

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 ≥ 126 mg/dl
- Casual blood glucose is ≥ 200 mg/dl
- Blood glucose is ≥ 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

Table 54–8 ORAL HYPOGLYCEMICS FOR TYPE 2 DIABETES

Class and Specific Agents	Actions	Major Adverse Effects
<i>Sulfonylureas</i> Tolbutamide [Orinase] Glipizide [Glucotrol] Glyburide [Micronase] (See Table 53–9 for other sulfonylureas)	Promote insulin secretion by the pancreas; may also increase tissue response to insulin	Hypoglycemia
<i>Meglitinides</i> Repaglinide [Prandin]	Promotes insulin secretion by the pancreas	Hypoglycemia
<i>Biguanides</i> Metformin [Glucophage]	Decrease glucose production by liver and increase glucose uptake by muscle	GI symptoms: decreased appetite, nausea, diarrhea Lactic acidosis (rarely)
<i>Alpha-Glucosidase Inhibitors</i> Acarbose [Precose] Miglitol [Glyset]	Inhibit carbohydrate digestion and absorption, thereby decreasing the postprandial rise in blood glucose	GI symptoms: flatulence, cramps, abdominal distention, borborygmus
<i>Thiazolidinediones</i> Troglitazone [Rezulin]* Rosiglitazone [Avandia] Pioglitazone [Actos]	Decrease insulin resistance, and thereby increase glucose uptake by muscle and decrease glucose production by the liver	Hypoglycemia, but only in the presence of excessive insulin Liver failure: rarely, and only with troglitazone

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

Cell Type	Synonyms	Primary Immune-Related Actions
<i>Major Cell Types</i>		
B lymphocytes	B cells	<ul style="list-style-type: none"> • Produce antibodies
Cytolytic T lymphocytes (CTLs)	Cytolytic T cells, cytotoxic T cells, CD8 cells	<ul style="list-style-type: none"> • Lyse target cells
Helper T lymphocytes	Helper T cells, CD4 cells	<ul style="list-style-type: none"> • Promote proliferation and differentiation of B cells and CTLs • Initiate delayed-type hypersensitivity
Macrophages		<ul style="list-style-type: none"> • Promote proliferation and differentiation of helper T cells and CTLs by serving as antigen-presenting cells • Participate in delayed-type hypersensitivity • Phagocytize cells tagged with antibodies • Phagocytize cells in the effector stage of delayed-type hypersensitivity
Dendritic cells		<ul style="list-style-type: none"> • Promote proliferation of cytolytic T cells and helper T cells by serving as antigen-presenting cells
<i>Accessory Cells</i>		
Mast cells		<ul style="list-style-type: none"> • Mediate immediate hypersensitivity reactions
Basophils		<ul style="list-style-type: none"> • Mediate immediate hypersensitivity reactions
Neutrophils	Polymorphonuclear leukocytes	<ul style="list-style-type: none"> • Phagocytize foreign particles (e.g., bacteria), especially those tagged with immunoglobulin G • Mediate inflammation
Eosinophils		<ul style="list-style-type: none"> • Attack helminths and other foreign particles that have been coated with immunoglobulin E • Contribute to immediate hypersensitivity reactions

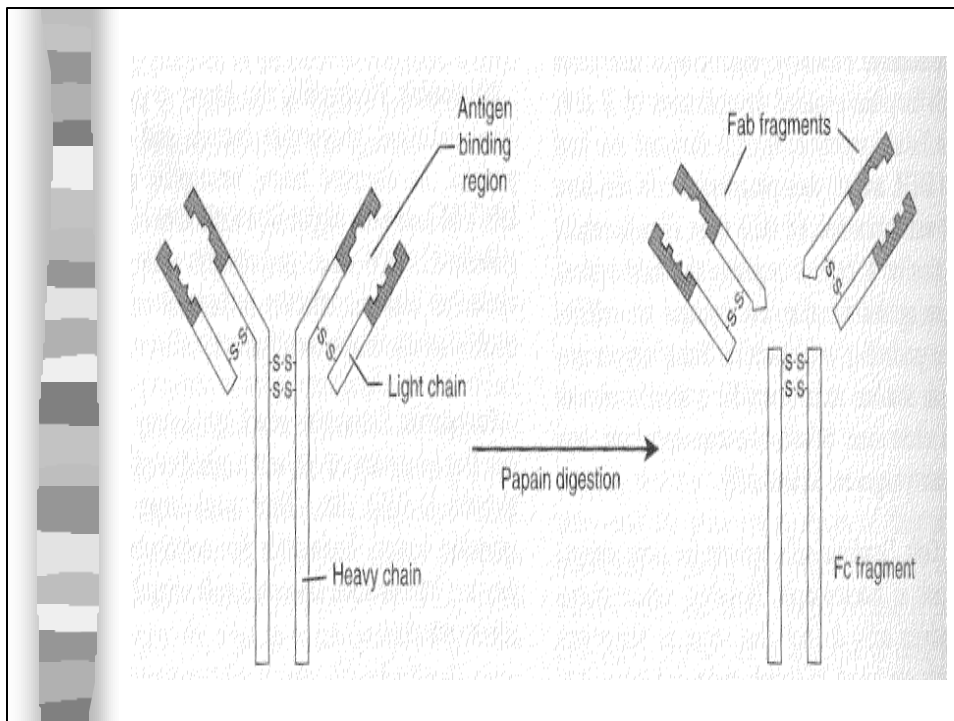


Table 63–2 FUNCTIONS OF ANTIBODY CLASSES

Class	Function
IgA	<ul style="list-style-type: none">• Located in mucous membranes of the GI tract and lungs and in many secretions, where it serves as the first line of defense against microbes entering the body via these routes• Transferred to infants via breast milk; is not absorbed from the GI tract but does protect the infant against microbes <i>in</i> the GI tract
IgD	<ul style="list-style-type: none">• Found only on the surface of mature B cells, where it serves as a receptor for antigen recognition (along with IgM)
IgE	<ul style="list-style-type: none">• Binds to surface of mast cells; subsequent binding of antigen to IgE stimulates release of histamine, heparin, and other mediators from the mast cells, thereby causing symptoms of allergy (e.g., hives, hay fever)• Binds to parasitic worms, after which eosinophils bind to IgE and release compounds that lyse the worms
IgG	<ul style="list-style-type: none">• Produced in copious amounts in response to antigenic stimulation, and hence is the major antibody in blood• Fixes complement and thereby promotes target-cell lysis• Binds target cells and thereby enhances phagocytosis• Transferred across the placenta to the fetal circulation, thereby providing neonatal immunity
IgM	<ul style="list-style-type: none">• First class of antibody produced in response to antigen• Fixes complement and thereby promotes target-cell lysis• Present on surface of mature B cells, where it serves as a receptor for antigen recognition (along with IgD)

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,