Physiology of Aging

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Objectives

Define aging

Discuss the major theories of aging.

Describe the physiologic changes with aging

Discuss the concept of “Functional Reserve” in the elderly.

Describe specific changes in various organ systems
“How old would you be, if you didn’t know how old you are”?

Satchel Paige
Naked Mole Rat vs. Mouse
Life Expectancy vs. Lifespan

- Human lifespan hasn’t changed in the last several hundred years, but life expectancy has!
- Life expectancy at birth in 1900 was 49 years
Jeanne Calment
Feb 21, 1875 – Aug 4, 1997
Life Expectancy Since 1900
Life Expectancy vs. Income
National Differences

Life Expectancy - 2002 - 13 nations

The Grandfather Economic Reports

http://mwhodges.home.att.net/

years life expectancy at birth

U.S.A.
Australia
France
Germany
HongKong
Italy
Japan
Canada
Swiss
England
Holland
Greece
Mexico

data: Statistical Abstract - Census
Maximum Life Span between Species

- Mice 4 years
- Dogs 29 years
- Cats 36 years
- Horses 62 years
- Chimpanzees 75 years
- Elephants 78 years
- Humans 122.4 years
- Galapagos tortoise 190 years
- Bowhead Whales 211 years
Extrinsic and Intrinsic Aging

Extrinsic: environmental and habitat pressures outside of the organism

Intrinsic: aging conditions intracellular, genetic, and organ based.
What is Aging?

- Aging is usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age.

- Aging is the loss of homeostasis.
Normal aging refers to those normal deteriorative processes that all human beings will experience if they live long enough, such as arterial wall stiffening, decreased bone mass, presbyacusis, and cataracts.
Characteristics of Aging

1. After maturation, mortality increases with age
2. Decreased ability to maintain homeostasis
   - Considered by many the hallmark of aging
   - Examples: temperature regulation, fluid balance
Characteristics of Aging

3. Changes in chemical composition of tissues
   - Increased lipofuscin
   - Increased collagen cross-linking

4. Progressive decrease in physiologic capacity
Characteristics of Aging

5. Increased vulnerability to many diseases

- Malignancies
- Atherosclerotic cardiovascular disease
- Infection
Theories of Aging
Theories of Aging

- Evolutionary
- Free radical
- Cellular aging
- DNA damage
- Genetic
- Cross linkage of large molecules
- Accumulation of waste products
Evolutionary Biology of Aging

No selective advantage to survival beyond the time necessary to reproduce and possibly raise offspring.

No selection pressure against genes deleterious later in life, particularly if advantageous early.
The evolutionary theories of aging predict:

- Specific genes selected to promote aging are unlikely to exist.
- Aging is not programmed but results largely from accumulation of somatic damage, owing to limited investments in maintenance and repair.
- Longevity is thus regulated by genes controlling levels of activities such as DNA repair and antioxidant defense.
Free Radical Theory

- Oxidative stress
- Accumulation of damage to macromolecules from free radicals
- Gene insertions increase catalase and superoxide dismutase (SOD) activity in Drosophila increase lifespan
- However, antioxidants do not delay human senescence
Calorie Restriction and Aging

- Calorie restriction to about 60% of ad lib amount leads to 30% to 40% increase in average and maximum life span (in rodents)
- Retards age related changes
- Most effective immediately after weaning
- Still significant when compared to greater caloric intake and exercise
- Unknown if this applies to primates
Cellular Aging

- Hayflick limit: maximum number of divisions of fibroblasts *in vitro* (50-70 divisions)
- Changes in signal transduction
- Telomere shortening
  - Progeria, very short telomeres
- Loss of proliferative potential
  - Slower onset of lymphocyte proliferation
- Slow rate of repair of UV damaged DNA from cultured fibroblasts
DNA or Chromosome Damage

- **Telomeres**
  - consist of repeats of the nucleotide sequence TTAGGG
  - form a protective cap around genomic DNA
- Telomere shortening occurs in many cells
  - Associated with loss of telomerase activity
  - Associated with inability to divide in “aged” cultured fibroblasts
- Chromosome rearrangements more common
- Increased deletions in mitochondrial DNA
  - mtDNA mutates up to 10,000 fold greater in the elderly
Genetics

Certain single-nucleotide polymorphisms are associated with longevity in humans.

Mutations in specific genes in Drosophila and C. elegans can dramatically increase or decrease lifespan.

Most relate to defense against stressors:
- Heat, UV light damage, free radicals

Some involve more integrative functions:
- C. elegans genes involving formation of larval stage

Lifespan is programmed before birth.
Cross-link Theory

- Also known as the collagen theory
- Chemical reactions create strong bonds between molecules that are normally separate
- Aging collagen becomes insoluble and rigid; this reduces cellular permeability
  - This causes reduced passage of nutrients, gases, metabolites, cells, antibodies, etc.
Cross-link Theory

- Elastin can also be prone to cross-linkage
  - Elastin changes the connective tissue throughout the body
  - Aging skin becomes dry, loses resiliency, elasticity, and tone
- Cross-linkage can also affect cell division
  - Prevents division of DNA (no mitosis)
Waste Product Theory

- Associate with increased pigment in aging cells
- Lipofuscin, the pigment, in a cellular inclusion that occurs as a result of autophagocytosis and other processes.
- It also may form as a end-product of free radical-induced lipid peroxidation
Normal Aging vs. Disease

- The Danish Twin Study found that genetics account for only 25% variation in longevity.
- Environment accounts for 50%.
- Organs in the same person age at varying rates.
- Normal aging resembles chronic disease.

Physiology of Aging in Specific Organ Systems
The concept where normal aging decreases the body's ability to withstand stress and challenges as homeostatic mechanisms decline over time.

These progressive changes start as early as the third decade of life.
Examples

- Difficulty maintaining water balance
- Thermoregulation
- Regulation of caloric intake
- Heart rate
- Renal concentrating ability
- Bone mass
Functional Residual Capacity

- All organs have functional reserves
- Kidney may lose up to 75% of nephrons before creatinine goes up.
- Symptoms occur only when organ capacity has dropped to levels that affect patient’s activities.
Skin
Are we as old as we look?

Cher 64

DOB: May 20, 1946
Not necessarily!

A large prospective trial from Copenhagen showed that wrinkles and baldness in men did not predict a shorter life.

However, men with no gray hair did have a slightly longer life expectancy.

62 years old

91 years old
Intrinsic (chronologic) aging of skin

- Gravity (sag)
- Expression lines, loss of elasticity
- Hormonal changes
- Atrophy
- Decreased vascularity and yellowing
- Slower wound healing
Extrinsic aging of skin (UV exposure, smoking, wind, etc.)

- Exaggeration of intrinsic aging
- Coarseness
- Mottled pigmentation
- Telangiectasias
- Actinic keratoses
- Deep wrinkles
Cardiovascular System

- Decreased maximal heart rate
- Decreased maximal oxygen uptake
- Decline in functional reserve much slower in those who exercise
- Arterial stiffness commonly increases but is not inevitable
Drop in VO$_{2\text{max}}$ with age

deVries, 1980
Pulmonary System

- 20-40 ml per year decline in vital capacity in adults
- 70-80 ml per year in smokers
Mr. Emphysema

- 70 y/o man who has been sedentary
- Presents because he can no longer play golf after a case of pneumonia
- Complains of severe dyspnea with moderate exertion
- He is confused when told he has severe emphysema
- Why didn’t he have symptoms sooner?
Musculoskeletal System

- 30% decline in muscle mass from about age 30 to age 70
  - Associated decline in strength
  - Associated decline in number of muscle fibers
- Partially reversible with exercise even in the very old
Muscle Aging

- Reversal of total body fat to muscle ratio
- Muscle fibers reduced by 25%
- Increase in slow vs. fast twitch fiber
- Prolonged contraction time
- Lower threshold for firing
- Aging muscle does not respond to anabolic stimuli
Renal System

- Continuous loss of nephrons
- Decreased glomerular filtration rate (GFR) with aging
- Cockroft-Gault formula:

\[
\frac{(140-\text{age}) \times (\text{wt in Kg})}{72 \times \text{Serum}_{\text{Cr}}} \times (0.85) \text{ in women}
\]
Renal System (cont.)

- Decreased ability to concentrate urine, predisposing to dehydration
- Decreased ability to limit excretion of sodium, predisposing to hyponatremia and decreased plasma volume
- Water balance problems are common in frail elderly
Bone

From age 40 to age 80:
- 25-30% bone loss in women
- 10-15% bone loss in men

Bone loss in women strongly related to estrogen decline at menopause

Peak Bone Mass occurs at age about age 35
Bone Aging

- Normal
- Osteoporotic
Brain Function

- Decline in performance on a number of cognitive tests
  - not tasks requiring experience and judgment
- Some decline in memory
- In some studies, cognitive performance improved by vigorous exercise
Aging Brain
The Heritability of Cognitive Functioning in Danish Twins Aged 70 Years and Older

- Overall level of cognitive functioning was highly heritable.

- However, the rate of linear change over time, was not heritable.

McGue M, Experimental Aging research 28: 435-451, 2002
Special Senses

- Decline in hearing
  - 39% over age 75 are hearing impaired
- Hardening of lens
- Diminished night vision
- Decrease in number of taste buds
Immune System

- Decreased T-cell function
  - Decreased proliferation in response to stimulus
  - Decreased response to IL-2 (*in vitro*)
- Decreased levels of specific antibody response
- Increased auto-antibodies
- Increased susceptibility to infection
Summary: Normal Aging

- Aging is associated with increased vulnerability to disease
- Decreased ability to maintain homeostasis
- Functional residual organ capacity gradually decreases
- Aging is not a disease, it is normal
- Disability with aging is not inevitable
Aging is mind over matter. If you don’t mind, it doesn’t matter.

Mark Twain
Questions?

The Scream by Edvard Munch