The AIDS pandemic

HIV/AIDS
- The problem is massive
  - 4th leading cause of death worldwide
  - ~40 million people are infected
  - 95% live in developing countries
- AIDS is the leading cause of death in Sub-Saharan Africa
  - Average life expectancy dropped from 62 to 47 yrs

The changing face of AIDS in the US
- Approx 46,000 new infections each year
  - 40% are from male-to-male contact
  - 30% from heterosexual contact
  - 25% from injection drug use
- Minority groups are disproportionately affected
  - AIDS affects nearly 7 times more African Americans and 3 times more Hispanics than whites
  - Why?

Pop quiz – Name the 3 main routes of HIV transmission
- Sexual intercourse
- Blood or blood products
- Mother-to-child transmission

HIV transmission in US
- The most common methods of transmission of HIV are:
  - Unprotected sex with an infected partner
  - Sharing needles with infected person
- Almost eliminated as risk factors for HIV transmission are:
  - Transmission from infected mother to fetus
  - Infection from blood products
Q2: What is the difference between HIV and AIDS?
- HIV is the virus that causes AIDS
- AIDS is the end stage disease

Q3: How can we avoid HIV infection? (AIDS prevention)
- Use condoms
- Don’t share needles
- Get tested
  - Many people infected with HIV have no symptoms

What makes HIV so lethal?
- The HIV retrovirus highjacks immune cells
  - Infected helper T cells (CD4 cells) which then make new copies of the virus
  - HIV infects and destroys the very cells that normally suppress viral attacks
- Long incubation period
  - The victim feels healthy but is highly infectious
  - Latent period can last 10 years

Molecular mechanism for HIV infection
- Why does HIV target the helper T cell?
  - One of the HIV coat proteins binds to the CD4 receptor – like a plug fits into a socket
  - Other cells have CD4 receptors: macrophages, monocytes and dendritic cells

HIV highjacks immune cells
- Like other viruses, HIV uses the cells it infects to make copies of itself
- HIV attaches to the membrane of CD4 cells
- Penetrates the cell
- Viral RNA is converted into DNA and integrated into the cell genome
- Human CD4 cells ‘manufacture’ the virus
- Virus eventually kills CD4 cells

HIV budding from an immune cell in culture
- Scanning electron micrograph of HIV-1 (in blue) budding from a cultured white blood cell
- The viruses bud so rapidly that the cell eventually lyses
**Course of HIV infection**
- Gradual deterioration of immune function
- HIV mainly damages helper T cells
  - Rapidly budding viruses lyse the cells
  - Body’s defenses attack the infected helper T cells
  - Helper T cells are initially replaced as fast as they’re destroyed
- Body’s ability to replace CD4 cells is slowly exhausted
  - When CD4 cell count falls below 200/ml, person is more vulnerable to other infections
  - Normal levels: 800-1200 CD4 cells/ml
- AIDS is the end stage of HIV infection

**Course of HIV infection**
- How does the loss of helper T cells affect the specific immune responses?
- Role of T\(_H\) cells?
  - secrete cytokines that activate B cells and cytotoxic T cells
- Drop in antibody production
- Drop in number of active “killer” T cells

**Treating AIDS: Antiretroviral (ARV) therapy**
- >30 drugs have been developed that suppress the virus
- Usually given in a “cocktail” of 3 - 4 pills
- Expensive, and must be maintained for the rest of the patient’s life
  - Avoid developing resistance to drugs
- Still no known cure or vaccine for HIV

**ARVs**
- Drugs that inhibit viral enzymes
  - Reverse Transcriptase inhibitors
    - viral enzyme that converts its RNA into DNA
    - AZT and ddI
  - Protease inhibitors
    - Cuts viral proteins into pieces to make the protein coat of new HIV particles

**Risk of HIV infection**
- 90% of HIV-positive people do not know they are infected
  - Long incubation period between infection and major illness
  - Most people have no access to testing
  - Stigma, absence of confidentiality
  - If there’s no treatment available, why get tested?
- Prevention is key
  - ABCs of prevention
    - Abstinence
    - Be faithful
    - Condoms

**Prevention efforts have lagged**
- ABC program - ineffective
- New approaches
  - HIV testing: Know your status
  - Take ARVs – reduce level of HIV and transmission
  - Male circumcision
  - Female condoms
  - Still in R&拢 stage
    - Vaginal microbicides
    - HIV Vaccine – the holy grail
Chapter 18: The Endocrine System

Hormones
- Molecules released in one part of the body that regulate the activity of cells in other places
  - Most hormones circulate in the bloodstream

Hormones
- Regulate various functions throughout the body
  - Control the activity of smooth muscle, cardiac muscle and some glands
  - Alter metabolism
  - Spur growth and development
  - Influence reproduction
  - Participate in circadian (daily) rhythms

The nervous and endocrine systems coordinate body functions
- These 2 systems act together to coordinate all body functions
  - Nervous system
    - Controls body activities thru nerve impulses and neurotransmitters
    - Act locally and quickly
  - Endocrine system
    - Controls body activities by releasing hormones
    - Slower responses, broader influence

Endocrine Glands
- Secrete hormones into interstitial fluid, which then diffuse into blood
- How are they different from exocrine glands?
  - Exocrine – secrete their products into ducts
  - Endocrine – ductless
How do hormones work?

Hormones affect specific target tissues
- Hormones are released into bloodstream by endocrine cells
- Hormones affect only target cells with specific hormone receptors
- Receptors are constantly turned over (produced and broken down)
  - Body can control the number of receptors and hormone activity

Hormones have a wide range of targets
- Some, like sex hormones, affect most of the tissues of the body
- Others, like glucagon, have only a few kinds of target cells (in this case, liver and fat cells)
- Some target other endocrine glands
  - For example, the hypothalamus targets the pituitary
- Some hormones elicit different responses in different target cells

Interleukin 2 (IL-2) is a local hormone
- IL-2 is released by helper T cells in the lymph node
  - Has both paracrine and autocrine activity
  - Activates nearby immune cells – paracrine
  - But it also stimulates the T cell that secreted it
- IL-2 stimulates other helper T cells to secrete IL-2, which strengthens the immune response

Hormone types: Circulating and Local Hormones
- Circulating hormones
  - Travel in blood and act on distant target cells
- Local hormones
  - Act locally without first entering the blood stream
    - Paracrine – act on neighboring cells
    - Autocrine – act on the same cell that secreted them

Chemical classes of hormones
- Lipid-soluble – bind to transport proteins in blood, can diffuse thru cell membranes
  - Steroid hormones
  - Thyroid hormones
- Water-soluble – circulate in a “free” form (not attached to plasma proteins)
  - Amines
  - Peptides/proteins
  - Eicosanoids
Mechanism of Action:
lipid-soluble hormones
1. Diffuse thru membrane
2. Bind to receptors inside target cells
3. The steroid-receptor complex binds to the DNA and alters gene expression
4. New proteins are made that affect the cell’s activity

Mechanism of action: estrogen
- The hormone estradiol stimulates cell growth in the breast and other parts of the body by binding to an estrogen-receptor protein inside the cell.

Mechanism of Action:
water-soluble hormones
- The hormone (first messenger) binds to receptors on plasma membrane of target cells
- This sets off a cascade of events inside the cell
- A second messenger is released inside the target cell
  - Amplifies original small signal
  - A common 2nd messenger is cyclic AMP (cAMP)
- Hormone-stimulated response alters cell functions

Water-soluble hormones
- Mechanism of action: using cyclic AMP as the second messenger:
  1. The hormone binds to its membrane receptor.
  2. The activated receptor activates adenylate cyclase.
  3. Adenylate cyclase converts ATP into cyclic AMP
  4. cAMP activates protein kinases which phosphorylate cellular proteins.
  5. Phosphorylated enzymes produce physiological responses

ADH – a peptide hormone
- ADH binds to receptors on the surface of cells of the collecting duct
- Binding of ADH activates G proteins which in turn triggers increased cAMP levels within the cell.
- This “second messenger” initiates a chain of events culminating in the synthesis and insertion of aquaporin-2 channels in the cell membrane.

Control of Hormone Secretion
- Most hormones are released in short bursts
- Hormone secretion is controlled by
  1. Signals from the nervous system
  2. Chemical changes in the blood
  3. Other hormones
- Most hormone secretion is regulated by negative feedback
“Master” endocrine glands: the hypothalamus and pituitary

Hypothalamus – major link between nervous and endocrine system
Hypothalamus secretes 9 hormones, the pituitary secretes 7.
Together these hormones regulate virtually all aspects of growth, development, metabolism, and homeostasis.

The Hypothalamus
- Is the main control center of the endocrine system.
- The hypothalamus is a highly complex structure in the brain that regulates many important brain chemicals.
- As part of the brain, the hypothalamus receives information from the nervous system and sends out appropriate responses.
- It controls secretion of hormones by the pituitary gland.

Pituitary Gland
- The pituitary gland is located in the sella turcica of the sphenoid bone and is differentiated into the
  - Anterior pituitary or adenohypophysis
  - Posterior pituitary or neurohypophysis

The posterior pituitary
- Composed of nervous tissue and is actually an extension of the hypothalamus
- It stores and secretes hormones made in the hypothalamus
  - Such as ADH

The hypothalamus directs water reabsorption in the kidneys
- The hypothalamus makes ADH with is stored and released by the posterior pituitary
- ADH promotes the reabsorption of water in the collecting ducts of the kidney

The anterior pituitary
- Composed of endocrine cells that synthesize and secrete numerous hormones directly into the blood
  - FSH, LH, and prolactin
- Secretion regulated by
  - Releasing and inhibiting hormones from the hypothalamus
  - Negative feedback
Regulatory hormones synthesized by hypothalamic neurosecretory cells are transported within axons and diffuse into capillaries. They are transported by hypophyseal portal system to target cells in the anterior pituitary. Stimulate or inhibit hormone secretion.

Human growth hormone
- The anterior lobe of the pituitary also secretes human growth hormone, which has a broad effect on the body.
- Cells in liver, skeletal muscles, bones and other tissues secrete IGFs (insulin-like growth factors) – cause cells to grow and multiply
  - Increase growth rate of skeleton and skeletal muscles

Pituitary gland disorders
- Disorders of hGH secretion
  - Hypossecretion of hGH results in pituitary dwarfism.
  - Hypersecretion of hGH
    - during childhood results in gigantism
    - during adulthood results in acromegaly
  - Enlarged bones in hands, feet and face

Abuse of hGH
- Athletes abuse hGH to bulk up their muscles
- Abuse can lead to
  - Disfigurement
  - Heart failure
  - Multiple cancers