Chapter 54: Drugs for Diabetes Mellitus

- **Sustained hyperglycemia**
  - Type I = insulin-dependent diabetes
    - Complete absence of insulin
    - Due to auto-immune destruction of pancreatic beta cells
  - Type II = non-insulin dependent diabetes
    - Due to cellular resistance to actions of insulin

- **Long-term complications**
  - Hypertension, heart disease, stroke, blindness, renal failure, lower limb amputations, impotence

- **Diagnosis of Diabetes**
  - Fasting plasma glucose is \( \geq 126 \) mg/dl
  - Casual blood glucose is \( \geq 200 \) mg/dl
  - Blood glucose is \( \geq 200 \) mg/dl 2 hours after an oral glucose challenge

- **Treatment**
  - Type I – treated with insulin replacement
  - Type II – treated with oral hypoglycemics and/or insulin in conjunction with diet modification and exercise
Insulin is anabolic
- Hormone promotes conservation of energy and buildup of energy stores
  - Stimulates uptake of glucose, AAs, nucleotides and potassium
  - Promotes synthesis of complex organic molecules (glycogen, proteins, triglycerides)
- Insulin deficiency puts body into catabolic mode
  - Glycogen converted to glucose, proteins degraded to amino acids, fats converted to glycerol and fatty acids (why?)

5 types of insulin used in USA
- Differ in response time and duration

Principle adverse effect is HYPOGLYCEMIA

Baseline Data
- Polyuria, polydipsia, polyphagia, weight loss
- ID high risk patients
  - Those using sympathomimetics, beta blockers, glucocorticoids (these can either raise or lower glucose levels)
- Teach patient & family how to inject insulin
Chapter 58: Androgens

- **Testosterone** – act on target tissues by binding to receptor in cytoplasm
  - Once bound to receptor is transported into nucleus and promotes transcription (mRNA)
  - Both males and females have testosterone
    - In females secreted by adrenal cortex and ovaries
    - In males secreted by Leydig cells of testes
Effects of testosterone
- Secondary sex characteristics
- Lower HDL and raise LDL levels
- Edema due to retention of salt and water

Use of Androgens (Anabolic Steroids)
- Enhance athletic performance
  - Nandrolone, stanozolol, androstenedione (‘Andro’)
  - Build up endurance, muscle mass
- Risks:
  - Edema, hypertension, testicular shrinkage (due to FSH & LH inhibition), acne, atherosclerosis, menstrual irregularity, virilization, rage, depression, etc……..

Chapter 59: Estrogen & Progestins

Control of menstrual cycle
- Know hormone and ovarian cycles
  - FSH, LH, estrogen, progesterone & functions
- Found in males

Secondary sex characteristics
- Bone: increase bone mass (blocks bone reabsorption)- rapid growth during puberty
- Cholesterol: lower LDL and raise HDL
Adverse effects
- Endometrial hyperplasia & carcinoma with prolonged use
- Breast cancer (?): not known for sure
- Use during pregnancy - risks during pregnancy out weigh any potential benefits (cancer and developmental abnormalities)
  - Diethylstilbestrol (DES)- nonsteroidal estrogen (causes adenocarcinoma of the vagina in women exposed to drug during fetal life)(used to decrease risk of miscarriage between 1948-1971)

Hormone Replacement Therapy (HRT)
- After menopause
  - Suppression of vasomotor symptoms: due to decline in estrogen – hot flashes, etc....
  - Prevention of urogenital atrophy
  - Prevention of osteoporosis (demineralization and weakening of bone
  - Protection against coronary heart disease
  - Reduction of risk of colorectal cancer
- Other benefits
  - Positive effect on wound healing, tooth retention, CNS function (memory retention), risk of Type II diabetes

Prostate cancer when prostate growth dependent upon androgens
Chapter 61: Drugs for Infertility

- Female: Causes and treatment
  - Disruption at any phase of cycle
    - Follicular maturation
    - Ovulation
    - Transport through fallopian tubes
    - Fertilization of ovum
    - Nidation (implantation)
    - Growth of conceptus
  - These occur only if hormones released and function

- Drugs that promote maturation and ovulation
  - Clomiphene & gonadorelin (induce FSH and LH release from pituitary)
  - Menotropins & follitropins (act on ovary to promote follicular development) and
  - Human chorionic gonadotropin (HCG) - acts on mature follicle to cause ovulation

- Unfavorable cervical mucus
  - Restored by estrogen treatment

- Luteal phase defect
  - Corpus luteum defect - treat with progesterone
**Endometriosis**

- Endometrial tissue implanted in abnormal site
  - Treat with surgery and/or drugs
    - Danazol and leuprolide treatment
      » Danazol – reduces synthesis of ovarian hormones, suppresses release of FSH and LH, and blocks hormone receptors on endometrial implants

**Androgen excess**

- Polycystic ovary syndrome (PCOS)
  - Characterized by presence of multiple follicles within a thickened capsule and absence of ovulation
  - Treat with clomiphene

**Male Infertility**

- At least 30% of infertility due totally to male
- Due to:
  - decreased density and motility of sperm
  - Abnormal volume or quality of semen
  - impotence
- Male infertility not generally responsive to drug therapy
Chapter 63: Immune System

- **Natural Immunity (Innate) vs Acquired (specific) Immunity**
  - **Natural:** non-specific defense systems
    - Skin, mucus, pH, secretions, normal flora, macrophages, natural killer cells, granulocytes
  - **Acquired:** specific B and T lymphocytes
    - Humoral (B cells)- antibody
    - Cellular (T cells)- interaction of self-MHC (class I and class II) + foreign antigen

- **B Lymphocytes**
  - Recognize native, soluble antigen (3-D)
  - Antibodies made by plasma cells
  - Defend against Ag’s in blood compartment
    - Viruses
    - Toxins
    - Bacteria
  - **5 Classes of Antibodies**
    - IgM= 1st Ab made, pentamer, activates C’
    - IgG= 2nd Ab made, monomer, activates C’, crosses placenta
    - IgA= dimer, crosses epithelial cells
    - IgE= allergy, binds to mast cells
    - IgD= function not known, present on early B cells
- Function of Abs: to clear Ag from system and block infectivity and disease ability
  - Opsonization (enhanced phagocytosis)
  - Blocking (block viral receptors)
  - Neutralizing (neutralize toxins)
  - Binds Complement (C’) lysis of cell membrane

- Antibody Structure
  - 2 light chains and 2 heavy chains
  - Constant and Variable regions
  - Binding of Ag by variable regions of light and heavy chains (idiotope region)
  - Fc region determines properties – can bind to Fc receptors on macrophages (IgG) and mast cells (IgE)

- Accessory cells
  - To help process antigen and present to T lymphocytes
    - Macrophages, dendritic cells, langerhans cells and B cells
  - T helper cells: CD4+, produce IL-2 to help stimulate B cells and other T cells
  - T cytotoxic cells: CD8+, kill target cells
    - Virally infected cells
    - Cancer cells
    - Tissue transplant cells
  - T cells recognize processed Ag only associated with self-MHC proteins
**MHC molecules**

- **Class I:** present on all nucleated cells
  - Presents antigen fragments that are made from inside cell
    - Self antigens
    - Viral antigens
- **Class II:** present only on antigen presenting cells (APCs)
  - Macrophages, B cells, dendritic and langerhans cells
  - Presents antigen fragments made external to cell
    - Toxins
    - Bacterial fragments
    - Viral fragments

**Cytokine Production**

- **IL-1:** stimulation of $T_H$ cells & produced by macrophages (and other APCs)
- **IL-2:** Stimulates proliferation of $T_H$, $T_C$ and B cells
- **IL-4:** Causes shift of antibody production from IgG to IgE
- **IL-10:** inhibits action of some $T_H$ cells
- **IFN gamma:** activates macrophages, NK cells, T & B cells, and increases MHC levels on cells (also act to inhibit viral replication)
- **Colony Stimulating Factors (CSFs):** activates growth of blood cells
### Vaccines

- **Passive:** pre-made antibodies (pooled serum, like gamma globulin)
  - Used to prevent disease after exposure
  - Fast acting, short lasting
- **Active:** make your own response and produce effector and memory cells
  - Live attenuated
  - “dead” non-living whole
  - Toxoids
  - Portions of peptides

### Allergies

- **Type I:** Anaphylactic (immediate, mediated by IgE attached to mast cells to cause degranulation)
- **Type II:** IgG or IgM mediated (blood type reactions), cell lysis due to C’ activation
- **Type III:** Immune complex reactions-antibody:antigen complexes cause IgG or IgM to activate C’ to destroy innocent bystander cells
- **Type IV:** mediated by T cells, delayed 48-72 hours (poison ivy reaction, tuberculin reaction)
### Table 63–1 CELLS OF THE IMMUNE SYSTEM

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Synonyms</th>
<th>Primary Immune-Related Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Cell Types</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B lymphocytes</td>
<td>B cells</td>
<td>• Produce antibodies • Lyse target cells</td>
</tr>
<tr>
<td>Cytotoxic T lymphocytes (CTLs)</td>
<td>Cytotoxic T cells, cytotoxic T cells, CD8 cells</td>
<td>• Promote proliferation and differentiation of B cells and CTLs by serving as antigen-presenting cells • Initiate delayed-type hypersensitivity</td>
</tr>
<tr>
<td>Helper T lymphocytes</td>
<td>Helper T cells, CD4 cells</td>
<td>• Promote proliferation and differentiation of helper T cells and CTLs by serving as antigen-presenting cells</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td>• Participate in delayed-type hypersensitivity • Phagocytosis cells tagged with antibodies • Phagocytosis cells in the effector stage of delayed-type hypersensitivity</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td></td>
<td>• Promote proliferation of cytotoxic T cells and helper T cells by serving as antigen-presenting cells</td>
</tr>
<tr>
<td><strong>Accessory Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast cells</td>
<td></td>
<td>• Mediate immediate hypersensitivity reactions</td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td>• Mediate immediate hypersensitivity reactions • Phagocytosis foreign particles (e.g., bacteria), especially those tagged with immunoglobulin G • Mediate inflammation • Attack helminths and other foreign particles that have been coated with immunoglobulin E • Contribute to immediate hypersensitivity reactions</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Polymorphonuclear leukocytes</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 64: Pediatric Immunization

- Killed vs Attenuated Vaccines
- Toxoids
- Passive vs Active Immunization

- Adverse Reactions
  - Do not give to immunosuppressed patients
  - Allergic reactions (horse & chicken)
Childhood Immunizations

- Measles, Mumps, Rubella (MMR)
  - Live virus, SC in arm
- Diphtheria, Tetanus, Pertussis (DTP)
  - Toxoids and attenuated bacteria (Pertussis), IM in thigh or deltoid muscles
- Poliomyelitis
  - Inactivated virus, 3 different types, oral
- Varicella (Chickenpox)
  - Live virus, SC in deltoid or thigh
- Hepatitis A and B
  - Inactive viral antigens, IM in deltoid

Schedule on page 742 (edition 4)

Chapter 65: Immunosuppressants

- Why give?
  - Tissue transplants
  - Autoimmune diseases
  - Allergy
- Precautions
  - Increased risk of infections
  - Increased risk of neoplasms
- **Cyclosporine**
  - Acts on T lymphocytes to inhibit production of IL-2
  - Does NOT suppress bone marrow

- **Glucocorticoids: (prednisone)**
  - Cause lysis of antigen-activated lymphocytes
  - Suppress lymphocyte proliferation
  - Alter movement (trafficking) of lymphocytes to reactive sites
  - Decrease IL-2 production and limit response of T cells to IL-1

- **Methotrexate** – (anti-cancer drug also)
  - Cytotoxic to B and/or T lymphocytes
  - Causes bone marrow dysfunction

- **Cyclophosphamide**
  - Anticancer drug and immunosuppressant
  - Cytotoxic to B and T cells
  - Pro-drug that is converted to active form by liver
    - Active form is an alkylating agent that cross-links DNA and results in death of cells undergoing cell division

- **Monoclonal antibodies**
  - Purified Ab from single clone of B cells
  - Can be used to kill specific cells if toxin or radioactive isotope attached to Ab
    - Can target tissue rejection cells, allergy cells, autoimmune cells, ……