



Geriatric Hematology

Session Chair: Harvey Jay Cohen

Biology and Physiology of Aging

Harvey Jay Cohen

We are in the midst of a dramatic demographic evolution. The number of older persons in this country, and indeed throughout the world, is increasing rapidly. In the United States the number of people over the age 65 will approximately double in the next 50 years, while the number of people over the age of 85 will almost quadruple. Since many hematologic disorders, including anemia and myelodysplastic disorders, occur with increasing incidence in the older portion of the population, it is important that planning for diagnoses and treatment of such disorders be placed in the context of aging-related changes that might be expected in the individual under consideration. This section discusses the relevant aspects of the biology and physiology of aging against which the description of the approach to specific hematologic issues such as anemia and myelodysplastic disorders can be framed.

Biologic Aging

Biologic aging is a process occurring in adult life, during which changes in structure and function occur that lead to a decrease in reserve capacity in most systems. This decline is in turn accompanied by an increasing vulnerability to age-related diseases and the overall forces of mortality which ultimately leads to death.⁽¹⁾ Although the terms “aging” and “senescence” are often used interchangeably, senescence more often refers to the latter stages of this process, more proximal to death, while aging can be considered to be the process that occurs throughout the adult life span, although at a somewhat variable pace. The general phenotype of aging created by various changes to be considered further below is generally quite recognizable and shares many features across a variety of mammalian species. The rate at which these processes occur, however, varies considerably among species. Thus, the maximum life span, which can

be defined as the oldest age to which any member of a species survives, can vary among mammals by almost 30-fold; from the approximately 3-year life span in rodents to the approximately 120-year life span in humans.^(2,3) These interspecies differences will be addressed again in our consideration of some of the theories of aging and the controlling mechanisms exerted upon this process.

Another term utilized to describe some of the outcome of the process of aging is “life expectancy.” This is the age to which 50% of a given population survive. While the maximal life span, as noted above, appears to be controlled by intrinsic processes, the average life expectancy is based to a considerable extent on external processes such as the occurrence of various diseases. In humans the life expectancy has increased dramatically over the last century and a half, while the more biologically fixed maximal life span has remain remarkably consistent.

Cellular Aging

Cellular models of whole organisms have long been sought as a way of explaining this extraordinarily complex process and to serve as models for possible intervention. The pioneering discovery of Hayflick and Moorehead identified the cultured human diploid fibroblast as a potential model for aging.⁽⁴⁾ In this system, which has now been replicated for a number of other cell types including endothelial cells, and lymphocytes, it has been demonstrated that cells placed in culture proliferate rapidly and vigorously initially, following which there is a period of declining proliferation and finally cessation of proliferation with continued survival in a quiescent fashion. A finite number of cell divisions, or population doublings, occur in a species-specific manner, after which cells will no longer divide. In humans

this occurs in approximately fifty population doublings for cells derived from newborn tissue. It is interesting that the number of population doublings of cells in culture appears to roughly relate to the lifespan of the species and age of the donor. It is important to point out, however, that while there are a number of parallels between these processes of cellular aging and overall aging for a complete organism, the extent to which such systems can serve as models of true aging is still debated. Thus, for example there is no obvious evidence of the accumulation of senescence cells in aging in vivo as is seen in vitro.^(3,5)

Theories of Aging

Despite extensive investigation with a variety of vitro and in vivo approaches no single explanation for the phenomenon of aging has yet been determined. Two major types of theories have been proposed: the cell damage/error theories and the program theories. It is likely that components of each of the concepts actually contribute to determining the aging process.^(6,7)

Cell Damage/Error Theories

Cell damage/error theories are generally stochastic in nature. That is to say, they assume that events occurring on a random basis gradually cause the accumulation of damage to vital areas of cellular organ function. This damage would then result in what we see as the phenotype of aging. The so-called "error catastrophe" theory was earliest of these, which proposed that random errors occurred during the synthesis of new proteins such that the rapid accumulation of such error-containing molecules would eventually be incompatible with normal function. However, little experimental evidence has been produced to support such a theory. On the other hand, there has been considerable experimental support for changes occurring at a post-synthetic (i.e., post-translational) point. The two major sources of damage currently thought to contribute to this process are free radicals and glycosylation.

Free radical theory

This theory proposes that highly reactive free radical species, which may be either externally generated, or internally generated as by products of oxidative metabolism, then react with key cellular components resulting in alterations in function leading to the changes consistent with aging. There are a number of reasons for the attractiveness of this theory. First, molecules of many sorts, including lipids, proteins, and DNA that are critical to survival, may be affected by free radical attack. The body has evolved an extensive system of intrinsic cellular antioxidant defenses that have the potential to control such reactions, suggesting that they are of con-

siderable importance. Thus, free radical generation in mammals inversely correlates with longevity and the levels of antioxidant enzymes have been noted to be higher in longer lived species. However, evidence of the role such processes has in truly determining longevity is incomplete, and it is of interest that over-expression of antioxidants in lower species does not necessarily increase survival. One particular focus for the potential effects of the free radical damage has been on the mitochondria, since this organelle is the site of much of the free radical production in cells. It is felt that free radical damage may be responsible for the decline in energy production that results as a cell ages perhaps as a result of mitochondrial DNA damage.

Glycosylation

Non-enzymatic glycation occurs with increasing frequency during the aging process. This non-enzymatic attachment of glucose to many vital components, including DNA and proteins but especially to some of the longer lived proteins such as collagen, appears to be associated with damage and functional alterations. This type of attack results in damage including cross-linking and accumulation of cross-linked protein within cells and tissues that appears to have the potential to affect bodily functions adversely, as well as to interfere with the biosynthetic and energy generating systems. In addition, the presence of advanced glycation end products (AGE) also appears to initiate inflammatory reactions. Such chronic inflammatory processes might create many of the phenotypes of aging, including a number of the degenerative processes occurring in this setting.^(5,7)

Program Theories

Program theories suggest that the processes of aging and senescence are a result of genetic programs somewhat analogous to the genetic programs controlling embryogenesis, growth, development and maturation. In this context aging is a result of certain genes being shut down while others become overly expressed. The fact that there is such a dramatic difference in interspecies maximal lifespan suggests that there is some degree of genetic control, at least at the species level. To what extent such controlling processes explain aging differences within any given species is not known.

While neuroendocrine and immunologic factors have been associated with the aging process and are noted to change during it, little evidence has been generated to support the role of either of these systems in directly contributing to the control of the aging process. On the other hand, a large body of work has now accumulated to suggest that there are at least several genes involved in genetic control of maximal lifespan. Such genes have been noted in nematodes, yeast, and fruit flies, but to a

much lesser degree in mammalian systems. There has been compelling evidence for genetic control of cellular aging with a number of genes including several tumor suppressor genes such as *Rb* and *p53*, implicated in replicative senescence at this level. How this translates to control of the aging process at the organism level is yet to be determined.

Another potentially important indicator of genetic control of senescence has also been determined in *in vitro* systems. This relates to the role of the telomere in controlling cellular senescence. Telomeres are the terminal ends of the chromosomes and appear to have as their major roles the prevention of chromosomal degradation and/or fusion with other chromosomal ends. It has been demonstrated that the average length of telomeres decreases during both *in vitro* and *in-vivo* aging of fibroblasts as well as peripheral blood lymphocytes. Such telomere shortening does not occur in immortalized cells, perhaps related to the reactivation of the enzyme telomerase in such cells. Recently it has been shown that activation of telomerase in human cells *in vitro* can significantly delay the onset of senescence and extend the lifespan of such cells, as can experimental elongation of telomeric length.⁽⁸⁾ Thus these structures may serve as a potential biological clock for counting the number of population doublings of cells and determining the shut off point for cellular proliferation. Once again how this will translate to control of the overall aging process in a whole organism is yet to be seen.

Physiology of Aging

A broad spectrum of physiologic changes occurs during the normal aging process and independent of disease.⁽⁹⁾ Before considering some of the individual organ changes in brief, it is useful to consider the overall impact of such changes. In general, most of the impact of these changes is noted in impaired responses to external stimuli. Thus, a decrease in physiological reserve generally leaves base line function of any given organ or indeed of a combination of organ functions relatively unchanged. But it leaves a smaller amount of reserve capacity with which the individual can respond to external stimuli and maintain basic homeostasis. This decrease in the functional reserve capacity has become a hallmark of the approach to the geriatric patient since it creates a setting of heightened vulnerability, which is so commonly played out in clinical settings. Several areas of regulatory function are affected, including blood pressure regulation with significant alterations of beta adrenergic receptor-mediated vasodilation; thermoregulation with reduced heat production, impaired vasoconstrictor activity and altered temperature perceptions; and volume regulation with decreased thirst drive and age-related renal changes to be described further below.

Individual organ system changes

Changes in organ systems of considerable importance to the care of the older patient with hematologic disorders will be considered here. Changes related to the hemopoietic system will not be considered here since they will be addressed in a subsequent portion of this session.

Cardiovascular system

Basic cardiovascular function is little changed with age. However, maximal and submaximal responses to catechol stimulation as well as sympathetic nervous system stimulation are markedly impaired in the older individual. Maximum heart rate declines with age so that cardiac output at maximal exercise decreases somewhat in spite of an increase in stroke volume. Both peripheral vascular as well as cardiac compliance and elasticity decrease, and there is an increased recovery time following exertion.

Pulmonary system

Decreased elasticity and somewhat reduced ciliary activity are seen in the aging lung. In addition, the loss of elastic tissue results in enlargement of alveolar ducts and decreased surface area for gas exchange. Pulmonary functional reserves decrease, with age-related decreases in forced expiratory volume and increasing residual volume, and ultimately an overall decrease in maximal oxygen consumption. However, many of these changes can be ameliorated by exercise though generally not to the level of healthy young individuals.

Endocrine system

Many age-related changes occur in the endocrine system, but in this case, in contrast to many other organ systems not all functions decline. Some of these may be physiologically adaptive phenomena. Thus, for example, blood levels of insulin increase with increasing age, perhaps as a response to decrease in peripheral tissue insulin responsiveness. On the other hand, insulin-like growth factor (IGF1) decreases with increasing age. Other hormones that increase with age include norepinephrine, parathyroid hormone, vasopressin, and atrial natriuretic peptide. In addition to IGF1 other hormones that decrease include 3,5,3 prime-tri-iodothyronine, growth hormone, renin, aldosterone, dehydroepiandrosterone, and the sex steroids in both women and men.

Gastrointestinal system

There are a number of changes throughout the gastrointestinal system but most are fairly modest. There are modest changes in the production of saliva by the salivary glands, generally preserved esophageal function but decreased amplitude of contraction and decreased secondary contractions. There are minimal alterations in gas-

tric motility, and impairment in adaptive relaxation of the stomach and some degree of reduction in gastric acid production but not nearly to the extent suggested by earlier studies. Small intestinal changes occur including impaired motility in response to a food bolus and somewhat decreased absorption of calcium, iron, lactose, xylose and vitamin D. Colonic changes include mucosal atrophy and functional changes resulting in slower transit and altered coordination of contraction, which may in part explain predispositions to constipation.

Nervous system

Brain weight decreases significantly with normal aging as does brain blood flow. There is neuronal loss but in the absence of disease this is relatively modest. Certain areas such as the hypothalamus, the pons and medulla as well as the entorhinal cortex appear to have modest neuronal losses. Biochemical changes in brain enzymes have somewhat inconsistently been reported; some of the more consistent changes being decreases in acetylcholinesterase, serotonin and dopamine receptors and substance P neurotransmitters. Changes in the special senses such as vision, hearing, taste and smell also occur with characteristic decreases in lens elasticity, high frequency greater than low frequency hearing loss, and decreased olfaction as well as taste sensation.

Insert new paragraph here

Organ systems relating to drug handling

There are changes in several organ systems which are of especial importance because of their impact on drug handling which may be of great importance in the therapeutic approach to hematologic disorders. These involve predominantly the hepatic and renal system in addition to the already noted gastrointestinal changes.^(9,10)

Immune system

Immune dysfunction occurs with aging. There is a progressive decrease in thymic mass and production of thymic hormones resulting in a decrease in naive lymphocytes and a corresponding increase in memory cells. Lymphocyte proliferative responses decline, perhaps related to decreased IL2 production. On the other hand, certain cytokines, IL6, IL-1 β , TGF β increase with age. Specific antibody response to a challenge decreases, but non-specific immunoglobulin levels may be elevated. Monoclonal immunoglobulin protein prevalence increases progressively with age, perhaps related to T-cell regulatory abnormalities and/or the influence of IL-6.

Hepatic function

Liver mass decreases with age as does hepatic blood flow. While hepatocyte number decreases slightly there is relatively little alteration in routine liver function tests. There

is major inter-person variability in hepatic metabolism to which age contributes a significant amount. There are not marked changes in the activity of either phase 1 microsomal oxidative enzymes or phase 2 conjugation enzymes as a consequence of age. However, cytochrome P450 metabolism of drugs is often slower in older people. This decreasing clearance appears to be largely due to the age-related reduction in liver mass. In addition, the decrease in liver blood flow results in reduced first pass effect resulting in decreased systemic bioavailability and plasma concentrations.

Renal function

There are a number of changes in renal function, which make this area one of the more dramatic for potential effects on physiologic functions, including drug handling. There is a generalized age-related loss of kidney mass involving entire nephron units. There is a loss of glomeruli by as much as 30-40% by age 80, and alterations in renal perfusion which may be the result of atherosclerotic changes not specifically those of aging. Total renal blood flow falls by about 10% per decade after the age of 20. The most dramatic changes are those of decreased glomerular filtration rate (GFR). After age 30 GFR falls by approximately 1% per year on average in the population. However, longitudinal studies have demonstrated that about one-third of people maintain their glomerular filtration rate at a fairly constant level throughout their age span. Thus, the use of a 24-hour creatinine clearance to provide an estimate of GFR may be necessary when contemplating therapeutic interventions. Because of the decreases in lean body mass that occur during aging serum creatinine alone is not a good reflection of renal function.

Other changes that may impact on drug handling include drug absorption, which, despite the many age-related changes in the GI system, generally has little pharmacokinetic effect, and drug distribution, which may be affected by the changes in weight and body composition that occur with age, leading to decreased lean body mass and total body water and an increase in body fat. Thus, water-soluble drugs might require lower loading doses, while fat-soluble drugs theoretically might require a greater initial dose. However, in reality these changes do not seem to have great practical impact.

Hopefully, incorporating the knowledge base concerning the biological and physiological changes occurring during the aging process will provide the appropriate context for determining the appropriate approach to the management of hematologic disorders in the elderly.

References

1. Cohen HJ: Biology of aging as related to cancer. *Cancer (suppl)* 74:7:2092, 1994

2. Miller RA: The biology of aging and longevity, in Hazzard WR, Blass JP, Ettinger WH, Halter JB, Ouslander JG (eds): Principles of Geriatric Medicine and Gerontology, 4th Ed. New York, NY, McGraw Hill, 1999, p 3
3. Troen BR, Cristofalo VJ: The biology of aging, in Cobb EL, Duthie EH, Murphy JB (eds) Geriatrics Review Syllabus, 4th Ed. New York, NY, American Geriatrics Society, 1999, p 5
4. Hayflick L, Moorehead PS: The limited *in vitro* lifetime of human diploid cell strains. *Exp Aging Res* 25:585, 1961
5. Baker GT, Martin GR: Molecular and biologic factors in aging: The origins, causes, and prevention of senescence, in Cassel CK, Cohen HJ, Larson EB, et al (eds): Geriatric Medicine, 3rd Ed. New York, NY, Springer, 1997, p 3
6. Cristofalo VJ, Tresini M, Francis MK, Volker C: Biological theories of senescence, in Bengtson VL, Schaie KW (eds): Handbook of Theories of Aging. New York NY, Springer 1999, p 98
7. Solomon DH: The role of aging processes in aging-dependent diseases, in Bengtson VL, Schaie KW (eds): Handbook of Theories of Aging. New York NY, Springer 1999, p 133
8. Fossel M: Telomerase and the aging cell: Implications for human health. *JAMA* 279:21:1732, 1998
9. Taffet GE: Age-related physiologic changes, in Cobb EL, Duthie EH, Murphy JB (eds) Geriatrics Review Syllabus, 4th Ed. New York, NY, American Geriatrics Society, 1999, p 10
10. Leipzig RM: Pharmacology and appropriate prescribing, in Cobb EL, Duthie EH, Murphy JB (eds): Geriatrics Review Syllabus, 4th Ed. New York, NY, American Geriatrics Society, 1999, p 23



The Effect of Age on Hematopoiesis and the Work-Up of Anemia in the Elderly

David A. Lipschitz

The Effect of Age on the Hematopoietic System

The Pluripotent Stem Cell

One of the cardinal features of cellular aging is a finite replicative capacity. Studies in fibroblasts have shown that after doubling approximately 50 times, the cell loses its ability to divide and dies. There is some evidence that the pluripotent hematopoietic stem cell (CFU-S) has a finite replicative capacity. CFU-S appears to have a heterogeneous self-renewal capacity and an age structure in which a young CFU-S with high self-renewal capacity produces older CFU-S with decreasing self-renewal capacity and increasing differentiation potential. This hypothesis has been strengthened by studies of long-term bone marrow culture, which show that maintenance of hematopoiesis in long-term bone marrow cultures varies inversely with the age of the donor from which the culture was initiated. Does this, however have any clinical relevance? Modeling studies have shown that the proliferative capacity of the hematopoietic stem cell compartment could support a life expectancy of hundreds of years. A very large proliferative potential explains why so few stem cells are required to repopulate the marrow after ablation. Thus the *in vitro* findings are of no clinical

relevance and cannot explain any change in hematopoietic function that accompanies aging.

Effect of normal aging on bone marrow function

Studies in both animals and in man have shown no age-related reductions in committed hematopoietic stem cell and differentiated hematopoietic cell number. This applies to erythroid, myeloid and megakaryocytic lineages. Erythrokinetic studies show that red blood cell survival is unchanged with aging, the plasma iron turnover and erythron iron turnover are unchanged, and red blood cell mass is normal.

The aging process is best characterized by a reduction in reserve capacity. A classic example is the age-related impaired ability to clear an intravenous glucose load. This reduction in reserve capacity also applies to hematopoiesis. For example, older mice recover their hemoglobin values more slowly after phlebotomy than do young mice. Studies have also shown that aging is associated with a significant impaired ability to mount a neutrophil response to infections.

The blunted hematopoietic response to stress has been ascribed to age-related deficits in marrow progenitor cell numbers, changes in the marrow microenvironment, de-