MCB 135K Final Review

May 11, 2005
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General Information

• Final Exam is cumulative
  – About 65-70% of questions will concern material from the last 1/3 of class

• Exam Breakdown
  – 60 pts Multiple Choice
  – 40 pts True/False
  – 100 pts Short Answer

• Exam Time and Location
  – Tuesday May 17, 2005
  – 12:30pm – 3:30pm
  – 230 Hearst Gym
Outline

• Neuroendocrine Theories
• Hypothalamo-Pituitary-Adrenal System
  – Homeostasis and Allostasis
  – Stress, Adaptation, and Regulation of Homeostasis
• Female and Male Reproductive Systems
  – Hormone Replacement Therapy
  – Prostate Aging
• Hypothalamo-Pituitary-Thyroid System
• Nutrition and Aging
  – Carbohydrate Metabolism, Diabetes, and Aging
• The Lung
• The Urinary Tract
• Aging of the Skin
• Osteoporosis
• Pharmacology
• Gastro-Intestinal Tract
Neuroendocrine Theories

- Hormones have both organizational and metabolic/behavioral actions throughout life
- Communication is the main function of the endocrine system
- Hormones
  - Secreted into blood
  - Specificity at target tissue through receptors
  - May stimulate or inhibit various actions
• Hormone Structures
  • Peptides
  • Modified Amino Acids
  • Steroids
  • Amines

• Types of Hormone Function
  • Autocrine
  • Endocrine
  • Paracrine

• During lifespan, hormone levels change as well as their function
Hypothalamus-Pituitary Interaction

- Anterior Pituitary
  - Connected to Hypothalamus via portal system
  - Releases Tropic Hormones under regulation of Hypothalamus

- Posterior Pituitary
  - “Extension of Hypothalamus”
  - Neurons project from Hypothalamus and secrete hormones
Hypothalamic hormones

(Dopamine) PIH

PRH

TRH

CRH

GHIH

GnRH

Portal system

Anterior pituitary

Prolactin

TSH

ACTH

GH

FSH

LH

(Gonadotropins)

Endocrine cells

To target tissues

Endocrine targets and the hormones they secrete

Thyroid gland

Thyroid hormones

Adrenal cortex

Cortisol

Somatomedins

Liver

Endocrine cells of the gonads

Androgens

Estrogens, progesterone

Germ cells of the gonads

Many tissues

Breast
Hypothalamo-Pituitary Adrenal Axis

• Adrenal Gland Structure
  – Cortex
    • Zona Fasiculata \(\rightarrow\) Cortisol (Glucocorticoid)
    • Zona Reticularis \(\rightarrow\) Sex Hormones
    • Zona Glomerulosa \(\rightarrow\) Aldosterone (Mineralocorticoid)
  – Medulla
    • Sympathetic Ganglia
      – Epineptherine & Norepineptherine
Glucocorticoid Action

- Changes with Age
  - Not significant in healthy non-stressed
  - Decreased glucocorticoid secretion compensated by decreased clearance
  - Some alterations to circadian rhythm
Regulation of Stress

- Stress
- Homeostasis
- Homeodynamics
  - Allostasis
- Pathophysiological Changes Due to Stress
- Allostatic Load
Stress

• **Types**
  – Physical
  – Chemical
  – Psychological
  – Emotional

• **Any change in an environment that may alter equilibrium and trigger a response to counteract that change**

• **Homeostasis** - **Optimal function of organism is at a steady state**
Homeodynamics

- Dynamic adjustments to achieve stable environment
- Stress generates adaptive responses
- Allostasis
  - Continual need for adjustment
- Continual adaptation to stress can lead to decline in the ability to adapt as well as disease
Pathophysiological Changes to Stress

- **Responses During Stress**
  - Cessation of energy storage
  - Access to energy storage
  - Reversal of energy storage steps

- **Responses After Stress**
  - Muscle wasting
  - Diabetes Type II
  - Ulcers
  - Inhibition of growth
  - Decreased testosterone

Tables – 10.6 and 10.7 have more details
Allostatic Load

- Physiologic toll exacted on the body through attempts at adaptation in response to cumulative effects of stress
- Increased load generates risk factors for morbidity and mortality in old age
- Moderate stress, short duration = good
- Severe and prolonged stress = bad
Hormesis

- Excitation induced by physical or psychological stress
  - Moderate Intensity
  - Short duration

- Benefits
  - Increased DNA Repair
  - Increased Immune Competence
  - Increased Neurologic Acuity
  - Increased Resistance/Adaptation to stress
Hormesis and Longevity

• Genome
  – the genetic material of an organism

• Phenome
  – the visible properties of an organism that are produced by the interaction of the genome and the environment

• Changes in the genome involve endocrine signaling that alter:
  – Energy consumption
  – Growth
  – Development
  – Reproductive Function
  – Resistance to stress

• Altering genome, changes phenome → increased longevity

• Review handout with examples of animal models
Aging and the Reproductive Systems

- Female
  - Anatomy
  - H-P-G Axis
  - Changes with aging
  - Consequences of aging

- Male
  - Anatomy
  - H-P-G Axis
  - Changes with aging
  - Consequences of Aging
Female: Anatomy

- **Ovaries**
  - Contain germinal cells
  - Contain endocrine producing cells
    - Granulosa
    - Thecal
  - Determine secondary structures and sexual characteristics
Female: H-P-G Axis
Hormonal Changes From Aging

• Gonadotropins:
  – LH
    • Change to pulsatile pattern: ↑Duration, ↓Frequency
  – FSH
    • “Monotropic FSH ↑
    • 1st Noticed prior to any change in cycle length

• Ovarian Steroidal Hormones
  – Estrone levels ↑ early in the cycle in older ovulatory women
    • Possible due to LH/FSH alterations
  – Eventually, H-P-G axis is unable to generate LH surge needed for ovulation
Female: Consequences of Aging

- Hormonal Changes
- Decreased Fertility and Fecundity
- Oocyte Structural Abnormalities
- Decreased Ovarian Reserve
- Hot Flashes
- Changes to Reproductive Tract
- Changes to Non-Reproductive Targets
Hormone Replacement Therapy

1. Loss of a body constituent
   • Metabolite, hormone, enzyme, vitamin, etc.

2. Constituent is necessary for the organisms survival and normal function

3. Involves the attempt to replace, or substitute, the lost constituent with a similar exogenous substance with comparable properties and actions
   • Dose, duration, metabolism, target cells, and side effects
Dihydroepiandrosterone (DHEA)

- DHEA is the principal adrenal androgen
  - Note-Does not bind androgen receptor
- DHEA(S) concentrations change throughout the human life
- DHEA(S) levels are lower in women than men
- Increased mortality is associated in men with a lower DHEA(S) baseline, but not in women
DHEA and Aging

Epidemiological Evidence

• Increased overall mortality and cardiovascular mortality in male subjects with lowest DHEA(S) levels
• Low levels found in severe diseases:
  – systemic lupus erythematosus
  – Dementia
  – Breast cancer
  – Rheumatoid Arthritis
• DHEA(S) levels may be indicative of a severe disease or predictive of a future disease

DHEA Replacement

• Adrenal Insufficiency
  – 25-50mg oral DHEA
    • Improves: androstendione and testosterone levels, depression, anxiety, and sexual function
• Healthy Elderly
  – 50 mg DHEA
    • No increase in well being, cognition, nor sexuality
• Elderly with impaired mood, cognition and sexual function
  – 50-100mg DHEA
    • Similar results to adrenal insufficiency study
Growth Hormone and Aging

• Study in 1990 demonstrated in small group of elderly men that GH and IGF I levels were reduced:
  – 12 out of 21 men injected with hGH over a 6 month period showed small increases in muscle mass and bone density (10-14%)
  – Suggests that GH might be responsible in part for decreased muscle and bone in elderly
Effects of GH Treatment

• 1998 study of ICU patients found:
  – Mortality increased from 19% to 44% in patients having GH therapy for 7-14 days
  – Length of hospital stay was prolonged by GH therapy

• Attributed to:
  – Decreased immune function
  – Increased insulin resistance
  – Multi-Organ Failure
Risks of HT

• Estrogen + Progestin
  – Increases Risk of:
    • Breast Cancer
    • Heart Disease
    • Stroke
    • Blood Clots
    • Dementia
  – Decreased Risk of:
    • Hip Fractures (Osteoporosis)
    • Colon Cancer
Risks of ERT

• Estrogen Alone
  – Only given to women that have had a hysterectomy
    • E alone is a risk factor for endometrial cancer
  – Does not improve long-term health
    • Decreases risk of fractures (osteoporosis)
    • Increases risk of stroke
  – May increase risk of ovarian cancer
  – Does not significantly effect coronary heart disease
  – Does not significantly alter breast cancer incidence
Male: Anatomy

- Primary Sex Organ
  - Testis
- Secondary Sex Organs
  - Epididymis
  - Vas Deferens
  - Ejaculatory Ducts
  - Seminal Vesicles
- Prostate
- Bulbourethral Gland
- Penis & Urethra
Male: H-P-G Axis

Diagram showing the Male H-P-G Axis:
- Hypothalamus
- Anterior pituitary
- Leydig cells
- Testosterone (T)
- Spermatocyte
- Testes
- Steroid cell
- Cell products
- Androgen-binding protein (ABP)

KEY:
- Integrating center
- Efferent path
- Effector
- Tissue response

To body for secondary effects
Male: Changes With Aging

• Male reproductive system remains relatively normal with aging
  – Does decrease after age 80

• Slight Change Seen
  – Decreased GnRH
  – Decreased Sensitivity to LH
  – Decreased Sensitivity of Negative Feedback between GnRH and LH
Male: Consequences of Aging

- Decreased Testosterone Levels
- Risk of Prostate Associated Problems
Prostate Related Problems

• Prostate growth is dependent on androgens
  – Testosterone is converted to DHT in prostate by 5-alpha-reductase
  – DHT stimulates prostate growth

• Normal Prostate Aging
  – Atrophy of smooth muscle, proliferation of connective tissue
  – Increased number of inner cells
  – Uniform Atrophy after 60

• Benign Prostatic Hypeplasia
  – Enlarged prostate size due to DHT stimulated growth

• Prostate Cancer
Prostate: BPH and Cancer

• BPH Risk Factors
  – Aging
  – Anabolic Steroid Use
  – Dietary Factors
  – Genetics
  – Environment

• Prostate Cancer Risk
  – Genetics
  – Tobacco
  – Cadmium
  – Vitamin A Deficiency
  – Vasectomy
  – STD
  – Hormonal Factors
  – Dietary Factors
Hypothalamo-Pituitary-Thyroid System

- **Thyroid Hormone**
  - Calorigenesis
  - Metabolism
  - Brain Maturation
  - Behavior
  - Growth and Development

![Hypothalamic-Pituitary-Thyroid System Diagram](image)
Thyroid Gland and Aging

- **Morphological Changes**
  - Distension of follicles
  - Flattening of follicular epithelium
  - Decreased mitoses
  - Increased Fibrosis
  - Vascular changes suggesting decreased hormone transport

- **Secretory Changes**
  - Lower circulating T3
  - Decreased secretion and clearance of T4
  - Decreased conversion of T4→T3
  - Decreased sensitivity of T3 receptors
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Graves’ Disease</th>
<th>Hashimoto’s Thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Status</td>
<td>Hyperthyroid</td>
<td>Hypothyroid</td>
</tr>
<tr>
<td>TSH</td>
<td>Generally undetectable</td>
<td>Normal to elevated</td>
</tr>
<tr>
<td>T4, T3 (serum)</td>
<td>Above normal</td>
<td>Below normal</td>
</tr>
<tr>
<td>Antibodies (ABs)</td>
<td>Stimulatory ABs compete with TSH at receptor sites Loss of TSH control over thyroid function</td>
<td>Some ABs block TSH actions</td>
</tr>
<tr>
<td>Autoantibodies against thyroglobulin, T3, T4, thyroid destroy thyroid microsomal and nuclear components</td>
<td>Generally present</td>
<td>Generally present</td>
</tr>
<tr>
<td>Lymphocytic Invasion</td>
<td>Limited</td>
<td>Marked</td>
</tr>
<tr>
<td>Female:Male Ratio</td>
<td>As high as 10:1</td>
<td>As high as 10:1</td>
</tr>
</tbody>
</table>
Table 13-1: Some Critical Aspects of Thyroid Hormone Regulation

1. **Major source of circulating T3** from peripheral deiodination of T4 (NOT from thyroid gland secretion)

2. The **negative feedback** at the pituitary anterior lobe is mainly through T4 (taken from circulation & converted into T3)

3. The peripheral deiodination of T4 depends on the physiological state of the organism. It allows an autonomy of response of the tissues to the hormones.

4. Deiodination can convert T4 (a less biologically active hormone) to T3 (a more active hormone). This conversion depends on the activity of the various deiodinating enzymes.
Nutrition and Aging

• Basal Metabolic Requirements (Elderly)
  – 1500 → 2200 kcal
  – Consider weight and biochemical parameters

• Fats 1gm=9kcal
  – Saturated = “Bad”
  – Unsaturated = “Good”
  – Trans = “Similar effect to saturated”
  – Omega 3 = “Good…but”

• Proteins 1gm=4kcal
  – Should be at least 12% of diet in elderly

• Carbohydrates 1gm=4kcal

• Fibers
  – Increase bowel movements
  – Can bind and impede absorption of medications
Nutrition

• Micronutrients daily intake
  – 1800 mg Calcium
  – 10-12 mg Iron
  – 50 ug Selenium
  – 150 ug Iodine
  – Less than 5mg NaCl

• Liposoluble Vitamins

• Hydrosoluble Vitamins

• Water
  – 1.5 – 2 Liters per day

• With age:
  • Sense of smell is obtuned
  • Dental structure is abnormal
  • Salivary secretion is diminished
  • Diminished appetite factors

• Therefore, check nutritional status by:
  • Clinical Tests
  • Biochemical Tests
Carbohydrate Metabolism and Diabetes

• Glucose Regulation
  – Hormones:
    • Insulin
      – Beta-cells of pancreas
    • Glucagon
      – Alpha-cells of pancreas

Image from Endocrineweb
Glucose Regulation

• **Insulin Action**
  – Lower blood glucose
    • Uptake into adipose and muscles
  – Stimulates metabolic glucose use
  – Increases glycogen synthesis
  – Slows gluconeogenesis
  – Promotes overall growth

• **Glucagon Action**
  – Opposes insulin action
  – Stimulates breakdown of glycogen in liver
  – Activates gluconeogenesis in liver
  – Increases blood glucose concentration
Changes With Aging: Diabetes

• Incidence of Diabetes Type II increases with age
  – Most common form of diabetes
  – Non-insulin dependent
  – Onset occurs years before noticeable symptoms

• Consequences of Type II Diabetes
  – Coronary Heart Disease
  – Glomerulonephrosis
  – Retinopathy
  – Stroke
  – Cataract
Glucose Intolerance

- **Glucose Intolerance**
  - **Insulin Alterations**
    - Change in receptors
    - Change in downstream receptor signaling
  - **Carbohydrate Metabolism Alterations**
    - Decreased muscle mass and increased adiposity
    - Increased gluconeogenesis
Table 14-8
Diabetes and Accelerated Aging

<table>
<thead>
<tr>
<th>DIABETES</th>
<th>AGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microangiopathy</td>
<td>---</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Accelerated Atherosclerosis</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Early decreased fibroblast proliferation</td>
<td>Decreased fibroblast proliferation</td>
</tr>
<tr>
<td>Autoimmune involvement</td>
<td>Autoimmune involvement</td>
</tr>
<tr>
<td>Skin changes</td>
<td>Skin changes</td>
</tr>
</tbody>
</table>
The Lung

• Major Functions
  – Regulation of gaseous exchange
  – Immunologic defenses
  – Metabolic functions
  – Endocrine functions

• Damage
  – Air pollution
  – Smoking
  – Airborne infections
  – Oxygen Toxicity
Aging Lung

• **Structural Changes**
  - **Alveolar Ducts**
    • Decreased elastic tissue
    • Increased fibrous tissue
  - **Thorax**
    • Calcification of bronchial and costal cartilage
    • Wasting of respiratory muscles
  - **Lung**
    • Enlarged alveolar ducts
    • Decreased pulmonary capillary network

• **Functional Changes**
  - **Thorax**
    • Decreased tidal volume
    • Increased use of diaphragm in ventilation
    • Decreased maximal voluntary ventilation
  - **Lung**
    • Increased mucus
    • Decreased gas exchange
    • Increased physiological dead space

Review tables 18-1, 18-2, 18-3,
Chronic Obstructive Pulmonary Disease (COPD)

Comprised of three distinct pathologies:

• Chronic bronchitis
  • inflammation of the bronchi and accompanied by hypersecretion of mucus & cough

• Emphysema
  • characterized by enlargement of air spaces, destruction of lung parenchyma, loss of lung elasticity and closure of small airways

• Chronic asthma
  • constriction of the bronchi
Impact of Aging on the Blood

• Changes in Hematological Profiles
  – Decreased
    • Hemoglobin
    • Hematocrit
    • RBC
    • Onset of Erythropoiesis after bleeding

• Regulators of Erythropoiesis
  – Erythropoietin
  – Testosterone
  – Interleukin-3

• Red blood cells turn over earlier and faster with age
  – Review table 18-15
Aging of the Urinary Tract

• Kidney
  – Structure
  – Function
  – Problems in elderly
    • Renal Failure
    • Incontinence
  – Drugs and the Elderly
Kidney

- Function
  - Water and electrolyte regulation
  - Metabolic products excretion
  - Hydrogen ion excretion and maintenance of blood pH
  - Endocrine Functions
Urinary Tract Problems

• Renal Failure
  – Impaired drug excretion
  – Urinary tract infections
  – Hypertension
  – Diabetes
• Signs of failure
  – Generalized edema
  – Acidosis
  – Circulating urea
  – Circulating excretion products

Incontinence
  – Physiological Requirements
  • Motivation
  • Cognitive function
  • Mobility and dexterity
  – Age-related changes contributing to incontinence (Table 19-8)
  • Male
  • Female
  – Management of incontinence
  • Table 19-9
Aging Kidney and Drug Clearance

• Kidney is susceptible to drug toxicity

• Questions to ask before giving drug:
  – Is drug excreted by kidney
  – Are kidneys competent
  – What are side effects
  – What are consequences of toxicity

• Why kidneys are susceptible:
  – High renal blood flow
  – Increased drug concentration and accumulation
  – Increased hepatic enzyme inhibition in elderly
  – Increased autoimmune disorders in elderly
Aging and the Skin

• Major Functions
  – Barrier
  – Temperature control
  – Receptor of sensory stimuli
  – Biosynthesis
  – Inflammatory/Immune Reactions
  – Excretion/Secretion
Skin Structure and Components

Collagen
Elastin
Keratin

http://skincancer.dermis.net/content/e01geninfo/e7/index_eng.html
Skin Changes with Aging

**Events**
- Epidermis
  - Decreased cell production, melanocytes, Langerhans cells
- Dermis
  - Decreased density, cell number, blood vessels
- Other
  - Decreased sweat, sebaceous gland, hair follicles

**Functional Consequences**
- Decreased
  - Wound healing, immunity, tanning, elasticity, clearance of foreign substances, thickness
- Increased
  - Blisters, infection, roughness, dryness, cancer, fragility, insensitivity
Treatments of Photo-Aged Skin

• Anti-oxidants
• Alpha-hydroxyacids
• Retinoids
  – Vitamin A (Retinol)
    • Important in: vision, development, growth, reproduction
    • Keratinocytes convert vitamin A into all-trans-retinoic acid (atRA)
  – atRA – regulates gene expression through nuclear hormone receptor (RAR)
Osteoporosis

- **Bone Remodeling**
  - To maintain calcium and phosphate levels
  - To respond to mechanical stress

- **Types of Bone**
  - Compact (Cortical)
  - Spongy (Trabecular)

- **Calcium Metabolism**
  - Need for calcium increases with age
    - Young adult – 800mg
    - Women over 50 – 1500mg
  - Regulated by:
    - Parathyroid hormone
    - Calcitonin
    - Calcitriol
    - Estrogen
    - Glucocorticoids
    - Growth Hormone
    - Thyroid Hormones
    - Insulin
Osteoporosis: Calcium Regulation

- Calcium Intake:
  - 800 mg/d for young adults
  - 1500 mg/d for women > 50 years

- Osteogenic Factors
- Osteolytic Factors

- Absorption:
  - GI Tract
  - Calcium

- Free Calcium
  - 1,25-(OH)_2 D_3
  - Calcium in Blood and Tissue Fluids

- Calcium Loss = Calcium Intake
- Excretion
  - Kidney
  - Urine

- FECES

Bone
Pharmacology

• Pharmacology:
  • *pharmakon* = drug
  • *logos* = discourse
  • study of the fate and actions of drugs
    – Pharmacokinetics
      • study of time course of drug concentration and the factors affecting it
    – Pharmacodynamics
      • study of the mechanisms of drug action
Pharmacology

- Pharmacological agents work via high affinity binding to their cellular targets (receptors)

- Agonist binding to receptors initiates physiological functions

- Antagonist binding to receptors blocks agonists from gaining access

- Partial agonist acts as an antagonist in the presence of a true agonist

- Pharmacokinetic Factors
  - Absorption
  - Distribution
    - Tissue Storage
    - Plasma Protein Binding
    - Target Site Availability
  - Biotransformation
  - Elimination
  - * Be familiar with these factors at the level of detail covered in lecture
Adverse Drug Reactions

The elderly are 2-3 times more at risk for adverse drug reactions due to:

• reduced stature
• reduced renal and hepatic functions
• cumulative insults to the body (eg., disease, diet, drug abuse)
• higher number and potency of medications
• altered pharmacokinetics
• noncompliance
Common problems of drug administration in the elderly

- **reduced homeostasis**
  - decreased renal and hepatic functions
  - increased target organ sensitivity

- **polypharmacy**
  - increased chance of adverse drug reactions

- **lack of available data**
  - fewer clinical trials on elderly populations

- **non-compliance**
Aging of the GI Tract

- **Goals**
  - Provide organism with:
    - Nutritive substances
    - Vitamins
    - Minerals
    - Fluids

- **Functions**
  - Digestion
  - Absorption
  - Motility
  - Secretion
GI Tract and Aging

• Functions of stomach
  – Food reservoir
  – Digestion of food
  – Secretion of gastric juice with digestive enzyme, mucus, hydrochloric acid
  – Secretion of hormones gastrin, glucagon, somatostatin, vasoactive intestinal polypeptide (VIP)
  – Secretion of intrinsic factor
    • necessary for Vitamin B12 absorption & maturation of RBCs
GI Tract and Aging

• Be familiar with
  – H. Pylori, Gastritis and Peptic Ulcer Disease
    • Box 20.1
  – Small Intestine Function
    • Table 20.4, 20.3
  – Liver Function and age associated changes
    • Table 20.6
  – Functions of Bile
    • Table 20.7
Other Topics to Review

– Functional Assessment of Elderly
– Cellular Senescence
  – Telomeres
  – Apoptosis
– Exercise and Aging
  – Aging of Skeletal and Cardiac Muscle
  – Immune System Changes with Aging
– Aging of the nervous system, repair, plasticity, disease
– Oxidants and Anti-oxidants
  – Imaging of the Brain
– Aging of the cardiovascular system