Good Lord, Ethel... you can't appear in public like that!
BIOLOGY OF AGING: Introduction

- More people surviving longer than ever before. Why?
  - Sanitation
  - Improved medical treatment
  - Improved diagnosis
  - Memory and Disease changes
    - Alzheimer's
    - Cancer
BIOLOGY OF AGING:
Introduction

- What is aging?
- How long can people live?
- Is there a limit to how long people can live?
- What is life span? versus life expectancy?
- Do all living life forms age?
What you will gain from the class:

- a knowledge of human anatomy and physiology and how different systems age
- an ability to read lay literature on aging and possible interventions, and to question what the literature is saying
- an ability to make intelligent decisions for yourself as you age
- an overall understanding of the process of aging
Definitions:
- life span---Longest time that species is capable of living (110 years for humans)
- life expectancy---Average time that species lives (72-76 years for humans)
- senescence---The process of aging at the cell and organismal levels
- gerontology---The study of aging
When does aging begin and what model systems can be used to study the aging process?

Model systems first--
- in vitro vs in vivo systems
- single celled vs multi-celled
- morphological vs biochemical changes
- animal vs other life forms (fruit flies, worms, etc....)
BIOLOGY OF AGING: Chapter One: Concepts & Theories

- When does aging begin?
  - how do you measure aging?
  - are there “aging markers”?
  - do all cells age at the same rate?
  - do all people age at the same rate?

- Levels of organization
  - molecular/ organelles/ cells/ tissues/ organs
Molecules:
- proteins- 22 amino acids
- nucleic acids- DNA (genes) and RNA
- lipids- composed of glycerol and FA’s
- carbohydrates- sugars used for energy

Major elements:
- carbon, nitrogen, oxygen, hydrogen, phosphorus, sodium, chloride
molecules made into cell organelles:
- ribosomes-- protein synthesis
- cell membrane-- selective, protection
- cell nucleus-- compartmentalization
- mitochondria-- production of ATP (energy)
- endoplasmic reticulum-- transport
- lysosomes-- packaging of enzymes
BIOLOGY OF AGING: BIOLOGY OF AGING:
Chapter One: Cells

● Many different types:
  - growth characteristics -- short lived (blood cells) vs long lived (muscle, connective tissue, nerve)
    » continuously divide (i.e..., epithelial, ...)
    » divide only when needed (i.e..., liver, ...)
    » never divide (i.e..., nerve)

● growth vs differentiation (specialization)
  - genes turned on and off at specific times
Chapter 1: Cells

- **Cell Types:**
  - Nerve - CNS & Peripheral: dendrite, axon and cell body make up nerve cells
    - sensory and motor neurons
    - autonomic and voluntary
    - sympathetic and parasympathetic systems
  - Connective - Blood, ligaments, tendons
  - Epithelial - skin, gut lining, secreting
  - Muscle - smooth, skeletal, cardiac
Chapter 1: Cells

- gene expression
  - all cells have same genes but express only 10% of genes in very organized manner (i.e., liver genes vs heart tissue genes)
- gene activity due to proteins that are made in response to external stimuli
- inappropriate gene expression alters cell function (mutations increase with age)
Chapter 1: Cells

- normal vs cancer cells
  - cancer cells are immortal
  - cannot divide and differentiate at the same time
  - do cancer cells age??

- Tissues
  - interrelated mass of cells having the same characteristics
  - If one set of cells ages and loses function then tissue may lose function
Chapter 1: Cells

- Organs
  - made up of different tissues, each having its own set of cells

- Individuals
  - hard to study to understand aging
  - use of statistics and demographics to show trends of aging to indicate which if any, variables affect aging processes
Chapter 1: Populations & Societies

- Rise and fall of Roman Empire is a classic example of the birth, growth, senescence and death of a society
- Aging research goes from molecules to populations and involves knowledge of molecular genetics, immunology, anatomy, physiology, statistics and population biology
- Different labs working with the same system and the same chemicals often have different conclusions (Fable of blind men and elephant)
Chapter 1: Evolution of Aging

- We become accustomed to combining a variety of visual and behavioral clues and arriving at a reasonable accurate impression of a person’s age.
- This awareness of “intrinsic mortality” leads to the view that aging is a form of inescapable deterioration that afflicts complex organisms in the same way that mechanical breakdown occurs in machines.
- Should aging mean deterioration??
- Is adverse aging inevitable??
Chapter 1: Evolution of Aging

- Be cautious about accepting the mechanistic view that adverse aging is inevitable.
- 1) Adverse aging is NOT intrinsic to all living organisms. Bacteria and Eukaryotic microorganisms can divide indefinitely, many plants can propagate for thousands of years, and some simple organisms have amazing regenerative powers that allow them to escape senescent changes.
- 2) After differentiation, an organism simply has to maintain what it has accomplished, and there are systems to correct or repair errors or defects. Can these be maintained?
Chapter 1: Evolution of Aging

- Why is Life Span limited?
  - all characteristics of living organisms are the result of natural selection
  - Aging and its logical outcome, death, are ubiquitous and have survived
  - therefore=implication is that aging and death confer success and are characteristics selected for during evolution. Why??
  - Remove all disease and still die at 100+
Chapter 1: Evolution of Aging

- There is a trade-off between somatic (body) maintenance and reproduction
  - the larger the fraction of energy invested in somatic maintenance the smaller the investment in reproduction (will see later that certain life forms live longer if they do not reproduce)
  - if somatic maintenance is too little then the animal will die. (Repair of soma is always less than what is required for indefinite somatic survival) **[Disposable soma theory of aging]**
  - conflicting goals of self-long-life and greatest number of progeny, and senescence is the negative component
Chapter 1: Definitions of Aging

- Physical changes that take place manifested as a decline of body functions
  - much variation from indiv-to-indiv
- Net effect of all these changes on the ability of the individual to survive (measured for a population)
- At the population level, the most concise def. of aging is that the overall progressive impairment of the functions of organs and tissues results in an increasing age-specific death rate (death results in greater levels the older you get!)
Chapter 1: Theories of Aging

1. Programmed Theory of Aging
2. Running out of Program Theory
3. Mutation Theory of Aging
4. Autoimmune Theory of Aging
5. Cross-linking Theory
6. Free-Radical Theory
7. Cycling/Non-Cycling Cell Theory
8. Error Catastrophe Theory
9. DNA Repair Mechanisms
10. Other Theories
Chapter 1: Theories of Aging

1. Programmed Theory & Running Out of Program Theory--
   - Programmed Theory--there is a genetic sequence activated at a particular time that regulates death.
   - Running Out Program--all events are specifically programmed into genome and are sequentially activated. After maturation genes have been activated there are no more programs to be played and as cells age there may be chance of inactivation of genes that cannot be turned on.
Chapter 1: Theories of Aging

- **Mutation Theory**
  - random mutation hits genes and changes in proteins occur (viruses may be involved)

- **Autoimmune Theory**
  - as one gets older there is a greater incidence of autoimmune disease. Regulation of self-recognition is breaking down

- **Cross-Linking Theory**
  - of DNA and proteins- cross linking prevents the molecules from functioning properly
Chapter 1: Theories of Aging

- **Free-Radical Theory**
  - highly reactive molecules that are formed during most chemical reactions. Cells can normally get rid of these but as a cell ages its ability to get rid of FR decreases (oxidation reactions)

- **Cycling/Non-Cycling Theory**
  - applies to tissues able to proliferate. Relates to whether a growing cell is blocked at a certain stage of proliferation and cannot continue to growth (i.e..., bone marrow cells)
Chapter 1: Theories of Aging

- **Error Catastrophe Theory**
  - postulates that nothing is perfect. There is a chance for a mistake to occur. The more occurrences that happen the greater is the chance that a mistake will happen. i.e..., live long enough, enough mistakes happen, death occurs

- **DNA Repair Mechanisms**
  - DNA constantly needs repairs (mutations, radiation, chemicals, polymerase, etc...). Repair mechanisms decrease with age
Chapter 2: Cell Structure & Aging

- Cell membrane
  - Lipid bilayer: hydrophobic and hydrophilic lipid form a bilayer with proteins (receptors)
  - membrane is semipermeable
  - proteins may act as markers for specific cell types
  - proteins may act in cell-to-cell interactions
  - may act to send signals to inside of cell
  - channel proteins for transport of materials

- If these change with Age?
Chapter 2: Cell Structure & Aging

- Cytoskeleton
  - network that connects organelles and is important for communication within a cell
  - composed of tubulin and actin proteins
  - chromosome movement during division directed by cytoskeletal proteins
  - cell motion
  - What happens with Age??
Chapter 2: Cell Structure & Aging

- **Protein Synthesis**
  - Ribosomes: where proteins are made
  - proteins are structural or ENZYMES
    » enzymes are CATALYSTS (i.e., speed up chemical reactions)
    » enzymes are not used up during a reaction
      - $E + S \rightarrow P + E$
    » enzymes are specific for their specific substrate
    » enzymes are composed of amino acids (20)
Enzymes coded for from DNA

DNA copied into RNA (Transcription)

RNA decoded in proteins (Translation)

- In DNA there are CODONS (64 codons with stop & start) made up of three of the 4 nucleotide bases in DNA
  - adenosine (Purine)
  - cytosine (Pyrimidine)
  - Thymine (Pyrimidine)
  - Guanine (Purine)
Chapter 2: Cell Structure & Aging

- Three types of RNA
  - messenger- takes code from DNA
  - transfer- brings AA to mRNA - ribosome and helps to place AA in correct sequence
  - ribosomal- structural component of ribosome

- What if there is a mutation in DNA?
- What if there is a mutation in RNA?
Chapter 2: Cell Structure & Aging

- **Nuclear Membrane**
  - double lipid layer
  - very selective
  - contains DNA
  - helps to regulate which genes are active and which are not by allowing certain substances into the nuclear space or not
Chapter 2: Cell Structure & Aging

- **DNA Structure**
  - deoxyribonucleic acid
    - 4 nucleotides
    - double helix
    - paired (one from mother and one from father)
      - does mother and father have same genes??
    - codes for proteins/ enzymes
      - codon table on pp 41
  - high mutation rate? Increase with age?
Chapter 2: Cell Structure & Aging

- Differences between DNA and RNA
  - uracil replaces thymidine
  - single stranded
  - gets out of nucleus into cytoplasm
  - carries code in form of codons
  - 3 types (mRNA, tRNA, rRNA)
  - oxygen is not removed as in DNA
Chapter 3: Tissues, Organs and Aging

- Tissue
  - groups of cells with a common origin, structure and function
  - tissue cells held together by extracellular “glue”
    » muscle tissue
    » epithelial tissue
    » nervous tissue
    » connective tissue
Chapter 3: Tissues, Organs and Aging

- Epithelial tissue
  - covers organs and cavities within body
  - environmental exposure
  - proliferates continuously
  - glandular, secretion, absorption, sweat, mucous, protection
  - damaged by UV, chemicals, environment & loss of proliferative capacity with age will affect individual
Chapter 3: Tissues, Organs and Aging

- **Connective Tissue**
  - functions to bind and support other tissues
    - anchors epithelia to underlying tissue
    - hold organs in place
    - stores fat
    - forms tendons & ligaments
    - forms bone
Different types of connective tissues

- **Bone**
  - mineralized connective tissue
  - osteocytes secrete collagen and Ca^{++} which harden into hydroxyapatite.
  - collagen lends flexibility to bone. Bone more flexible in young than old. Older people gain more minerals than collagen.

- **Osteoporosis** - loss of Ca^{++} resulting in brittle bones
Chapter 3: Tissues, Organs and Aging

- **Muscle Tissue**
  - skeletal, smooth (visceral), cardiac
  - cardiac muscle beats 75 X/minute for about 75 years which = 2,956,500,000 beats

- **Blood**
  - provides nutrients to all bodies cells
    - erythrocytes (red blood cells: \( O_2 \) & \( CO_2 \))
    - white blood cells
      - macrophages, lymphocytes, granulocytes
Chapter 3: Tissues, Organs and Aging

- **Erythrocytes**
  - hemoglobin
  - $140 \times 10^6$ new RBC’s made every minute
  - cells made in red bone marrow
  - life span of RBC’s about 120 days

- **White Blood Cells**
  - live about 4 days
  - fight disease
  - help to clot blood (platelets)
  - T and B lymphocytes
Chapter 4: Integration and Regulation

- In order to achieve life the cells tissue and organs must be integrated into a single entity that has a means of regulating itself.
- Nerves and Hormones are the controlling mechanisms in humans. Also the immune system integrates and regulates many body systems
- Failure of the immune system (sexual maturity) may upset regulation
Chapter 4: Integration & Regulation

- Nervous System:
  - propagates electrical impulses and regulates other tissue and organs

- 3 main cell types
  - neurons
  - glial cells - support and metabolic activities that maintain neurons
  - myelin sheath cells (Schwann cells) - support and insulation (speed). CNS unmyelinated, long nerves myelinated
Chapter 4: Integration & Regulation

• Neurons-
  ➔ cell body contains nucleus
  ➔ axon- brings impulse away from cell body
  ➔ dendrite- brings impulse to cell body

• Sensory neurons- Types ............

• Motor neurons

• Reflex arc- involves no “thinking” (i.e., sensory- -->spine -->motor ---->muscle) as opposed to (sensory --->spine --->brain --->spine --->motor --->muscle)
Chapter 4: Integration & Regulation

- Signal Transmission
  - Signal has to be transmitted along a neuron and across a synapse. Neuron transmission is by electrical flow of electrons (ions = charged particles) and synaptic transmission is by chemical diffusion.

- Membrane potential
  - $K^+$ and $Na^+$ movement most imp’t. More $K^+$ inside than outside and more $Na^+$ outside. When depolarization occurs $Na^+$ moves in.
Synapse

- at end of axon there are vesicles that contain certain chemicals. Some are excitatory and others are inhibitory. (page 70 lists these)

- Vesicles rupture and release contents when electrical impulse gets to end of axon. These diffuse across synapse and stimulate dendrite receptors to initiate depolarization of next neuron. Each synapse is responsive to only 1.
The synaptic chemicals are destroyed by specific enzymes. Impact control/ regulating process.

AGING changes on regulation of nerves:
- effect rate of transmission
- effect on ion exchange and depolarization
- effect on myelin
- effect on synaptic chemicals
Chapter 4: Integration & Regulation

- Dysfunction of neurons:
  - Curare-- poison competes with neurotransmitter for receptor binding sites on motor neurons causing paralysis
  - Myasthenia gravis-- autoimmune disease that destroys receptors to acetylcholine and muscles respond spasmodically.
  - diazepam (Valium)-- increases binding of GABA (nerve inhibit) to its receptors and slows excess nerve transmission (calmness)
Chapter 4: Integration & Regulation

- **Endocrine System**
  - **Hormones**: manufactured by cells and can have autocrine, paracrine or endocrine effects
  - Major endocrine glands (pp77) are hypothalamus, pineal and pituitary and are located in brain

- **Hypothalamus**:
  - neuroendocrine gland that initiates endocrine signals appropriate to environmental conditions
  - breeding, temperature, hunger, growth
Chapter 4: Integration & Regulation

- Pituitary Gland
  - Located at base of hypothalamus: anterior (makes own hormones) affects growth, development and behavior
  - Posterior- stores hormones made by hypothalamus and releases them on command

- Production/Targets/Action
  - Hormones secreted--->
  bind to specific receptors on target cells --->
  target cells respond thru signal transduction processes
Chapter 4: Integration & Regulation

- Regulation of Response
  - Short-lived vs long-lasting hormones
  - Receptor downregulation
  - Receptor number decreases with age not level of hormones
  - Signal transduction molecules may decrease with age (PKC)
Chapter 4: Overview of Immune Function

- 2 main components of immune system
  - lymphatic system
  - cell population system

- Lymph
  - connected to circulatory system
  - fluid with WBC’s
  - Lymph nodes, thymus, spleen, bone marrow
Chapter 4: Overview of Immune Function

- **Cellular System**
  - Specific vs non-specific (adaptive vs innate)
  - **humoral vs cellular response**
    - antibodies vs direct cell killing
  - **self vs non-self recognition** (highly specific), and tolerance
  - receptors
    - antibody (as receptors)-- 5 classes
    - antigen receptors (CD4, CD8, IL-2, etc....)
    - B cells and T lymphocytes (Thelper, Tcytotoxic)
Chapter 4: Overview of Immune Function

- **Humoral**
  - uses antibodies
  - attacks antigens found outside cells (soluble Ag’s) i.e., viruses, bacteria, fungus, parasites

- **4 ways that Ig’s work**
  
  1. opsonization- “greased pig” action
  2. blocking- block viral receptors
  3. complement activation- lysis
  4. neutralization- blocks toxin receptor
Chapter 4: Overview of Immune Function

- **B lymphocytes**
  - bone marrow stem cells
  - each B cell produces only 1 specific Ig but Ig class can switch as B cell matures
  - once Ig selected for will not change specificity
  - memory B cells
  - antibody levels in serum (long vs short)
  - Ig recognize “native” antigen
Chapter 4: Overview of Immune Function

- **T Lymphocytes**
  - $T_{\text{helper}}$ cells - produce IL-2
  - $T_{\text{cytotoxic}}$ cells - kill virally infected cells, cancer cells, tissue transplant cells
  - $T_{\text{suppressor}}$ cells - suppress specific cells
- Must recognize self antigens and foreign antigens together (MHC + Foreign)
- Educated in thymus
Chapter 4: Overview of Immune Function

- Aging and immune system
  - less “naive” cells and more memory cells
  - tolerance breaking down
  - more autoimmune reactions
  - less IL-2
  - decrease following sexual maturity
  - Dietary restriction
  - Melatonin
Chapter 5: Measurement of Cell Aging

- Cells of different tissues age in different ways and on different time scales.
- Hayflick Limit--found that cells taken from tissues of infants would divide about 50 times before senescing and dying.
- Cells from older individuals would go thru less doublings than cells from young.
- Only cancer cells are “immortal”
Chapter 5: Measurement of Cell Aging

- **DNA**: changes in DNA during aging:
  - resistance to nuclease enzyme in young liver was 50% while in older liver resistance was 63%. Suggests that if DNA is damaged there is less efficiency at repair.
  - there are more single strand breaks in DNA in older neurons
  - embryonic, cancer and immune cells have less methylation which keeps proliferation genes more active
Chapter 5: Measurement of Cell Aging

- Aged cells have less methylation of DNA and this may act to cause malfunction in cells because of too many genes being active.
- New proteins are required for senescence and genes coding for these proteins may be dominant over genes regulating the immortal phenotype (transferring genes from old cells into young induces senescence).
- Proteins have been discovered that extend longevity in certain species (BCL-2).
Use of anti-sense mRNA

- Endothelial cells from young animals have low levels of interleukin (IL)-1 and senescent cells have high level. Transformed (immortal) cells have no IL-1. Therefore this cytokine may be involved in senescence.

- Use anti-sense mRNA to bind to sense mRNA and get double helix that is not functional. Cells treated with anti-sense to IL-1 extended life span from 60 doublings to 140 doublings.
Chapter 5: Measurement of Cell Aging

- Aged cells show altered proteins
- Damaged proteins probably due to improper post-translational modifications rather than due to genetic defects
- There is a gradual decrease in protein synthesis in aged cells
- All of this may lead to DNA damage because of lower level of functional repair enzymes
Chapter 5: Cellular Immunology and Aging

- Generation of the large diversity of immune response depends upon DNA rearrangement
  - there is no evidence that there is a decrease in the efficiency of the gene switching mechanism (where to look for immune senescence??)

- Increased autoimmune disease with age (lupus, arthritis, etc...). This is due to failure of lymphocytes to recognize foreign vs self
The age defect in Ig production is due primarily to a T cell defect, not in B cells.

- T cells from young humans augment Ig production while T cells from old donors suppress it.
- There is a higher incidence of autoantibody production and more autoantibody producing cells in older animals.
Chapter 5: Cellular Immunology and Aging

- The overall number of T and B cells does not change significantly with age, but the make-up (%) of the subpopulations does change
  - Increase in the proportion of immature T cells with age and an increase in $T_{\text{suppressor}}$ cells (this is from the book but I think it is the opposite!!)
  - There is an increase in memory cells and a decrease in naive cells so that repertoire of response is not as great in old individuals
  - Higher concentration of Ag needed to stimulate response (hepatitis shots)
Chapter 5: Cellular Immunology and Aging

- Tolerance - lack of responsiveness
  - caused by either clonal deletion (not reversible) or suppression (reversible)
  - sequestered antigens may be released
  - increased cell death may release more Ag’s
  - Ts cells may not function as well
  - increased cancer may be due to change in suppressor/ auto-idiotypic antibody systems
Chapter 5: Cytology of Aging Cells

- **Cytology of Aging Cells**
  - “age pigment” = lipfuscin
    - Recycling of metabolic products is normally done in lysosomes, but in older people the lysosomes do not perform as efficiently and partially processed cell debris accumulate. It is a MARKER of old cells but has not other effect.
Chapter 5: Cytology of Aging Cells

- **Changes in Organelles**
  - **Mitochondria**
    - respiratory activity produces high levels of free radicals which damage membrane and mitochondrial DNA
    - abnormal shape and size, pigmentation
Chapter 5: Programmed Cell Aging

- Stem cells of the hematopoietic system do not age.
- The cells produced from these stem cells do have a finite life span.
- RBC’s “live” about 120 days (lack nucleus): may produce “age” antigen on surface.
- WBC’s if unchallenged live a few days (3-4)
  - If challenged some T and B cells form memory cells and can live throughout an individual's lifetime.
Chapter 5: Programmed Cell Aging

- Short life of lymphocytes caused by production of foreign antigen on their cell surface that are not recognized as “self” by immune system (self regulation of immune reactivity)

- APOPTOSIS- programmed cell death; glucocorticoids initiate this in the thymus and in old cells

- These are normal process and do not in themselves lead to aging
Chapter 6: Aging of the Organism

- Is death of cells aging? Or is it part of the process of differentiation?
- Do we define aging as only the phenomena that lead to decreased abilities in a whole organism?
- The aging of different tissues does not occur simultaneously. People of the same chronological age show very different aging patterns. (muscle, memory, blindness, wrinkles, etc.)
- How is it best to study the process of aging and to understand what and how it occurs? Study simple organisms!
Chapter 6: Aging of the Organism

- Does aging in a protozoa resemble aging in a macrophage? The macrophage is part of a whole organism and is under the influence of other factors, but if they resemble each other then what is found in the protozoa could be extended to macrophages.

- Single celled protozoa, algae and slime molds age and have been used in aging studies.
  - In paramecium there is a doubling of 40-60 populations then the division rate slows (Hayflick?). If 2 different populations that reached end point are mated then they go thru 40-60 doublings (meiosis process rejuvenates??)
  - Look at Plasmodia life cycle (pp 116-118)
Chapter 6: Aging of the Organism

- Invertebrates as aging models
  - Nematode roundworm (*Caenorhabditis elegans*) and fruit fly (*Drosophila*)
- *C. elegans* composed of only 1000 cells, and lives only about 20 days. Tom Johnson has found that there are a set of genes which when they are active the worm lives its normal 20 days. If inactivated the worm lives 40 days! (*AGE-1* and *AGE-2* genes)
  - trying to find similar genes in humans
Chapter 6: Aging of the Organism

- **Drosophila**
  - live about 40 days. By restraining flies from breeding they live 80 days. They are stronger, more active than normal flies
  - Long-lived flies have more SOD than short-lived flies

- **Vertebrates - non-mammalian vertebrates** not too valuable in studying aging (frog, fish, reptiles, etc...). Most important studies involve the use of mice, rats, monkeys and humans, but it is not always possible to perform all of the experiments that the researcher would like.
Chapter 6: Aging of the Organism

- Embryogenesis - aging begins at conception?? There is programmed cell death (webs between fingers, etc..) but this is not really senescence.

- Adolescence and Adulthood - going from one to the other involves going thru puberty, characterized by large hormonal alterations. Extension of life is associated with timing of puberty (sexual maturation). The later puberty the more long-lived the organism. Nutrient restriction (reduced caloric intake) extends life span.
Chapter 6: Aging of the Organism

- **PROGERIA**—a genetic disorder that occurs in 1 in 8 million births and characterized by normal birth and first months of life, followed by rapid change involving loss of hair, weight and height. Over the next few years osteoporosis occurs, atherosclerosis and occlusion of coronary arteries develop and strokes are common. Most patients die of heart attacks between ages of 11-14. They do not have other symptoms of aging such as arthritis, cataracts, diabetes or cancer. They seem to follow many aspects of aging, but certain parts of senescence are left out.
Menopause-- during 5th decade of life there is a decline in estrogen levels (and other hormones). What causes decline is unknown. In the absence of hormone the tissues of the vulva, vagina, cervix, uterus and ovaries show atrophying or diminishing function
Chapter 7: Nervous System Changes

- As we age we become:
  - forgetful, bewildered, can’t think as fast, can’t react as fast, can’t recall as well, can’t remember short term memory.
  - our ability to process information from outside and our ability to retrieve internal memories slow down with age
  - individuals show different symptoms, not all the same
  - difficulty in learning new operations, not old ones
Senile Dementias:

- most are probably symptoms of disease rather than normal processes of aging. These “hit” people who are old, but not due to old age.

- **HUNTINGTON’S DISEASE:** (chorea- from dancing or spastic motions) incurable degeneration of specific neurons, especially those sensitive to the neurotransmitter GABA {inhibits neuronal activity}

- Leads to progressive motor dysfunction, psychological aberrations and intellectual deterioration.

- No effective treatment
Chapter 7: Nervous System Changes

- Huntington’s chorea—results in complete disability and death 15-20 years after onset of disease
- Caused by a dominant genetic locus that if present will be active (high penetrance)
- Has a 50% chance of being passed on to the progeny of the carrier.
- Does not show symptoms until carrier is 35-45 by which time the carrier has had children
- Probably arose as a mutation in the 16th century (new disease).
Chapter 7: Nervous System Changes

- Prediction for Huntington’s disease by looking at family history. Should you have children if their chances are 50:50 for having disease??
- Working on being able to isolate gene and test for abnormal gene in people. If found what should you do? Do you want to find it??
- Nothing is currently known about how the disease progresses. If gene is found can clone it into other cells and try to understand its function.
- Markers for the HD gene indicate that it is on chromosome # 4
Chapter 7: Nervous System Changes

- Parkinson’s Disease:
  - Involuntary motion, with muscle weakness
  - A degenerative condition in which a specific populations of brain cells vanish from a small portion of the CNS
  - Cannot prevent or cure disease, but can alleviate symptoms
  - Clinical symptoms:
    - slowness of movements, tremor in one or more limbs, rigidity, postural instability
    - Absolute diagnosis only on post-mortem exam
Parkinson’s disease:

- 1% of all people over 60 are affected. May be due to environmental causes
- Due to progressive deterioration of neurons in specific part of the brain = substantia nigra
  - these neurones manufacture dopamine, and when neurons die dopamine levels decrease
  - the surviving neurons try to increase their production of dopamine and may lead to build up of toxic products resulting in more cell death
Chapter 7: Nervous System Changes

- Environmental factors contributing to Parkinson’s Disease
  - contaminant in heroine
  - contaminant in “designer drugs” (MPTP) leads to symptoms identical to Parkinson’s (chemical to induce disease in model systems so can study!)
  - High pesticide usage
  - Brain damage (boxing-- Ali)
  - OTHERS??
Chapter 7: Nervous System Changes

- Treatment for Parkinson’s disease:
  - L-dopa can be taken up by brain cells and made into dopamine
    » neuronal degeneration continues until no amount of L-dopa can alleviate symptoms
    » L-dopa may accelerate symptoms
    » L-dopa usage does prolong the “useful life” of a Parkinson’s victim
Chapter 7: Nervous System Changes

- Transplants-
  - adrenal gland cells produce dopamine and can be placed in brain tissue. Cells do not survive long.
  - fetal brain cells can be transplanted into brains of Parkinson’s patients and do survive (issue of fetal tissues being used. Why??)
Chapter 7: Alzheimer’s Disease

- Alzheimer’s Disease
  - reduces life expectancy by about 1/2
  - only definitive way to diagnose is post-mortem brain tissue examination
  - each individual progresses at own rate, but eventual result is complete idiosyncrasy and memory loss and ultimately death
  - may be 5 months, 5 years, 10 years or more
Chapter 7: Alzheimer’s Disease

- leads to diminished mental abilities, forgetfulness and loss of intellectual function. Major early symptom is memory loss. Gets so bad that person cannot remember last sentence they said of family members names. Later stages include abnormal behavior patterns (wandering, anxiety, restlessness).

- physical deterioration occurs- incontinence and diminished ability to perform simple functions (finding things, etc...)


Chapter 7: Alzheimer’s Disease

- Diagnosis: changes can be found to some level in all aging people. Must eliminate other causes to diagnose A.D. Drug intoxication is most common cause of forgetfulness, confusion and disorientation in the aged.
- Simple test questions to determine the state of dementia that exists (pp 143 Box 7.1)
- BRAIN changes: presence of “tangles and plaques” in specific areas of brain. Not known what causes these, but the protein **UBIQUITIN** is always found in the central parts of the tangles. (binds to and marks proteins for degradation)
Chapter 7: Alzheimer’s Disease

- Plaques—structural abnormalities with a core of protein called AMYLOID. Surrounding this core are degenerating pieces of brain cells. Amyloid seems to always be present in these brain plaques.
- The amyloid gene can produce 3 different mRNA’s and two of these transcripts produce a protease inhibitor that prevents the breakdown of amyloid, while the 3rd one only produces the amyloid. It is the 3rd type of amyloid that increases in A.D. and it is thought that this leads to increased amyloid degradation and cell death.
Chapter 7: Alzheimer’s Disease

- It is not necessarily the presence of the tangles and plaques that lead to A.D. but it is the amount that seems to interfere with mental processes.

- Another significant change—deficiency in the enzyme used to manufacture acetylcholine (acetylcholine transferase). Decrease with age normally, but up to 90% in A.D. patients.

- What causes A.D. to occur?? Genetics?? Environment?? Viruses?? NOT KNOWN!!
Chapter 7: Alzheimer’s Disease

- A.D patients have an impaired sense of smell. Olfactory neurons are interesting because they are the only neurons in the mammalian CNA to proliferate throughout life. This could be used as a model to study A.D. in living tissue.

- CAUSES -- identical twin studies suggest that it is genetic (FAD = Familial A.D.). Greater likelihood of getting A.D. if someone in your family had it.
  - Aluminum(??)- present in antacids
  - Prion (pure protein that causes disease)
Chapter 7: Alzheimer’s Disease

- **Cure**
  - there may be things that can alleviate some symptoms. Only 1 drug has been approved by FDA (Cognex) which enhances acetylcholine levels and results in an increase in short-term memory, but effects are not long lasting
  - hope lies in finding out which genes are involved and in being able to regulate their function
Chapter 7:
Alzheimer’s Disease

- Must realize the trauma that is associated with the family of A.D. patient, not only what it does to person themselves.
- Finding of A.D. markers to get early start on treatment of patient.
- Fetal transplants of tissues (and related issues)
Diagnosis of cancer may cause depression and a feeling of hopelessness which are not good for a positive outlook while aging. Aging is stressful enough!

Is cancer incidence increasing with advancing age?

Cancer definition:
- occurs in all organisms
- uncontrolled growth of cells (what controls growth??)
- 1 out of 4 people will die of cancer
- cancer cells require high levels of nutrients and blood supply
- benign vs malignant forms of cancer
Chapter 8: Cancer

- Causes of cancer:
  - Growth control tightly regulated by genes and proteins that are produced. If they are unable to regulate properly then cell grows unregulated.
  - Cells must sense environmental signals (hormones, chemicals, toxins, pollutants) by receptors and then signal transduction processes send signals to nucleus by second messengers. DNA then replicates and cell divides.
  - Inducer and suppressor genes for growth proteins. Required for normal growth and differentiation
Chapter 8: Cancer

- The proteins that regulate growth do so by:
  - promoting other proteins (growth factors)
  - binding to DNA
    - suppressing vs inducing
  - genes may be mutated or altered (oncogenes vs proto-oncogenes)
  - oncogenes first identified in viruses and shown to cause cancer in many species
  - differ by a single AA
Chapter 8: Cancer

- carcinogen - induces changes towards cancer
- tumor promoter - does not cause cancer itself but promotes the initiation events of carcinogens or other substances that may not cause cancer by themselves. (Butylated Hydroxy toluene {BHT})
- Things that cause cancer:
  - toxic wastes, radiation, chemicals, smoking, drinking, viruses,
  - malignant cancer requires at least 2 mutations: one in the DNA and one to stabilize the change
People vary in susceptibility to cancer
- genetics, immune system surveillance, other factors (diet, environmental exposure, dosage exposure, fitness, DNA repair processes)

Immune system recognizes self from non-self, and cancer cells are from self and are therefore not attacked.

In aged immune function decreases and aged people more susceptible to cancer occurring

Some cancers more common in young, but most cancers arise as person gets older
Chapter 8: Cancer

- Cancer Classification - classified according to type of tissue from which they arise
  - Carcinomas are cancer of the epithelial tissue (skin, breast, liver, pancreas, intestines, lungs, prostate, thyroid).
  - Adenocarcinomas are cancers of various glands
  - Sarcomas arise in connective tissue (muscle, bone)
  - Leukemias are cancers of the blood (excessive WBC's)
Cancers are localized geographically and occupationally (Japanese have far fewer colon cancers than US and 2nd and 3rd generations still have fewer cases (diet), but this is expected to increase as they acclimate to US diets and environment).

Electromagnetic Forces (EMF’s), radon, pesticides, radiation, power plants)

There may be “hot pockets” of cancer in specific locations that are higher than general levels, but this does not mean that there is any real concern living in those areas (breast cancer incidence at a certain school). Look at epidemiology.
Chapter 8: Cancer

- Cancers are not really “diseases of aging”, but they do appear frequently with aging.
- Skin cancers have increased but this may be due to either the thinking that tans are good and more people are doing this, or changes in the ozone layer.
- Increased incidence of cancer due to:
  - change in DNA repair mechanisms
  - changes in immune responses
  - changes in diet and living conditions
  - changes in environmental exposures
- Cancer not necessarily inevitable with age.
Chapter 8: Cancer

- Embryonic cells and cancer cells are doing the same things in regards to growth.
- Cancer cells are neoplastic and exhibit many characteristics of embryonic cells, but lack fetal controls.
- Many adult cells are programmed not to divide again (muscle, nerve), some can divide when stimulated (liver) while others divide continuously (epithelial, hematopoietic).
Chapter 8: Cancer

- Cancer cell characteristics:
  - release from density-dependent inhibition (contact inhibition)
  - no longer dependent upon FBS for growth
  - loss of normal functional specificity
  - malignant cell growth into other tissues (metastasis)
  - neovascularization to get food
  - benign tumors also dangerous (blockage, pain)
Chapter 8: Cancer

- Cures & Possibilities: Older people more frail and not in best of health, so what are their options?
  - Surgery may not be a viable option because of illness, weakness and/or location of cancer
  - Use of drugs to combat cancer may affect other drugs that elderly patient is taking
  - Radiation & chemotherapy in older people?
  - Immunotherapy - designer Ab’s
  - Oncogene therapy or repair of faulty genes (anti-oncogenes or anti-sense mRNA into cells
  - Prostate cancer options as example
Chapter 8: Cardiovascular Disease

- Heart pumps blood to all parts of body. 60 X/min, 33 million beats/yr, 2.5 billion beats in 70 yrs. Failure to pump blood can result in circulatory diseases, heart attacks, and strokes.

- Brain and heart most sensitive to lack of $O_2$.

- Efficiency of heart related to pressure that heart has to pump against. Pressure made by arteries & capillaries (not veins). Discuss anatomy!

- Coronary damage NOT just a disease of “old age”
Atherosclerosis & arteriosclerosis: fatty deposits accumulate in the lining of arteries (plaque). Enlarge the artery, build up pressure, occlude it and lead to strokes.

Build up of plaque correlated with intake of fats, especially cholesterol. Becomes complexed with either LDL (bad), which carries cholesterol to the cell membrane receptor of cells that can use and metabolize it or complexed to HDL (good) which carries excess cholesterol to the liver for removal. Must measure ratio of 2 types!

Excess plaque can cause emboli to form and travel to other parts of the circulatory system and block blood.
Chapter 8: Cardiovascular Disease

- Hypertension- high blood pressure. Common to aging population
- Result of occluded arteries, but other factors may be involved also
- Contributions to cardiovascular disease:
  - Intake of fats and excessively large meals
  - A life that requires rapid eating (fast foods)
  - Ignoring warning signs from our bodies
  - A feeling that one is supposed to deteriorate with age, so a faster heartbeat and an inability to climb stairs is considered normal
Chapter 9: Body Changes - Senses

- Touch, smell, taste, hearing, and vision all depend on the nervous system functioning properly.
- Problems can occur at receptor level, at transmission of impulse along fiber to CNS (and brain), to interpretation of the signal by brain, and by transmission back to signal for response.
- Accepted that one loses sense of taste and smell as you age, the why? remains unknown.
  - sensory cells for taste and smell last only a short time and then are replaced: maybe cell division rates decrease or reconnection is inappropriate.
  - Destroyed by environmental influences
Taste-- consists of molecules in food interacting with receptors on tongue. Must be solubilized to be “tasted”. 4 basic tastes (sweet, sour, bitter, salt). Rest of what we call taste is really smell.

Smell-- Olfactory area located high in upper part of nasal cavity. Contains chemoreceptors (only volatile substances can be smelled). If nose is stopped up then cannot “smell or taste” food. Many environmental contaminants (smoke, pollution, ....) can alter these receptors.
Chapter 9: Senses: HEARING

- See page 169 for anatomy of ear:
  - outer auricle
  - external auditory meatus (canal)
  - tympanic membrane
  - ear ossicles (hammer, anvil, stirrup)
  - semicircular canals
  - cochlea (with round window)- hair receptors
  - eustachian tube

- Ear takes sound waves and converts them to mechanical vibrations (middle ear) and then converts them to fluid waves (inner ear)
Chapter 9: Senses: HEARING

- each receptor in cochlea is specific for a particular energy wavelength and will send that sound to brain for interpretation. If receptor is destroyed then no sound will be heard at that particular wavelength (dog whistles, tone deaf)
- not known why receptors in cochlea destroyed
- if tympanic membrane becomes ruptured or rigid then do not hear as well
- if ossicles become fused or damaged cannot hear
- these last two can be corrected for, but not the first
Chapter 9: Senses: VISION

- see page 170 for anatomy
- know the following: pupil, lens, cornea, iris, aqueous fluid chamber, vitreous fluid chamber, retina, fovea centralis, optic nerve, cones, rods
- Most people in 80’s will have up to 80% loss of visual acuity (many causes: glaucoma, cataracts, farsightedness {presbyopia})
- lens continues to grow throughout life. Fibers made on anterior surface but are not lost on posterior surface. Lens becomes crystalline and opaque decreasing light transmission, and a cataract is developed
Glaucocma - increased pressure of fluid in anterior chamber of eye (aqueous humor) where fluid is made but not drained. Increased pressure destroys many cells and functions.

Night blindness - lack of vitamin A (carrots) and function of rods and cones.

Deterioration of the senses is not necessarily inevitable with age, and to many the loss of certain senses can be medically treated, so even if they get worse with age this can be successfully maintained if you go to a competent doctor.

Senses are relatively simple to treat when compared to muscle and bone!!
Chapter 9: Muscles & Bone

- 2 of the most serious ailments of the aging muscle system are Parkinson’s Disease and Myasthenia gravis. Both result in poor muscle control and are due to the dysregulation of muscle by the nervous and immune systems (autoimmune disease).
- Muscles atrophy with age. May be due to lack of innervation, or lack of neurotransmitter present.
- May be prevented by exercise (good for muscles, heart, blood vessels, bone).
Chapter 9: Bones

- Bones serve as structural supports as well as for production of blood cells. Bones need to be replaced in injury (breaks), to replace old cells with new, and remodeled for growth (osteocytes vs osteoclasts). With age people get smaller.

- Bones move against each other and there must be some lubrication: cartilage (teflon type material) covers ends of long bones; synovial fluid acts as lubricant for joints, bursal sacs help buffer jolting effects between bones. Cartilage gets thinner with age, synovial fluid dries up, bursa can be damaged and this can result in osteoporosis and arthritis.
Chapter 9: Bones

- Osteoporosis
- Loss of bone mass due to the loss of calcium. Loss of calcium leads to weaker bones which are porous and break easily.
- Generally more intense in women and is considered normal for women in their post-menopausal years. This suggests a strong hormonal influence on the onset and severity of disease. Inactivity also leads to more severe osteoporosis.
- Not known why osteoporosis occurs:
  - May be loss of receptors on bone cells for hormones, may fail to process the hormone-receptor complex, may be due to decrease in hormones.
- Smoking, diet, inactivity may lead to condition.
- Hormone supplements, diet, activity help to stop shrinkage.
Chapter 9: Arthritis

- One of the most common joint ailments in humans and other mammals as they age. 2 Types:

- Osteoarthritis- most common. By age of 70-80 most humans have some form. Disease affects cartilage around the joints that causes wear. Disease presents as stiffness and pain in the joints that increases with time. Enlargement of joint and may be joint becomes immovable (caused by degeneration of cartilage and there is inflammation, calcification and cross-linking of collagen, as well as unregulated growth of bone.
Chapter 9: Arthritis

- Rheumatoid Arthritis: involvement of immune system. Starts in connective tissue surrounding joints, the synovial membrane, and you see thickening and inflammation of membrane. There is a high degree of vascularization that allows blood cells into area, edema and immune reactions. (autoimmune responses may be initiated by bacteria or viruses in tissue area).

- Strong evidence suggests that RA has nerve as well as endocrine and immune system involvement. (RA absent on paralyzed side of hemiplegic patients)
Chapter 9: Other Organs (Internal)

Lungs: exchange of $O_2$ and $CO_2$ in blood in alveoli
- oxygen must be dissolved in water and blood must flow quickly
- Blood pressure important for proper exchange
- Surfactant important for wetting of alveoli surface to make sure water is not in droplet form
- large surface area for exchange
- proper function of muscles for inflation of lungs (lung is not a muscle!!) Lung is elastic (affected by age)
- Lung inflation and deflation causes friction with pleural membranes (must be lubricated properly)
- Lungs need to be kept clean (cilia & mucus in trachea)
Chapter 9: Intestine, Liver, Kidney, Pancrease and Spleen

- **Intestines** -- cells regenerate for lining. Peristalsis occurs. Both affected by environmental influences present in food and drink. Diverticulitis (outpocketing) and atrophy of muscles.

- **Liver** -- detoxifies all chemicals before they get into blood and around body. Very susceptible to environmental toxin damage & alcohol. Can regenerate to a point. Metabolizes drugs (Pharmacy of older people different from young:: not as much clearance and drugs last longer)

- **Mouth** -- Worn away by grinding, loss, breakage, gingivitis, pain (can be alleviated)
Chapter 10: Normal and Successful Aging

- Do not know why people become more debilitated with age. People of the same chronological age can have vastly different aging responses.
- More people are retaining vitality, an interest in life, and the ability to be active in some way physically and/or mentally.
- SOME PEOPLE CAN AGE WELL!!
- Most studies done on the aged are done in clinics where only “sick” people come. These people are eager to contribute to studies, but healthy older people are not seen by doctors or researchers.
Chapter 10: Normal and Successful Aging

- No way to characterize what a “normal aging” process is.
- Many changes that have been associated with aging are no longer unavoidable (inc blood pressure, inc in body weight, inc in serum cholesterol, inc in cancer)
- Rural areas exhibit different age-linked changes than urban: Industrial countries are different than un-developed nations
Chapter 10: Normal and Successful Aging

- Diseases such as Osteoporosis have other contributing factors other than just age that cause loss of calcium from bones:
  - cigarette smoking
  - heavy alcohol intake
  - inadequate calcium intake
  - inadequate exercise

- Mental faculties decrease with age?
  - always exceptions to the rule. Some older people may be sharper than when they were younger
  - when one compares old to young to show a difference and then look at young when they are older, not much difference will be seen
Chapter 10: Normal and Successful Aging

- Why don’t cohort studies and studies between young and old show that when it has been shown that 50 & 60 year olds exhibit a diff, in 10 yrs the 50 yr old do not show the same decline in function as the 60 yr old had 10 yrs previously???
  - differences in time of growing up (i.e., depression era teens vs children, war years vs fun yrs,...). They faced different challenges and stresses which could affect future mental and physiological health

- To determine if intelligence drops with age the best study would be to test 20 year olds and then 20 years later to test the same group again, NOT to compare 20 year olds with different 40 year olds.
Chapter 10: Normal and Successful Aging

- Exercise may be one of the major factors involved in increasing the numbers of the elderly who do not display so many debilitating aging symptoms.
  - decreases osteoporosis
  - enhances cardiovascular ability
  - restores lung capacity
  - prevents loss of muscle tone

- Diet is very important in slowing aging changes:
  - not one proper diet for all people
  - high fat diets lead to inc heart attacks
  - colon cancer is inc by red meats and decreased by complex carbohydrates and by fiber
Chapter 10: Normal and Successful Aging

- While it seems that some people die young no matter how healthy they try to keep themselves (diet, exercise, ...) they probably outlive what they would have otherwise.

- (Science, Jan 1993) Shows that low cholesterol can lead to depression (low cholesterol levels inhibit serotonin, a neurotransmitter) and there is a higher suicide rate (balancing lowered risk of heart attack).

- No real connection between life styles of centenarians except for “intellectual curiosity” that is retained by all.
Chapter 10: Normal and Successful Aging

- People who lose interest in life age more quickly.
- Does successful aging lead to intellectual curiosity, or does intellectual curiosity lead to successful aging?
- Intellectual activity in old age has shown that there is an increase in the number of dendrites and synapses (put rats in a stimulating environment in old age and study brain).
- Early life diseases and trauma and experiences may shape aging processes (chicken pox --> shingles, athletic injuries --> arthritis, ...).
Chapter 10: Normal and Successful Aging

- Women and Aging: Women live longer than men. Why? Very little research done on women (Why?)
- Menopause (climacteric) involves major change in hormonal balance affecting the immune and nervous systems.
- Changes in behavior and attitude occur. Is not a disease
- Aging and Sex: changes in vaginal lubrication, ability to attain and maintain an erection, and in abilities and desires to be stimulated. Sex and old age do go together! (Parents and GP do it!!)
Chapter 10: Normal and Successful Aging

- Nursing homes do not cater to old age and sex and intimacy for couples. This can lead to a variety of social and personal problems. Important to recognize for self-esteem issues and happiness.

- Older people can hold hands, engage in sex, and even get married and should not be looked at in disbelief or disgust.

- Sex at any age between compatible partners bolsters emotional health, elevates self-esteem and helps to keep one aware of the world and interested in keeping in good health (like intellectual curiosity?)
Those who took Biology 20 years ago know almost nothing of the new discoveries. Technology has made incredible advances.

Goals of aging research:
- extension of human life span beyond the present apparent limit of 110 years
- the ability to guarantee a full and healthy life up to the last moment of allotted span

These goals raise ethical questions:
- extension of life assumes that all faculties will be functional (do not want to be dependent for 200(?) years {read “Steel Beech” nanobots?})
Chapter 12: Goals & Responsibilities of Aging Research

- Live life healthy until you die (if you are healthy then why die? paradox)
- Through use of medicine, technology, etc... can extend “life expectancy” for those who have access to this technology (developed vs undeveloped countries)
- Elimination of one cause of death may lead to a different cause of death (i.e., from cancer to alzheimer’s)
- In developing countries, smoking and carcinogens may be very low on priority list of needs to improve health
If life is to be extended to use our 110 years then there must be a limit put on birth rates!! Controversial to say the least

Concerns over euthanasia and the right to die (living wills) but State may decide who lives and dies in certain situations of health and disease

Keeping people alive may be very expensive. Who pays? Taxpayer ultimately. Are we willing? Who should decide? (Kevorkian)

Implantation of fetal tissues can help in Parkinson’s and Alzheimer’s diseases. Controversy
Chapter 12: Goals & Responsibilities of Aging Research

- Study of aging is a multi-discipline process
- What are the models for studying aging??
- Any theory of aging must encompass ALL organisms, from single cells to complex humans. The question is: What do all aging organisms have in common??
- All aging organisms are able to undergo differentiation. A cell that does not differentiate does not age. Cells that do not differentiate only take in food, grow and divide. Can change food requirements by changing active genes and enzymes
Chapter 12: Goals & Responsibilities of Aging Research

- What cells “live” like this?
- Bacteria and cancer cells do not age (they are immortal. as long as there is a food supply and wastes are taken away they will continue to grow and divide)
- As cells differentiate they need to be able to respond to external stimuli. Do this by receptors. Need to remove waste products and toxic substances and these processes require a lot of energy. The use of energy for these processes takes away energy for reproduction. Sexual reproduction takes a lot of energy from individual cells.
Aging is species specific (mice live 20 X shorter than humans). It is not the failure of individual cells that causes aging, but a breakdown in communication and response processes between cells so that the system is no longer controlled.

Mice and people have different metabolic rates. Does this create the difference in life span?

Many studies needed and many things need to be found out to fully understand aging and how to delay the overall effects of aging in humans.