasis machineries. For instance, an impaired ER unfolded protein response can lead to elevated macroautophagy. To gain a thorough understanding of the role these machineries play in the diseases of aging, it may be advantageous to develop systems biology tools to address the relative contribution (and interactions) of each of these machineries in the context of a range of chronic diseases of aging.

- Recent studies suggest that proteostasis pathways have an endocrine and or paracrine nature, which may be integrated with – or independent of – inflammatory or stress signaling (see above). These intriguing findings need to be explored in depth, with a focus on strategies to induce this signal in the absence of specific stress, as a possible hormetic approach to treating aging and associated diseases.

**Stem Cells and Regeneration** - Aging is accompanied by intrinsic changes to adult stem cells from many tissues and the niches they inhabit. Recent evidence indicates that these changes may underlie several aspects of aging, but the extent to which these changes promote age-related diseases remains poorly understood.

**Recommendations:**

- Assess to what extent age-related perturbation of stem cells and their associated niches contributes to chronic disease states in different organs. Changes in the niche should also be tested for their effects on maintenance of differentiation and function in their progenitor populations. The impact of age-associated changes in metabolism and inflammatory signals on the stem cells and their niche should be explored in relation to chronic diseases.

- Determine in the context of chronic disease how aging impacts the renewal capacity of stem cells and their ability to replace damaged tissue. This should be done for “rejuvenated” endogenous stem cells as well as exogenous stem cells (e.g., isolated stem cells or induced pluripotent stem cells, which are the pillars of cell-based therapies).

- Understand to what extent adult stem cell populations undergo macromolecular damage during aging and how this impacts their ability to effectively maintain their pool sizes and to generate differentiated cells in a range of tissues.
CLOSING STATEMENT

The goal of this Summit was to open new ways to understand how common mechanisms governing aging might underlie the occurrence and pathology of diverse chronic diseases. Here, recommendations have been extracted from the Summit’s presentations and discussions that could help accomplish that goal. A second goal was to promote new pathways for collaboration among researchers in these varied diseases specifically in the context of aging. The numerous cross-references between the diverse mechanisms of aging and chronic diseases, made during the Summit, have been captured here, as well. It is hoped that some of these recommendations can be transformed into new research initiatives to better understand the relationship between aging and chronic disease and degenerative conditions, which is at the heart of geroscience.