Chapter 36: Drug Abuse

- **Drug Abuse**
  - **Using a drug in a fashion inconsistent with medical or social norms**
  - **Drug abuse is culturally defined**
  - **Drug abuse can change within the same culture from time-to-time**
  - **Differences of opinion of what constitutes drug abuse and what drugs should be legalized**
  - **Does drug abuse occur with legal drugs???**
- **Addiction**
  - **Disease process characterized by the continued use of a specific psychoactive substance despite physical, psychological or social harm**
  - **Physical dependence is neither necessary nor sufficient for addiction to occur**

- **Tolerance**
  - **State in which a particular dose elicits a smaller response than it did with initial use**
- **Cross-tolerance**
  - **State in which tolerance to one drug confers tolerance to another drug**
- **Psychologic dependence**
  - **Intense subjective need for a particular psychoactive drug**
- **Physical dependence**
  - **State in which an abstinence syndrome will occur if drug use is discontinued (a result of neuroadaptive processes in Brain due to extended drug use)**
- **Cross dependence**
  - **Ability of one drug to support physical dependence on another drug (drug "A" prevents withdrawal symptoms from discontinuation of another drug**
- **Withdrawal syndrome**
  - **Symptoms that occur after drug withdrawal**

- **Factors contributing to drug abuse**
  - **1st take drugs out of curiosity, peer pressure**
  - **Leads to occasional (social) use**
  - **Evolves into compulsive use**
  - **Continue use because drug makes you feel good, experience is pleasurable (euphoric state, reduction of anxiety and stress)**
- **Drugs that are most commonly abused by people**
  - **Alcohol**
  - **Opioids**
  - **Barbiturates**
  - **Cocaine**
  - **Amphetamines**
  - **Nicotine**
  - **Caffeine**
  - **Animals will administer these drugs in preference to eating, drinking and sex**

- **Physical dependence**
  - **Occurs mostly in people who take large doses for a long time**
  - **Physical dependence is just one of many factors that lead to addictive behavior**
  - **Taking the drug after the onset of withdrawal symptoms may contribute to reinforce the desirability of continuation of the drug**
- **Psychological Dependence**
  - **The very strong feeling that your sense of well-being is dependent upon using the drug**
- **Social Factors**
- **Drug availability**
- **Vulnerability of the individual**

- **The Controlled Substances Act**
  - **Enacted in 1970**
  - **One objective was to reduce the chances that durgs originating from legitimate sources will become available to drug users-- regulations for the handling of controlled substance by manufacturers, distributors, pharmacists, nurses and physicians**
    - ***Written record must be kept of all transactions***
    - ***Inventory must be reported to the DEA every 2 years***
    - ***Many hospitals may require that stocks of controlled substances be counted at the beginning and end of each nursing shift***
- **DEA Schedules**
  - **Schedule I- drugs have high potential for abuse and no approved medical use in US**
  - **Schedule II-V: II has highest level of potential abuse, but all are approved for medical purposes**
  - **Schedule II prescriptions- must be written in ink and signed by prescribing physician: Oral prescriptions used only in emergency and must have written prescription w/i 72 hours**

Chapter 37: Drug Abuse- Alcohol

- **Most commonly used and abused drug in US**
- **When used in moderation can increase health by reducing risk of stroke, prolonging life, and "increases the joy of living"**
- **When used in excess reduces the quality of life and causes disease (liver) and cancer**
- **Alcohol is a CNS depressant**
  - **Works by enhancing the effects of GABA**
  - **When dosage low affects higher brain centers (cortical areas)**
  - **When dosage is high affects primitive brain (medulla)**

- **Depression of Cortical Areas of Brain**
  - Thought processes and learned behaviors changed
  - Inhibitions released
  - Self-restraint replaced by sociability
  - Impairment of motor function
  - Reflex action slowed
  - As dose increases a state of anesthesia occurs
- **Chronic Effects of alcohol use**
  - Wernicke's encephalopathy- confusion and abnormal ocular movements
    - *Due to thiamine deficiency resulting from poor diet and alcohol induced suppression of thiamine absorption*
    - *Reversible with thiamine*
  - Korsakoff's psychosis- caused by thiamine deficiency
    - *Characterized by polyneuropathy, inability to convert short-term memory to long-term memory*
    - *NOT reversible*
  - Long-term excessive alcohol induces enlargement of cerebral ventricles (loss of intellectual function and memory

- Alcohol may be used to induce sleep, but in reality disrupts sleep (intensify snoring and cause sleep apnea)
- Alcohol causes dilation of cutaneous blood vessels (increases blood flow to body surface)
  - Do not use to keep warm
- Alcohol causes direct damage to myocardium
- Alcohol produces a dose-dependent elevation of blood pressure
- 5 or more drinks a day promote cardiac disease--low alcohol ingestion may protect from coronary artery disease (CAD) by increasing levels of high-density lipoprotein (HDL)
- Causes hepatitis and cirrhosis and carcinoma
- Causes ulcers in stomach
- Increases risk of breast cancer

- **Absorption**
  - **Stomach and small intestine**
  - **Milk and food retard absorption**
  - **Crosses blood-brain barrier and placenta**
  - **Metabolized by liver enzymes (alcohol dehydrogenase)**
- **Chronic consumption causes tolerance**
- **Chronic use leads to physical dependence**

- **Drugs used in Treatment of Alcohol Abuse**
  - **Benzodiazepines – reduce risk of withdrawal symptoms, reduce delirium tremens (DTs)**
- **Drugs used to maintain abstinence**
  - **Disulfiram**
    - ***Inhibit alcohol metabolism- build up of acetaldehyde to toxic levels, producing unpleasant sensations***
  - **Naltrexone**
    - ***Pure opioid- decreases alcohols pleasurable effects***

Table 36–2 CLASSIFICATION OF CONTROLLED SUBSTANCES BY THE DRUG ENFORCEMENT AGENCY

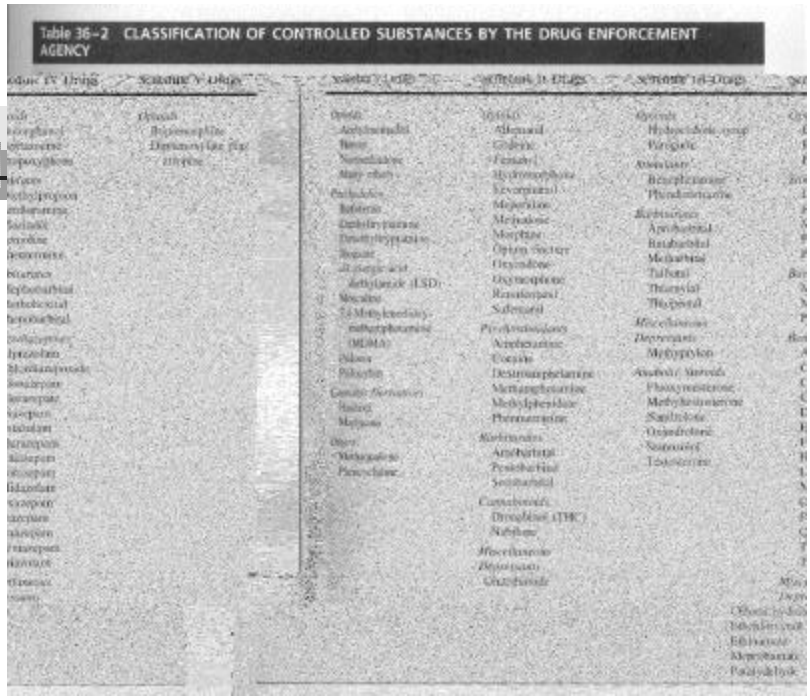


Table 37–1 CENTRAL NERVOUS SYSTEM RESPONSES AT VARIOUS BLOOD ALCOHOL LEVELS

Blood Alcohol Level (%)	Pharmacologic Response	Brain Area Affected
0.50		
	Peripheral collapse	Medulla
0.45		
	Respiratory depression	
0.40	Stupor, coma	Diencephalon
0.35	Apathy, inertia	
0.30	Altered equilibrium	Cerebellum
	Double vision	Occipital lobe
0.25	Altered perception	
0.20	↓ Motor skills	Parietal lobe
	Slurred speech	
0.15	Tremors	
	Ataxia	
0.10	↓ Attention	Frontal lobe
	Loquaciousness	
	Altered judgment	
0.05	Increased confidence	
	Euphoria, ↓ inhibitions	

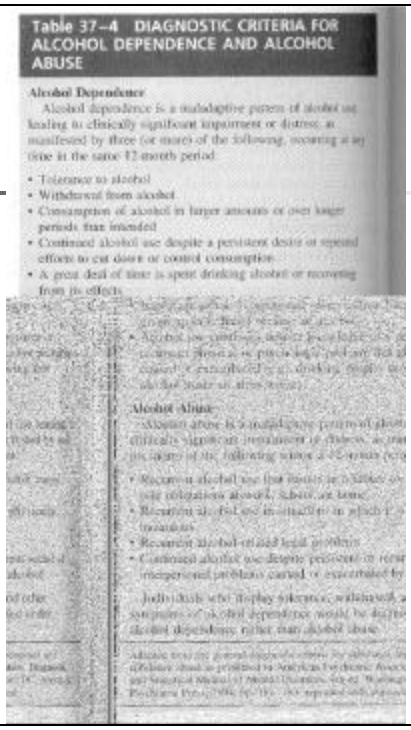


Table 37–4 DIAGNOSTIC CRITERIA FOR ALCOHOL DEPENDENCE AND ALCOHOL ABUSE

Alcohol Dependence

Alcohol dependence is a maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- Tolerance to alcohol
- Withdrawal from alcohol
- Consumption of alcohol in larger amounts or over longer periods than intended
- Continued alcohol use despite a persistent desire or repeated efforts to cut down or control consumption
- A great deal of time is spent drinking alcohol or recovering from its effects

Alcohol Abuse

Table 37–5 DRUGS USED TO FACILITATE ALCOHOL WITHDRAWAL

Drug	Benefit During Withdrawal
Benzodiazepines	
Chlordiazepoxide Diazepam Oxazepam Lorazepam	Decrease withdrawal symptoms; stabilize vital signs; prevent seizures and delirium tremens
Beta-Adrenergic Blockers	
Atenolol Propranolol	Improve vital signs; decrease craving
Alpha-Adrenergic Blocker	
Clonidine	Decreases withdrawal symptoms
Antiepileptic Drug	
Carbamazepine	Decreases withdrawal symptoms; prevents seizures

Chapter 38: Opioids & Others

- **Opioids**
  - **Heroin- produces a sensation in lower abdomen similar to sexual orgasm– lasts for ~45 seconds**
  - **After this there is a prolonged sense of euphoria**
  - **When first use heroin nausea and vomiting occur and if not for peer pressure continued use might not occur**
  - **Has high lipid solubility (cross blood-brain barrier)**
  - **Nurses and Physicians who abuse heroine usually choose Meperidine (Demerol)**
    - ***Effective when administered orally***
    - ***Has less pupillary constriction (miosis)***
    - ***Does not cause constipation and urinary retention***
  - **Tolerance**
  - **Physical Depression**
  - **Acute Toxicity**

- **Methadone**
  - **Long duration of action**
  - **Because of cross-dependence, methadone replaces heroine without withdrawal symptoms**
  - **Give methadone in smaller quantities (takes ~10 days for complete withdrawal)**
- **Use of Opioid Antagonists to Maintain Abstinence**
  - **These help to discourage renewed abuse**
  - **Block euphoria and all other opioid effects and thereby eliminate reinforcing properties of drug use**
  - **Naltrexone is best for treating opioid abuse**

- **Abuse of General CNS Depressants– Barbiturates**
  - Barbiturates with highest potential for abuse have a short to intermediate duration of action
  - Produce tolerance and physical dependence
  - Use Phenobarbital (has a long ½ life) to help with withdrawal from short acting barbiturates
- **Abuse with Cocaine**
  - Stimulant of CNS
  - Can produce anesthesia and vasoconstriction
  - Administered intranasally (snorted) or IV
  - Causes activation of dopamine receptors and blockade of dopamine re-uptake (overall effect is to increase reactivity of dopamine)
  - Difficult to treat (prevent all access to drug??)

- **Abuse with Amphetamines**
  - "ice" or "crystal meth" administered IV or orally
  - Promote arousal and elevation of mood (euphoria)
  - Sense of increased physical strength and mental capacity, feel little or no need for food and sleep, and orgasm is delayed, intensified and more pleasurable
  - Production of psychotic state (hallucinations)
  - Excessive stimulation of heart (produce hypertension and angina)
- **Marihuana**
  - Cannabis sativa (Indian hemp plant)
    - *Psychoactive compounds found in all parts of plant, but greatest concentration in flowering tops of female plants*
  - Major psychoactive substance is delta-9-tetrahydrocannabinol (THC)
  - Acts on specific cannabinoid receptors in brain
  - Receptor is anandamide- activation of phospholipase A2→ PGE2, and may promote release of dopamine

- **Effects of Marihuana**
  - Euphoria
  - Heightened sense of the humorous
  - Increased sensitivity to visual and auditory stimuli
  - Enhanced sense of touch, taste and smell
  - Increased appetite and ability to appreciate the flavor of food
  - Distortion of time perception
  - Impairment of short term memory
  - Decrease capacity for perform multi-step tasks
  - Impairment of driving skills
  - Inability to distinguish between past, present and future
  - Decreased ability to perceive the emotions of others
  - With High Doses there are adverse psychological effects– hallucinations, paranoia, delusions

  - With Chronic use– amotivational syndroms
    - *Apathy*
    - *Poor grooming*
    - *Reduced interest in achievement*
    - *Disinterest in attaining goals*
  - Physiological Effects
    - *Dose dependent increase in heart rate*
    - *Bronchodilation, but when used chronically the drug causes airway constriction*
    - *Decreased spermatogenesis and decreased testosterone levels:: In females the drug reduces levels of FSH*
  - Can produce tolerance and dependence when used chronically
- **Therapeutic Uses**
  - Suppression of emesis (reduces nausea and vomiting induced by cancer therapy)
  - Appetite stimulation (AIDS, anorexia, …)
  - Glaucoma

- **Psychedelics**
  - **D-lysergic Acid Diethylamide (LSD)**
    - ***Acts by inducing serotonin receptor activation***
    - ***Hallucinations, color images, sensory experiences***
    - ***Tolerance occurs after only 3-4 doses***
    - ***Flashbacks- without concurrent usage of LSD***
    - ***Acute panic episodes***
  - **No recognized therapeutic applications**
- **3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy)**
  - **Mixed properties of a psychedelic and psychostimulant**
  - **Low doses produce psychelelic effects like LSD**
  - **High doses produce amphetamine-like effects**
  - **Causes irreversible destruction of serotonin neurons resulting in passivity and insomnia**

- **Mescaline, Psilocybin, Psilocin and Dimethytryptamine**
  - **LSD-like drugs that cause perceptions and feelings that are normally restricted to dreams**
  - **Hallucinations and psychosis**
  - **Shorter lasting responses than LSD and less potent**
- **Nicotine**
  - **Greatest single cause of preventable illness and premature death is smoking**
  - **Action of nicotine results from actions at nicotinic receptors (can be activated or inactivated)**
    - ***Low doses activate***
    - ***High doses inactivate***
  - **Smoke contains– CO, hydrogen cyanide, nitrosamines and tar (proven carcinogen)**
  - **Actions in CNS mimic those of cocaine**
  - **Nicotine from cigarettes absorbed from lung into blood then goes to brain**

- Nicotine from cigars and chewing tobacco absorbed from the mouth
- Nicotine easily enters breast milk and is passed along to newborn
- Nicotine crosses placenta and affects fetus

- **Effects of Nicotine**
  - Vasoconstriction, acceleration of heart rate :: these result in increase blood pressure and increase work load of heart (cause of cardiovascular deaths??)
  - Increased production of gastric acid and motility of GI tract
  - CNS stimulant
    - *Increases alertness, facilitates memory, improves cognitive function, suppresses appetite*
    - *Causes release of dopamine and this results in "pleasure" response*
  - Produces tolerance and dependence

- **Treatments to help stop smoking**
  - Nicotine replacement therapy (NTR)
    - *Transdermal patches*
    - *Chewing gum*
    - *Nasal spray*
    - *Inhaler*

- **Anabolic Steroids– Abuse**
  - Androgenic compounds
    - *To help with athletic endurance and strength*
    - *With long-term use and addiction syndrome develops*
      - *Acne*
      - *Violence*
      - *Cancer*
      - *Death*

Chapter 39: Diuretics

- **Drugs that increase the output of urine**
  - **Used to treat**
    - ***Hypertension***
    - ***Mobilization (removal) of edematous fluid associated with heart failure, cirrhosis and kidney disease***
- **Anatomy of kidney**
  - **Glomerulus**
  - **Proximal convoluted tubule**
  - **Loop of Henle**
  - **Distal convoluted tubule**
  - **Collecting ducts**
- **Function of kidney**
  - **Cleansing of blood**
  - **Maintenance of fluid volume and composition**
  - **Maintenance of acid-base balance**
  - **Excretion of metabolic wastes**

- **1. Filtration- occurs in glomerulus**
  - **All small molecules filtered and go through glomerular membrane into proximal convoluted tubule**
  - **Large molecules prevented form being filtered**
  - **Each minute the kidney produces 125 ml of filtrate**
    - ***Most of this must be reabsorbed or you will lose all fluid quickly***
- **2. Reabsorption- 99% of water reabsorbed**
  - **Electrolyes and nutrients reabsorbed by active transport**
  - **Water follows passively**
- **3. Active secretion**
  - **Pumps that transport compounds from the plasma into the lumen of the nephron**
    - ***One pump is selective for organic acids***
    - ***One pump is selective for organic bases***
    - ***Eliminate wastes, drugs, toxins***
  - **Located in proximal convoluted tubule**

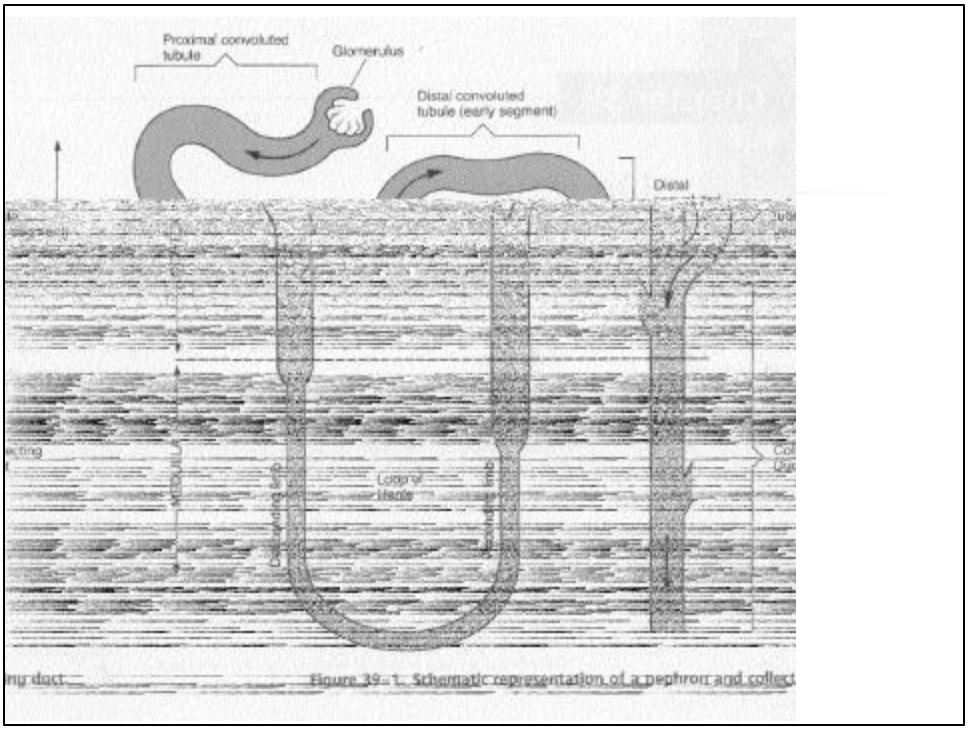
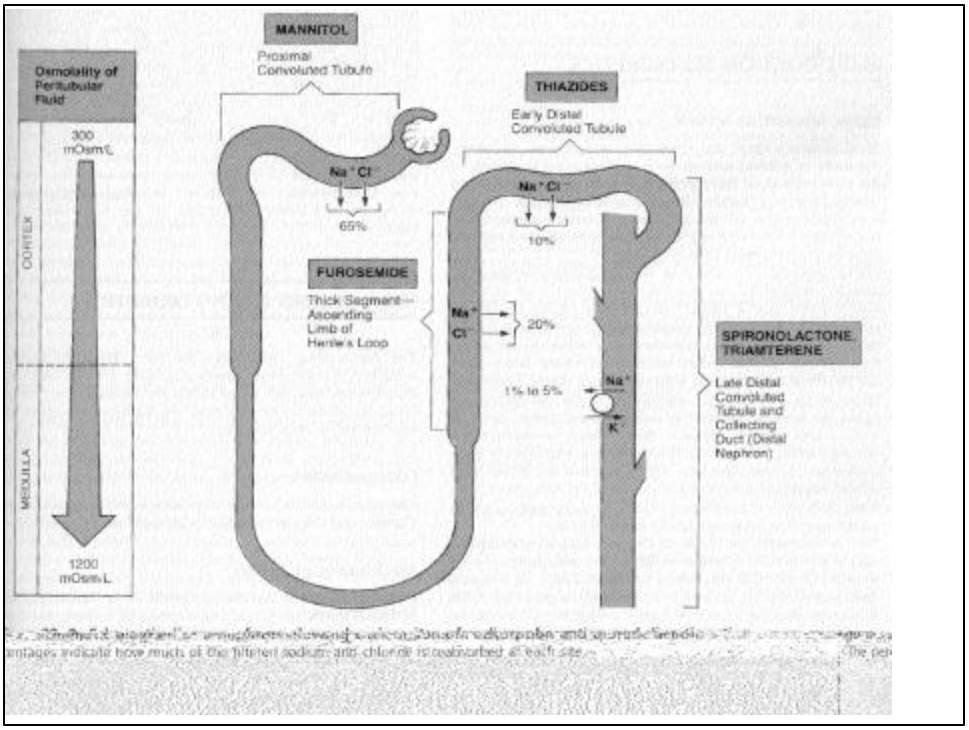
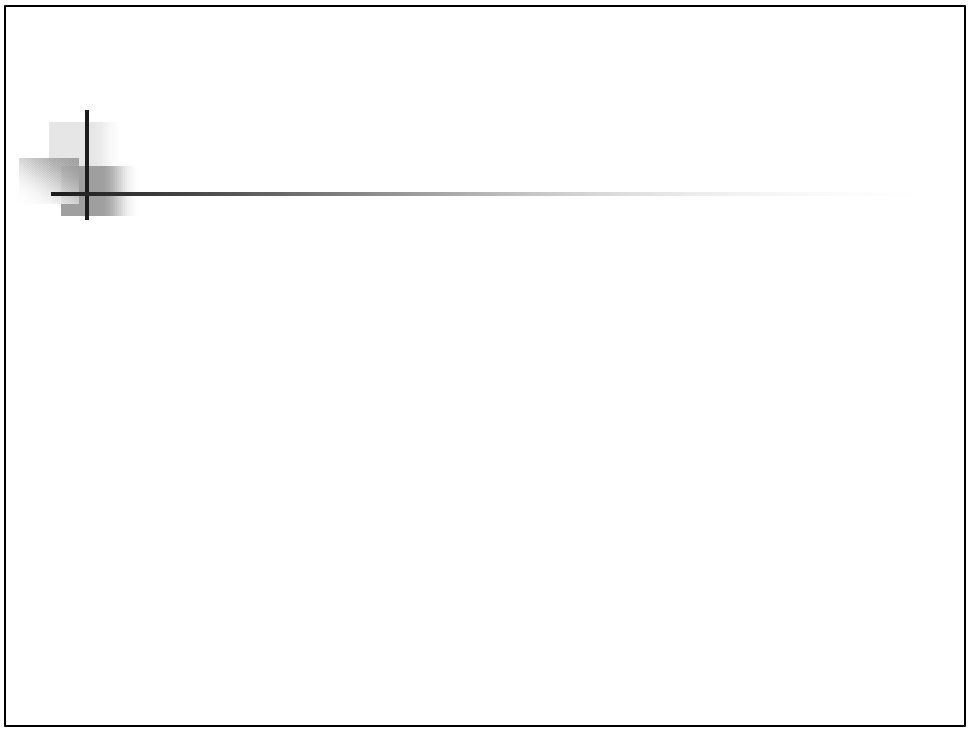


Figure 39–1. Schematic representation of a nephron and collect



- **Diuretics**
  - **Work through the blockade of sodium and chloride reabsorption**
    - ***By blocking this process, no osmotic gradient occurs and water cannot move out, back into the general circulation***
    - ***Understand the meaning of solute/solvent ratios in the understanding of diffusion and osmosis***
- **Classification of diuretics**
  - **High ceiling loop diuretics (furosemide)**
  - **Thiazide diuretics (hydrochlorothiazide)**
  - **Osmotic diuretics (mannitol)**
  - **Potassium-sparring diuretics**
    - ***Aldosterone antagonists (spironolactone)***
    - ***Non-aldosterone antagonists (triamterene)***
  - **Caarbonic anhydrase inhibitors – used only to lower intraocular pressure (IOP) and not to increase urine production**

- **High ceiling (loop) diuretics**
  - **Furosemide**
    - ***Blocks reabsorption of sodium and chloride in the ascending limb of Henle's loop***
  - **Therapeutic uses**
    - ***Pulmonary edema associated with congestive heart failure (CHF)***
    - ***Edema of hepatic, cardiac or renal origin that is not responsive to lower potent drugs***
    - ***Hypertension that cannot be controlled with other diuretics***
- **Thiazides**
    - ***Blocks reabsorption of sodium and chloride in the early segment of the distal convoluted tubule***
  - **Therapeutic uses**
    - ***Hypertension (1st choice of drugs)***
    - ***Edema due to moderate heart failure***
    - ***In Diabetes Insipidus, characterized by increased urine production, Thiazides REDUCE urine output. Why??? Is unknown????***



Chapter 40: Volume and ion content of body fluids

- **Maintenance of fluid volume and osmolality of extracelluar fluid is job of kidneys**
- **Abnormal states of hydration**
  - **Volume contraction (decrease in total body water)**
    - ***Isotonic contraction- volume contraction in which sodium and water are lost in isotonic proportions (e.g., there is a decrease in total volume of extracellular fluid but no change in osmolality***
      - ***Replace with isotonic fluids (0.9% NaCl in water)***
    - ***Hypertonic contraction- loss of water exceeds loss of sodium (loss of fluid with increase in osmolality & water drawn out of cells)***
      - ***Replace with hypotonic solution (0.11% NaCl)***
    - ***Hypotonic contraction- loss of sodium exceeds loss of water (both volume and osmolality of extracellular fluid reduced due to Na loss)***
      - ***Replace with 3% solution of NaCl***

- Volume expansion (increase in total body water)
  - *Isotonic expansion*
  - *Hypertonic expansion*
  - *Hypotonic expansion*
- May result from an overdose with therapeutic fluids or with disease states
- Treatments-- use of diuretics

Acid-Base Disturbances– Regulated by:

- Bicarbonate-carbonic acid buffer system
- Respiratory system- blow off CO_2
- Kidneys
- Four types of acid-base imbalance
  - *Respiratory alkalosis (hyperventilation increases pH)*
    - *Rebreathe own air*
  - *Respiratory Acidosis (retention of CO_2 by impaired ventilation)*
    - *Correct impairment or inject sodium bicarbonate*

- *Metabolic Alkalosis (increase in both pH and bicarbonate content of plasma due to excessive loss of gastric acid by vomiting)*
  - *Corrected by infusion of solution containing both sodium chloride + potassium chloride which promotes renal excretion of bicarbonate*
- *Metabolic Acidosis- chronic renal failure, loss of bicarbonate during severe diarrhea and over production of lactic acid– also poisoning by methanol and aspirin*
  - *Treatment by correction of underlying cause*

Potassium Imbalances

- Hypokalemia
  - *Deficiency of potassium in blood caused by treatment with thiazide (loop diuretics)*
    - *Adverse effects on skeletal muscle, smooth muscle and heart*
    - *Treatment by administration of potassium chloride*
- Hypekalemia (withhold foods that promote K^+ accum.
  - *Excessive elevation of serum potassium- due to tissue trauma, untreated Addison's disease*
  - *Disruption of electrical impulses of heart*

Chapter 41: Review of Hemodynamics

- **Overview of circulatory system**
  - **Two functions**
    - ***Delivery of oxygen, nutrients, hormones, electrolytes***
    - ***Removal of carbon dioxide, metabolic wastes***
  - **Pulmonary and systemic circulation**
- **Components**
  - **Heart**
  - **Arteries → arterioles → capillaries → venules → veins**
    - ***Arteries more muscular and not as elastic as veins (small increases in venous pressure cause large increase in diameter of veins)***
  - **In human ~5 liters of blood (9% in pulmonary circ, 7% in heart, 84% systemic)**
  - **64% in venous system, 20% arterial system**

- **Blood flow**
  - **From greater to lesser pressure**
  - **Vessel diameter gives resistance to flow (the larger the vessel, the smaller the resistance and blood flow increases: constriction increases resistance and flow of blood declines. When resistance increases blood pressure must rise also)**
  - **Blood flow through veins– very low pressure: muscle contraction, valves, movement toward vacuum (thoracic cavity and heart diastole)**

Cardiac output (CO) = heart rate (HR) X stroke volume (SV)

Heart rate controlled by autonomic nervous system

sympathetic vs parasympathetic responses that innervate SA node

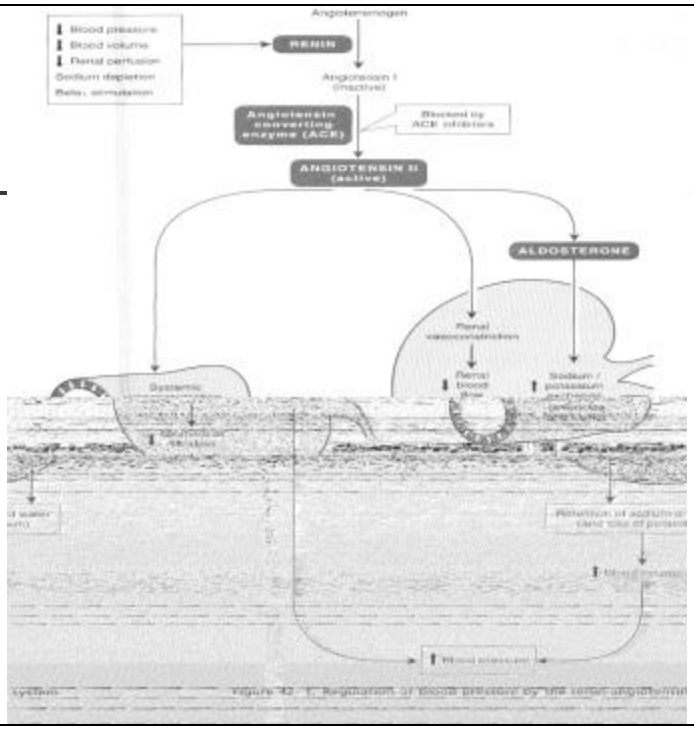
Starling's Law: the force of ventricular contraction is proportional to muscle fiber length (when more blood enters heart, more blood is pumped out)

- **Arteriole pressure = peripheral resistance X cardiac output (AP= PR X CO)**
  - ***Increase in PR increases AP***
  - ***Increase in CO increases AP***
  - ***PR regulated by vasoconstriction and vasodilation***
  - **Baroreceptors help maintain AP at predetermined level (carotid sinus and aortic arch: sense AP and send impulses to medulla)**
- **Renin-Angiotensin System**
  - **Supports AP by:**
    - ***Constriction of arterioles and veins (mediated by hormone angiotensin)***
    - ***Retention of water by kidney (mediated by aldosterone)***
- **Drugs that dilate veins intensify and prolong postural hypotension**

Chapter 42: Drugs Acting on the Renin-Angiotensin System

- **Angiotensin converting enzyme (ACE) Inhibitors**
- **Antiotensin II receptor blockers (ARBs)**
  - **Effects result from interfering with the renin-angiotensin system (RAS)**
  - **Treatment for hypertension and heart failure, myocardial infarction, and diabetic nephropathy**
  - **ARBs approved only for hypertension**
- **Angiotensin**
  - **Angiotensin I, II and III**
    - ***Angiotenisn I is precursor to angiotensin II which can be degraded to angiotensin III.***
    - ***Angiotensin I has no biological activity***

- **Angiotensin II**
  - **Mediates all of the effects of the RAS: vasoconstriction and stimulation of aldosterone release (both raise blood pressure)**
  - **Angiotensin II acts directly on vascular smooth muscle to cause contraction-- more prominent in arterioles than veins**
  - **Also acts indirectly on smooth muscle constriction by acting in the CNS to increase sympathetic input into blood vessels and by acting on adrenal medulla to increase release of epinephrine**
  - **Acts on adrenal cortex to promote synthesis and release of aldosterone– aldosterone acts on kidney to cause retention of sodium and excretion of potassium (thereby increasing blood volume and blood pressure)**
    - ***Receptors for release of aldosterone have greater affinity than receptors for vasoconstriction, and at low levels there may not be constriction of vasculature but there is release of aldosterone***



- **Angiotensin II**
  - **May cause hypertrophy of heart and blood vessels (enlargement, increased mass of a structure) and remodeling (redistribution of mass within a structure)**
    - ***May be responsible in causing increased thickness in blood vessels in atherosclerosis***
- **Renin**
  - **Catalyzes the formation of angiotensin I from angiotensinogen (inactive form)**
  - **Renin is produced by the juxtaglomerular cells of the kidney**
  - **Release triggered by:**
    - ***A decline in blood pressure***
    - ***Reduced blood volume***
    - ***Decreased sodium content***
    - ***Decrease renal pressure***

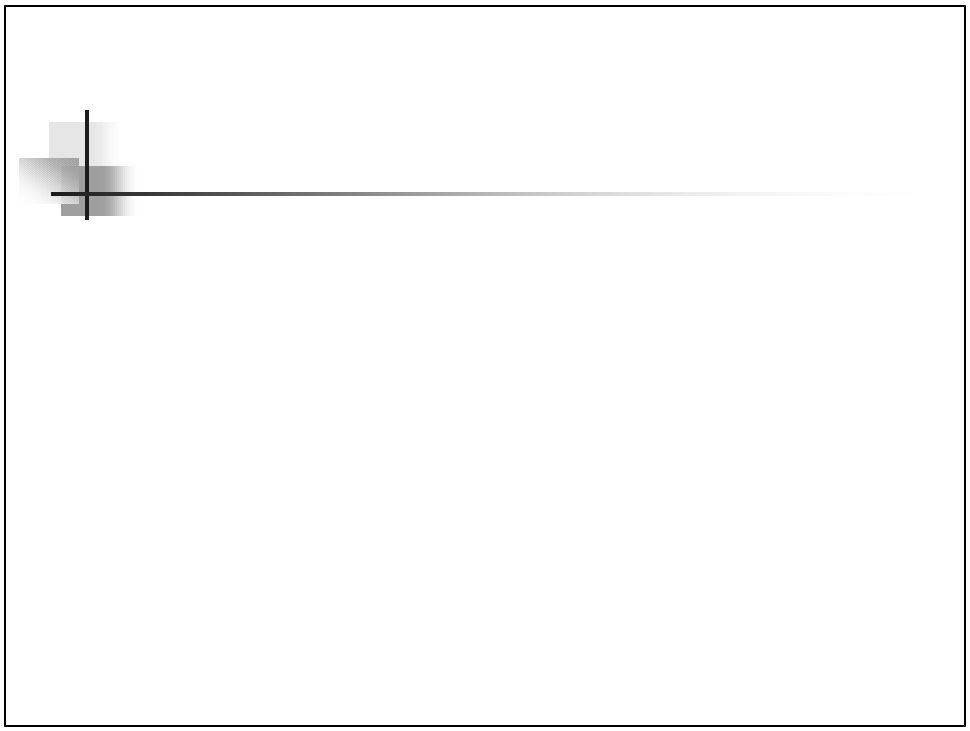
- **Angiotensin Converting Enzyme (ACE, also known as Kinase II)**
  - **Catalyzes the conversion of Angiotensin I (inactive) to Angiotensin II (highly active)**
  - **ACE located on the surface of all blood vessels (especially high in the lungs)**
  - **Conversion occurs immediately upon conversion of angiotensinogen to angiotensin I**
- **Angiotensin-Converting Enzyme Inhibitors**
  - **Treatment of hypertension and heart failure**
  - **CAPTOPRIL- 1st ACE inhibitor used worldwide**
    - ***Prevents formation of angiotensin II***
    - ***Results in vasodilation***
    - ***Taken orally and absorption is 70% but is reduced greatly by food (take 1 hour prior to meals)***

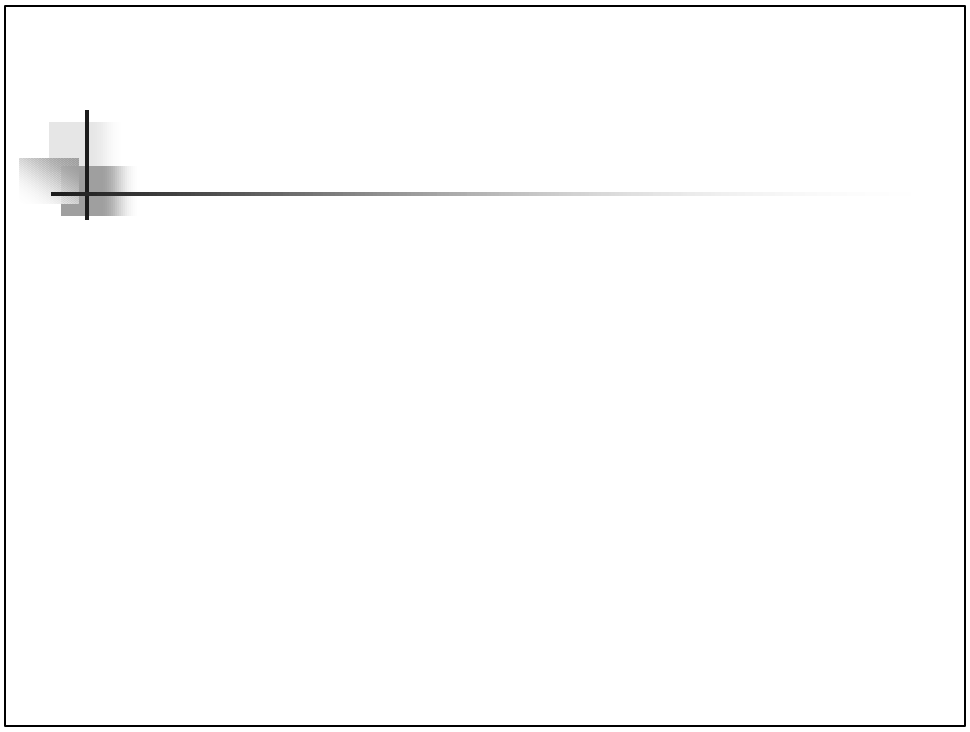
- **Angiotensin II Receptor Blockers (ARBs)**
  - **Blocks action of angiotensin II at receptor site**
  - **Similar effects as ACE inhibitors**
  - **5 ARBs have been approved for treatment of hypertension:**
    - ***Losartan (Cozaar) -- approved ONLY for hypertension but may be useful in heart failure***
    - ***May cause birth defects during 2nd and 3rd trimsesters***
    - ***Blocks receptors for angiotensin II on blood vessels, adrenals and other tissues***
      - ***Causes vasodilation***
      - ***Increases renal excretion of sodium and water but does NOT increase levels of potassium even though it lowers aldosterone levels***
      - ***Vasodilation causes increased excretion of water because of increased blood flow through kidneys***

Chapter 43: Calcium Channel Blockers

- **Calcium channel blockers (CCBs)**
  - **Prevent calcium ions from entering cells**
  - **Exert greatest effects on heart and blood vessels**
  - **Used to treat hypertensin, angina pectoris, and cardiac dysrhythmias**
  - **Safety issues have arisen since 1995 about use of calcium channel blockers**
- **Vascular smooth muscle (VSM)**
  - **CCBs act selectively on peripheral arterioles and arteries and arterioles of the heart-- no effect on veins**
  - **Calcium channels in heart associated with $beta_1$-adrenergic receptors in SA node, AV node and myocardium**

- When calcium channels open and calcium and
- calcium movement into cells increases, discharge of impulses increases
- In heart, calcium channel receptors are coupled to beta$_1$ receptors
- Both CCBs and beta blockers have same action on heart: they both reduce force of contraction and slow heart rate and suppress conduction through AV node
- 3 Classes of CCBs:
  - Dihydropyridines (Nifedipine)
  - Phenylakylamines (Verapamil)- arterioles and heart
  - Benzothiazepines (Diltiazem)- arterioles and heart
- Site of action
  - Dihydropyridines: act on arterioles only
  - Verapamil- angina pectoris, hypertension, dysrhythmias





- **Verapimil: 5 effects**
  - Blockade at peripheral arterioles to cause dilation and reduce arteriole pressure
  - Blockade at arteries and arterioles of the heart increases coronary perfusion
  - Blockade at SA node reduces heart rate
  - Blockade at AV node decreases AV node conduction
  - Blockade of myocardium decreases force of contraction
    - *May be indicated for migraine also*
- **Activation of baroreceptor reflex to cause lowering of blood pressure (increases firing of sympathetic neurons)**
  - Has opposite effects that counteract each other
- **Are Calcium Channel Blockers Safe??**
  - Increased risk of mortality in patients with myocardial infarction and unstable angina and hypertension
  - UNKNOWN AND CONTROVERSIAL!!!!

- **CCBs**
  - In blood vessels calcium channel blockade causes vasodilation
  - In heart, calcium channel blockers cause decreased heart rate, decreased AV and SA node conduction, and decreased contractility
  - All CCBs cause vasodilation and are useful in treatment of hypertension and angina
- **Pre-administration Assessment**
  - For all patients determine blood pressure and pulse rate, evaluations of liver and kidney function, and baseline data for frequency and severity of anginal attacks
  - Not indicated for patients with severe hypotension and liver dysfunction

Chapter 44: Vasodilators

- **Types of vasodilators (Table 44-1)**

Table 44–1 TYPES OF VASODILATORS

Category	Examples
Angiotensin-Converting Enzyme Inhibitors	Captopril Enalapril Lisinopril
Angiotensin II Receptor Blockers	Losartan Valsartan
Organic Nitrates	Nitroglycerin Isosorbide dinitrate
Calcium Channel Blockers	Verapamil Nifedipine Diltiazem
Sympatholytics	
Alpha-adrenergic blockers	Phentolamine Phenoxybenzamine Prazosin Terazosin
Ganglionic blockers	Mecamylamine
Adrenergic neuron blockers	Reserpine Guanethidine Guanadrel
Centrally acting agents	Clonidine Guanabenz Methyldopa
Other Important Vasodilators	Hydralazine Minoxidil Nitroprusside Diazoxide

- **Treatment uses range from hypertension to angina pectoris to heart failure**
- **Selectivity of vasodilatory effects**
  - **Vasodilators may differ from each other in the types of blood vessels they affect**
    - ***Hydralazine- effect on arteriole dilation***
    - ***Nitroglycerin- selective dilation of veins***
    - ***Prazosin- equal effects on arterioles and veins***

Table 44–2 VASODILATOR SELECTIVITY

Vasodilator	Site of Vasodilation	
	Arterioles	*Veins*
Hydralazine	+	
Minoxidil	+	
Diltiazem	+	
Nifedipine	+	
Verapamil	+	
Prazosin	+	+
Terazosin	+	+
Phentolamine	+	+
Nitroprusside	+	+
Captopril	+	+
Enalapril	+	+
Lisinopril	+	+
Losartan	+	+
Nitroglycerin		+
Isosorbide dinitrate		+

- **Adverse Effects related to Vasodilation**
  - **Postural hypotension**
  - **Reflex tachycardia- arteriole and venous dilation cause decreased return of blood flow to heart, and baroreceptors sense this and cause heart rate to increase in an attempt to increase pressure and blood flow.**
    - ***Since the vasodilator was given to reduce heart rate and lower blood pressure this response is undesirable and puts stress on heart.***
  - **Expansion of blood volume- response of body to try to maintain blood pressure: by secretion of aldosterone (promotes retention of sodium to increase water reabsorption) , and by decreasing renal filtration**

Chapter 45: Hypertension

- **Affects ~50 million Americans**
- **Untreated, can lead to heart disease, kidney disease, blindness, and stroke**
- **Drug therapy does NOT cure hypertension, only reduces symptoms**
  - **Treatment must continue for lifetime**
- **Hypertension**
  - **Systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg**
  - **If systolic > 140 and diastolic < 90 then a diagnosis of *isolated systolic hypertension* applies**
- **Types of hypertension**
  - **Primary hypertension**
  - **Secondary hypertension**

Table 45–1 CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGE 18 AND OLDER*

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal†	<120	*and*	<80
Normal	<130	*and*	<85
High normal	130–139	*or*	85–89
Hypertension‡			
Stage 1	140–159	*or*	90–99
Stage 2	160–179	*or*	100–109
Stage 3	≥180	*or*	≥110

* Not taking any antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify blood pressure status. For example, 160/92 mm Hg should be classified as stage 2 hypertension, and 174/120 mm Hg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as SBP of 140 mm Hg or higher and DBP below 90 mm Hg and staged appropriately (e.g., 170/82 is defined as stage 2 isolated systolic hypertension).
† Optimal blood pressure with respect to cardiovascular risk is below 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.
‡ Based on the average of two or more readings taken at each of two or more visits after an initial screening.
Data from the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1997).

Table 45–2 TYPES OF HYPERTENSION AND THEIR FREQUENCY

Type of Hypertension	Frequency (%)
Primary (Essential) Hypertension	92
Secondary Hypertension	
Chronic renal disease	4
Renovascular disease	2
Coarctation	0.3
Primary aldosteronism	0.2
Cushing's syndrome	0.1
Pheochromocytoma	0.1
Oral contraceptive-induced	1

- **Primary Hypertension (Essential hypertension)**
  - **Has no identifiable cause**
  - **Chronic and progressive**
    - ***Older people have more hypertension than younger***
    - ***Black Americans have more hypertension than White Americans***
    - ***Post-menopausal women have more hypertension than pre-menopausal women***
    - ***Obese people have more hypertension than people of "normal" weight***
  - **In older people, resistance to blood flow increases because of hardening of the arteries, and when there is more resistance there must be a compensatory increase in pressure to maintain blood flow**
- **Secondary Hypertension**
  - **Elevation of blood pressure due to a specific cause**
  - **If cause is known, then it might be possible to treat and cure hypertension**

- **Objectives of Therapy**
  - **To reduce morbidity and mortality without decreasing quality of life**
- **Risk Stratification and Selection of Treatment Protocol**
  - ***Determined by blood pressure and the presence of target organ damage***
  - **1st step: evaluate patient for major cardiovascular risk factors, for clinical cardiovascular disease (CCD), and for target organ damage (TOD)**
  - **Treatment Options**
    - ***Lifestyle modification plus drug therapy***
      - ***If patient has stage 1 hypertension and is classified in risk group B, the recommended treatment is lifestyle modification (for up to 6 months)***
      - ***If patient with stage 1 hypertension is in risk group C, recommended treatment would be immediate drug therapy along with lifestyle modification***

Table 45–3 RISK STRATIFICATION AND TREATMENT OF PATIENTS WITH HYPERTENSION

I: FACTORS IN CARDIOVASCULAR RISK STRATIFICATION

Major Cardiovascular Risk Factors	Clinical Cardiovascular Disease/ Target Organ Damage (CCD/TOD)
Diabetes Smoking Dyslipidemia Age older than 60 years Male sex Female sex (after menopause) Family history of cardiovascular disease: women under age 65 or men under age 55	Heart diseases • Left ventricular hypertrophy • Angina pectoris • Prior myocardial infarction • Prior coronary revascularization • Heart failure Stroke or transient ischemic attack Nephropathy Peripheral arterial disease Retinopathy

II: CARDIOVASCULAR RISK GROUPS

Group	Definition
A	No major cardiovascular risk factors and no CCD/TOD
B	At least 1 major cardiovascular risk factor (but not diabetes) and no CCD/TOD
C	Presence of CCD/TOD, diabetes, or both (with or without other risk factors)

III: RECOMMENDED TREATMENT BASED ON BLOOD PRESSURE CATEGORY AND CARDIOVASCULAR RISK GROUP

Blood Pressure Category (mm Hg)	Treatment		
	Risk Group A	*Risk Group B*	*Risk Group C*
High normal (130–139/85–89)	Lifestyle modification	Lifestyle modification	Drug therapy*†
Stage 1 hypertension (140–159/90–99)	Lifestyle modification (up to 12 months)	Lifestyle modification‡ (up to 6 months)	Drug therapy*
Stage 2 or 3 hypertension (≥160/≥100)	Drug therapy*	Drug therapy*	Drug therapy*

* All patients undergoing drug therapy should also undergo lifestyle modification.
† Drug therapy is recommended for patients with heart failure, renal insufficiency, or diabetes.
‡ For patients with multiple risk factors, consider drugs plus lifestyle modification as initial therapy.
Based on information from The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1997).

- **Lifestyle modifications**
  - **Weight loss**
  - **Sodium restriction**
  - **Alcohol restriction**
  - **Exercise**
  - **Smoking cessation**
  - **Maintenance of potassium and calcium intake**
- **Principle Determinants of Blood Pressure**

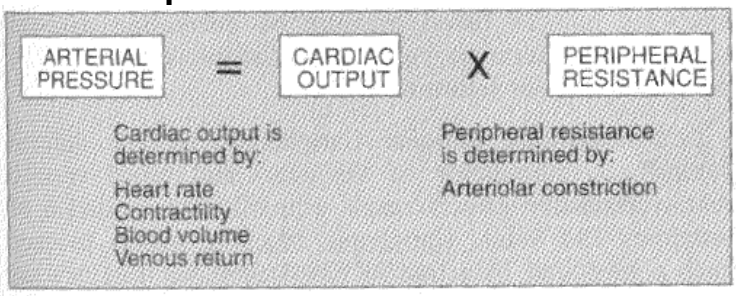


Figure 45–1. Primary determinants of arterial blood pressure.

- **Systems the regulate blood pressure**
  - **Sympathetic Baroreceptor Reflex**
    - ***Baroreceptors- in aortic arch and carotid sinus relay blood pressure information to brainstem***
    - ***When BP low, brainstem sends impulses along sympathetic nerves to stimulate heart and blood vessels***
    - ***BP elevated by stimulation of beta$_1$ receptors in heart, causing increased cardiac output, and stimulation of vascular alpha$_1$ receptors causing vasoconstriction***
    - ***When BP restored then sympathetic stimulation stops***
    - ***"Set point" of baroreceptors is HIGH in people with high BP and use of drugs to lower BP will result in person body trying to elevate BP back to what it perceives as normal-- must use a beta blocker to compensate for this***
  - **Renin-Angiotensin System**
    - ***Renin released from kidney due to reduced blood flow in kidney***
    - ***Conversion of angiotensin I → angiotensin II that constricts systemic and renal blood vessels***
    - ***Reduces glomerular filtration (inc Na+ retention)***

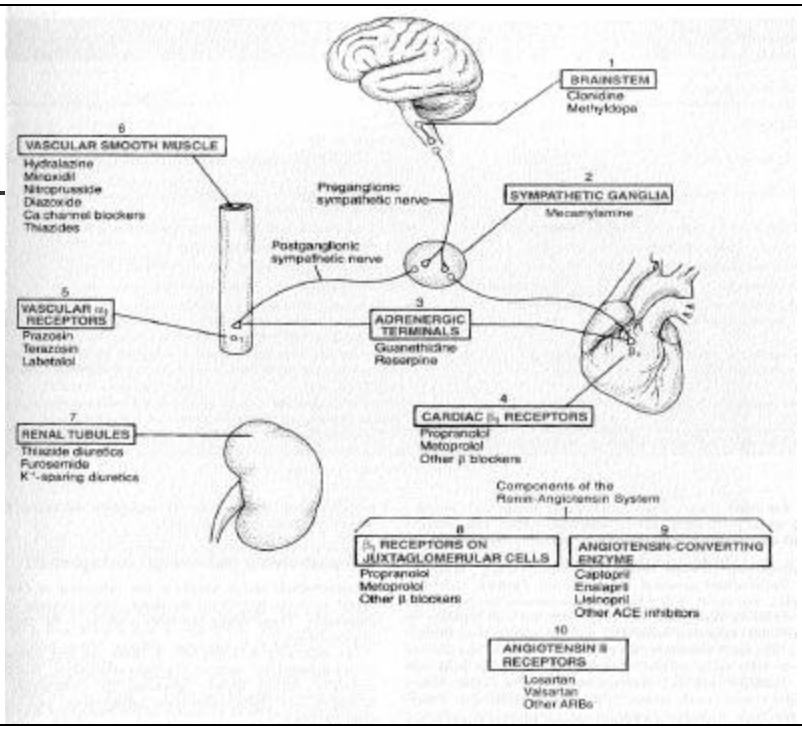
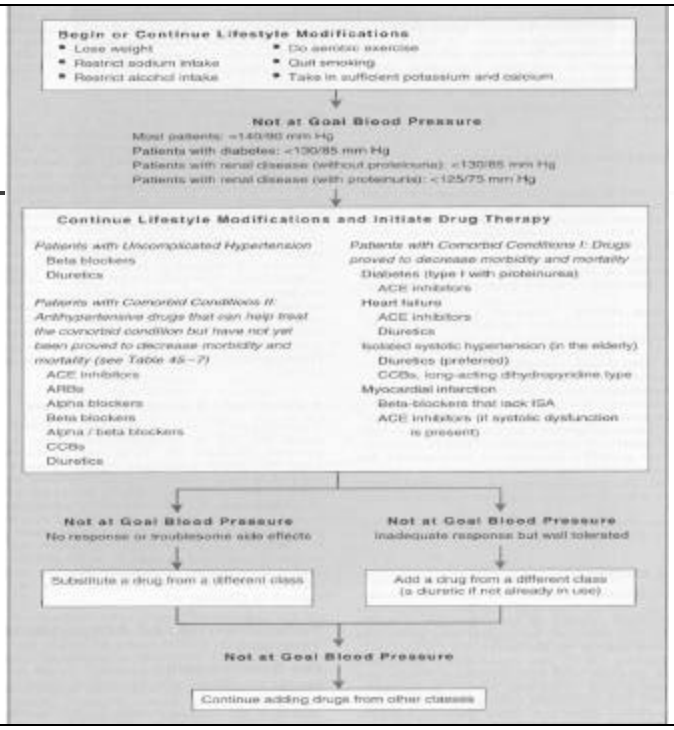


Table 45–4 SUMMARY OF ANTIHYPERTENSIVE EFFECTS ELICITED BY DRUG ACTIONS AT SPECIFIC SITES

Site of Drug Action*	Representative Drug	Drug Effects
1. Brainstem	Clonidine	Suppression of sympathetic outflow decreases sympathetic stimulation of the heart and blood vessels.
2. Sympathetic ganglia	Trimethaphan	Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels.
3. Adrenergic nerve terminals	Guanethidine	Reduced norepinephrine release decreases sympathetic stimulation of the heart and blood vessels.
4. Cardiac beta$_1$ receptors	Propranolol	Beta$_1$ blockade decreases heart rate and myocardial contractility.
5. Vascular alpha$_1$ receptors	Prazosin	Alpha$_1$ blockade causes vasodilation.
6. Vascular smooth muscle	Hydralazine	Relaxation of vascular smooth muscle causes vasodilation.
7. Renal tubules	Chlorothiazide	Promotion of diuresis results in decreased blood volume.
8. Beta$_1$ receptors on juxtaglomerular cells	Propranolol	Beta$_1$ blockade suppresses renin release, resulting in (1) vasodilation secondary to reduced production of angiotensin II, and (2) prevention of aldosterone-mediated volume expansion.
9. Angiotensin-converting enzyme (ACE)	Captopril	Inhibition of ACE decreases formation of angiotensin II and thereby prevents (1) vasoconstriction, and (2) aldosterone-mediated volume expansion.
10. Angiotensin II receptors	Losartan	Blockade of angiotensin II receptors prevents angiotensin-mediated vasoconstriction and aldosterone-mediated volume expansion.



- **Initial Drug Selection**
  - **Based on the presence or absence of comorbid conditions -- pathologic states in addition to hypertension**
    - ***For patients with NO comorbid conditions the preferred drugs for initial therapy are diuretics and beta blockers***
    - ***For patients with comorbid conditions, preferred treatment depends on what the comorbid condition is***
  - **When using two or more drugs to treat hypertension, each drug should come from a different class (different mechanism of action)**
  - **Significant benefits when using two or more drugs**
  - **Dose should be low initially then gradually increase**
  - **Step-Down Therapy-- after BP has been controlled for one year, attempt should be made to reduce dosages and number of drugs in therapeutic regimen**
- **Hypertension is most common complication of pregnancy– use METHHYLDOPA**
- **Hypertensive emergency occurs when diastolic BP > 120 mm Hg – use Nitroprusside (IV)**

- **Pre-Administration Assessment**
  - **Goal – to prevent long term sequelae of hypertension (heart disease, kidney disease, blindness, stroke)**
  - **Baseline Data**
    - ***Blood pressure***
    - ***Electrocardiogram***
    - ***Compete urinalysis***
    - ***Hemoglobin and hematocrit***
    - ***Blood levels of Na^{+}, K^{+}, Ca^{++}, creatinine, glucose, uric acid, triglycerides and cholesterol (total HDL)***
  - **Implement Life-Style changes**
  - **Promote compliance**
  - **Ongoing evaluation**

Chapter 46: Angina Pectoris

- **Sudden pain beneath the sternum, moving into left shoulder**
- **Caused when the oxygen level to heart is too low to meet demand**
- **May occur due to atherosclerosis of coronary arteries**
  - **Angina is a SYMPTOM of disease**
- **Therapy**
  - **Involves prevention of myocardial infarction (MI)**
  - **Involves prevention of myocardial ischemia and anginal pain**
- **Two Drugs used:**
  - **Cholesterol lowering drugs**
  - **Antiplatelet drugs**

- **Antiginal Drugs**
  - **Organic nitrates (nitroglycerin)**
  - **Beta blockers (propranolol)**
  - **Calcium-channel blockers (verapamil)**

- **Factors that contribute to oxygen demand**
  - **Heart rate**
  - **Myocardial contractility**
  - **Intramyocardial wall tension**
    - ***Cardiac preload – amount of tension (stretch) applied to a muscle prior to contraction – determined by ventricular filling or force of venous return***
      - ***An increase in preload will increase stroke volume***
    - ***Cardiac afterload – defined as the load against which a muscle exerts it force (load a muscle must overcome in order to contract) – arterial pressure that left ventricle must overcome***
      - ***As afterload increases, stroke volume will decrease***
      - ***Determined by peripheral resistance***

- **Oxygen supply**
  - ***Coronary vessels***
    - ***Under normal conditions almost all oxygen is removed from coronary arterioles by heart***
    - ***When oxygen demand increases coronary arterioles dilate to increase flow***
    - ***Myocardial coronary flow occurs ONLY during diastole since the vessels are squeezed shut when heart contracts***
- **Angina Pectoris**
  - **Chronic Stable Angina (Exertional Angina)**
    - ***Triggered by increase in physical activity, emotional excitement, large meals and cold exposure***
    - ***Underlying cause is coronary artery disease (CAD) – due to plaque build-up in arterial wall (decreases oxygen supply to heart (in CAD, the arterioles are already dilated and cannot dilate any more to accommodate increased exercise), obesity, smoking, …***
    - ***Must increase cardiac oxygen supply***
      - ***Decrease oxygen demand***
        - ***Drugs: organic nitrates, beta blockers, Ca^{++} channel blockers: to reduce risk of MI patient should receive an antiplatelet drug (aspirin)***
        - ***Avoid things that cause O_2 demand (above)***

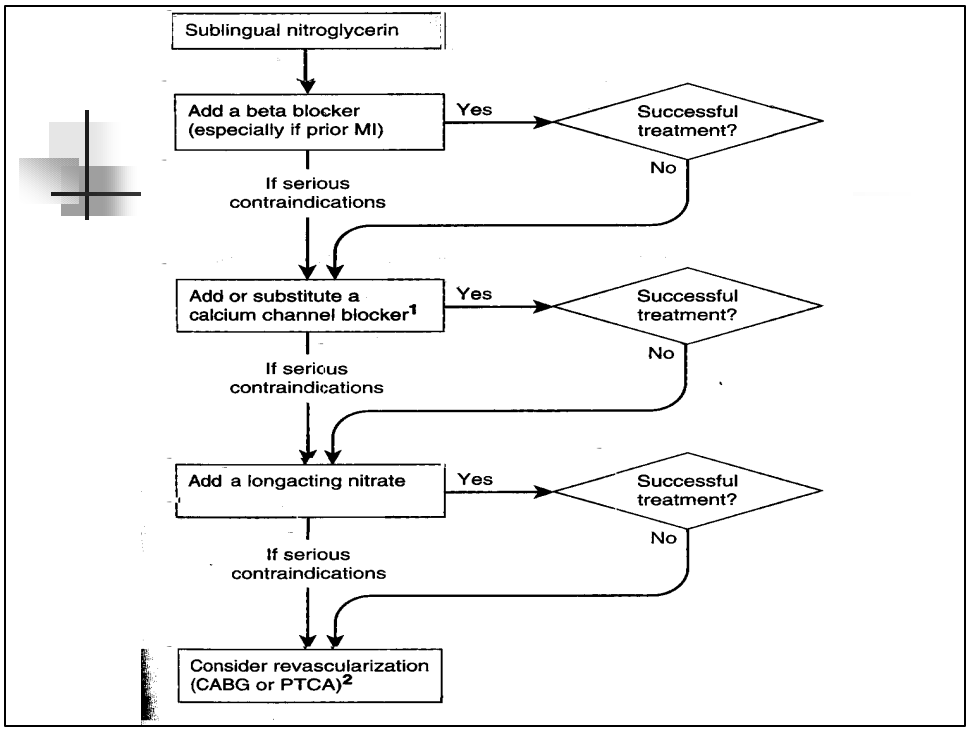
- **Variant Angina (Prinzmetal's Angina, Vasospastic Angina)**
  - **Caused by coronary artery spasm (restricting blood flow to myocardium)**
  - **Can occur at any time**
  - **Treated by increasing cardiac oxygen supply with vasodilators (can work here because angina not due to plaque and restricted blood flow)**
    - ***Treat with Ca^{++} channel blockers and organic nitrates***
- **Drugs do not get at underlying cause of angina with either Stable or Variant Forms**
- **Unstable Angina**
  - **Medical emergency**
  - **Result from severe CAD complicated by vasospasm, platelet aggregation and transient coronary thrombi or emboli**

- **Treatment:**
  - ***Maintain oxygen supply***
  - ***Decrease oxygen demand***
    - ***Anticoagulants (heparin and aspirin) to maintain O_2***
    - ***IV nitrates to increase O_2 supply and decrease demand***
    - ***Beta blockers to reduce O_2 demand***
    - ***Calcium channel blockers if nitrates and beta blodkers do not work***
    - ***Morphine if pain persists***

- **Organic Nitrates (nitroglycerin, since 1879)**
  - **Relieve angina by causing vasodilation**
  - **Acts directly on vascular smooth muscle (VSM), primarily on veins**
  - **Uptake of nitrate → conversion to active form (nitric oxide- NO){requires presence of sulfhydryl groups} → NO activates guanylate cyclase (enzyme that catalyzes formation of cGMP) → decrease of intracellular Ca^{++} levels → leads to vasodilation**

- **Mechanism of Action of Nitroglycerin (Cont')**
  - By dilating veins, nitroglycerin decreases venous return of blood to heart, decreases ventricular filling, and results in decreased myocardial wall tension (pre-load) and thereby decreases O_2 demand
  - Does not increase blood flow to ischemic areas of heart
  - Nitroglycerin relieves angina by acting on the peripheral circulation, not by affecting coronary blood flow
  - Nitroglycerin is highly lipid soluble – administered sublingual, buccal, transdermal)
  - Nitroglycerin undergoes rapid metabolism and inactivation by hepatic enzymes (½ life of 5-7 minutes)
- **Tolerance develops quickly to nitroglycerin-induced vasodilation**
  - By depletion of sulfhydryl groups? & cannot convert NO to active form

- **Beta Blockers (propranolol)**
  - Provide sustained protection against effort-induced angina (NOT effective against vasospastic angina)
  - Therapeutic effect comes from blockage of beta receptors in heart which decrease heart rate and contractility as well as reducing arterial pressure (afterload– reduces heart rate due to pressure effects), i.e. , increase time in diastole and get more blood flowing through myocardial arterioles
- **Calcium Channel Blockers (verapamil)**
  - Result in arteriole dilation and reduction of peripheral resistance and can relax vasospasm's
  - Treats both stable and variable angina
- **Revasularization Therapy (CABG and PTCA)**
  - Coronary artery bypass graft surgery (CABG)- increase blood flow to ischemic areas
  - Precutaneous Transluminal Coronary Angioplasty
    - *With stable angina*
    - *Deflated balloon inserted into femoral artery and threaded up to aorta → inflated to flatten obstruction*



Chapter 47: Heart Failure

- **Ventricular dysfunction, reduced cardiac output, insufficient tissue perfusion, signs of fluid retention (edema)**
  - **Congestive heart failure- due to fluid build-up in lungs**
- **Principle Drugs used for treatment:**
  - **Angiotensin-converting enzyme (ACE)**
  - **Diuretics**
  - **Beta blockers**
  - **Digoxin**
  - **Spironolactone (new)**
- **Major causes**
  - **Chronic hypertension**
  - **Myocardial infarction**
  - **Valvular disease, CAD, congenital heart disease, aging of myocardium**

- **Early Symptoms**
  - **Fatigue**
  - **Shortness of breath**
  - **Venous distention**
  - **Peripheral edema**
  - **Pulmonary edema**
- **After initial heart failure the heart undergoes remodeling (ventricles enlarge and become more spherical, which puts more strain on heart)**
  - **Remodeling mediated by neuorohormonal factors:**
    - ***Renin-angiotensin system***
    - ***Cause cardiac fibrosis and myocyte death***
    - ***Produces decline in heart function (cardiac output)***
  - **Cardiac enlargement**
  - **Decrease in arterial pressure (increase heart rate)**
  - **Increased venous tone (increase ventricular filling)**

- **Water Retention**
  - ***Reduced cardiac output causes a reduction in renal blood flow, decreases glomerular filtration, and urine production decreased (increase in blood volume)***
  - ***Activation of renin-angiotensin system in response to reduce renal blood flow. Promotes water retention by increasing levels of aldosterone , (retention of sodium and water) and angiotensin II (constriction of renal blood vessels, decreases urine production)***
- **Vicious Cycle of "Compensatory" Physiologic Responses**
  - **Reduce cardiac output leads to compensatory responses**
    - ***Cardiac dilation***
    - ***Activation of sympathetic nervous system***
    - ***Activation of renin-angiotensin system***
    - ***Retention of water and expansion of blood volume***
  - **Can make things worse**
    - ***Excessive heart rate leads to reduced ventricular filling***
    - ***Excessive arterial pressure can cause pulmonary and peripheral edema***

- **Classification of Heart Failure Severity**
  - **Class I – no limitation of ordinary physical activity**
  - **Class II – slight limitation of physical activity: normal activity produces fatigue, dyspnea, palpitations or angina**
  - **Class III – marked limitation of physical activity: mild activity produces symptoms**
  - **Class IV – Symptoms occur at rest**

- **Treatment Goals & Strategies**
  - **Relief of pulmonary and peripheral congestive symptoms**
  - **Improvement of functional capacity and quality of life**
  - **Prolongation of life expectancy**
- **To Achieve these goals**
  - **Treat correctable underlying causes (hypertension, dysrhythemias and aortic stenosis)**
  - **Implement Non-Drug measures**
  - **Drug therapy if no response from first two**

- **Drug Overview**
  - **ACE Inhibitors-**
    - ***vasodilators- Drugs that dilate veins decrease venous pressure. This decreases venous return and cardiac filling, which decreases ventricular stretching and cardiac O_2 demand. Also decrease pulmonary congestion and peripheral edema***
    - ***Drugs that dilate arterioles -- reduces cardiac afterload and allows stroke volume and cardiac output to increase. By increasing cardiac output and dilating arterioles in the kidney, these drugs increase renal perfusion and promote loss of fluid.***
  - **Diuretics –**
    - ***First line drugs for patients with signs of volume overload***
    - ***By reducing blood volume, these drugs decrease venous pressure, arterial pressure, pulmonary edema, peripheral edema, and cardiac dilation***
  - **Beta Blockers**
    - ***Use with CAREFUL CONTROL – Can improve left ventricular ejection, increase exercise tolerance, slow progression of heart failure, reduce need for hospitalization, prolong survival***

- **Spironolactone: An Aldosterone Receptor Blocker**
  - **Can reduce symptoms, decrease hospitalizations, and prolong life in patients with moderate to severe heart failure**
  - **Blocks receptors for aldosterone in heart and blood vessels**
    - ***Aldosterone promotes myocardial remodeling (impairs pumping of heart)***
    - ***Aldosterone promotes myocardial fibrosis (increases risk of dysrhythmias)***
    - ***Aldosterone activates sympathetic nervous system and suppresses NE uptake in heart (produces dysrhythmias and ischemia)***
    - ***Aldosterone promotes vascular fibrosis (decreases arterial elasticity and increases hypertension)***
    - ***Aldosterone promotes baroreceptor dysfunction***

- **Criteria for selecting specific drugs**
  - **ACE inhibitors – all patients (in absence of contra-indications) should take ACE inhibitors. If edema is present, should take diuretic also.**
  - **Diuretics – all patients with edema should receive a diuretic. Assessment by body weight to see if treatment is effective. Should not be used alone. Aspirin and non-steroidal anti-inflammatory agents decrease effects of diuretics and should not be taken**
  - **Beta Blockers – all patients with class II or III heart failure should receive a beta blocker (in combination with an ACE inhibitor and diuretic**
  - **Digoxin -- used in combination with ACE inhibitors, diuretics and beta blockers.**
    - ***Has not been shown to prolong life as others above***
  - **Spironolactone – shown to prolong life and should be given to all patients**

- **Cardiac Glycosides (Digitalis)**
  - **Naturally occurring compound**
  - **Effects mechanical and electrical properties of heart**
    - ***Can suppress dysrhythmias and improve mechanical function of heart***
  - **High incidence of toxicity**
  - **Positive inotropic action (increases force of ventricular contraction and increases cardiac output)**
    - ***Inhibits enzyme: sodium, potassium-ATPase***
    - ***By inhibition, calcium accumulates in heart muscle which causes increased contractile force of the myocardium (increases interaction of actin-myosin proteins)***

Chapter 48: Antidysrhythmic Drugs

- **Abnormality in the rhythm of the heart**
  - **In mildest forms dysrhythmias have only mild effects on cardiac output**
  - **In severe forms they can disable heart so that no output occurs**
- **Two Types of dysrhythmias**
  - **Tachydysrhythmias – increased heart rate**
  - **Bradydysrhythmias – heart rate is slowed**
- **Drugs that treat these diseases can cause these diseases**
- **Use of these drugs in decreasing because they may have increased risk/benefit effects**

- **Dysrhythmias**
  - **Result from: alteration in electrical impulses that regulate cardiac rhythm**
- **SA Node-**
  - **Pacemaker of heart**
  - **Impulses spread rapidly from SA node so atria contract together**
  - **Impulses move along internodal pathways to AV node where there is a short delay prior to ventricular contraction**
  - **AV node transmits impulses through ventricles using His-Purkinje System to produce simultaneous ventricular contraction**
- **EKG**
  - **P wave- depolarization in atria (atrial contraction)**
  - **QRS wave- depolarization of ventricles (ventricular contraction)**
  - **T wave- repolarization of ventricles (not associated with physical activity of heart)**

- **PR wave – represents the time between onset of the P wave and onset of the QRS complex.**
  - ***Prolongation indicates delayed AV conduction***
- **QT wave – the time between onset of the QRS complex and completion of the T wave.**
  - ***QT prolongation indicates delayed ventricular repolarization***
- **Ventricular dysrhythmias – disrupt cardiac pumping to a greater degree than supraventricular dysrhythmias**

- **Quinidine- (Class I) blocks sodium channels and delays ventricular repolarization**
- **Propranolol- (Class II) blocks cardiac beta$_1$ receptors**
- **Bretylium – (Class III) only used for short term therapy. Blocks release of NE from Sympathetic nerves**
- **Verapamil – (Class IV) blocks cardiac calcium channels and reduces SA node activity (slows)**

- **Dysrhythmias arise from 2 causes**
  - **Disturbances of impulse formation – occurs in either SA or AV nodes, and Purkinje system**
  - **Disturbances in impulse conductivity –) AV block= delayed conduction (not prevented entirely)**
- **Classification of Antidysrhythmic Drugs**
  - **Class I – sodium channel blockers**
    - ***Class I A –***
    - ***Class I B –***
    - ***Class I C –***
    - ***Other Class I –***
  - **Class II – beta blockers**
  - **Class III – potassium Channel Blockers (drugs that delay repolarization)**
  - **Class IV – Calcium Channel Blockers**
  - **Other Antidysrhythmic Drugs --**

Table 48–1 VAUGHAN WILLIAMS CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

Class I: Sodium Channel Blockers

Class IA
- Quinidine [Quinidex, others]
- Procainamide [Pronestyl, others]
- Disopyramide [Norpace]

Class IB
- Lidocaine [Xylocaine]
- Phenytoin [Dilantin]
- Mexiletine [Mexitil]
- Tocainide [Tonocard]

Class IC
- Flecainide [Tambocor]
- Propafenone [Rythmol]

Other Class I
- Moricizine [Ethmozine]

Class II: Beta Blockers
- Propranolol [Inderal]
- Acebutolol [Sectral]
- Esmolol [Brevibloc]

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)
- Amiodarone [Cordarone]
- Bretylium [Bretylol]
- Sotalol [Betapace]

Class IV: Calcium Channel Blockers
- Diltiazem [Cardizem, others]
- Verapamil [Isoptin, Calan, Verelan]

Other Antidysrhythmic Drugs
- Adenosine [Adenocard]
- Digoxin [Lanoxin, Lanoxicaps]
- Ibutilide [Corvert]

Table 48–2 TREATMENT OF COMMON DYSRHYTHMIAS

Type of Dysrhythmia	Acute Treatment: *Preferred*	Acute Treatment: *Alternatives*	Long-Term Suppression
Supraventricular			
Supraventricular tachycardia	Vagotoni naneuver	To terminate: Beta blocker (II) Verapamil (IV) Diltiazem (IV) Digoxin Adenosine	Quinidine (IA)* Procainamide (IA) Other drugs
rial flutter and fibrillation	DC cardioversion	To slow ventricular respons Beta blocker (II) Verapamil (IV) Diltiazem (IV) Digoxin	Quinidine (IA)* Procainamide (I Other drugs
ntricular			
Sustained ventricul tachycardia	DC ardioversion	Lidocaine (IB) Procainamide (IA) Amiodarone (III) Bretylium (III)	Quinidine (IA) Procainamide (IA Sotalol (III) Other drugs
ibr	Defibrillation	Lidocaine (IB)† Procainamide (IA)† Amiodarone (III) Bretylium (III)†	Amiodarone (III)
ent ilar premature beat	Asymptomatic patients need no treatment	Beta blocker (II)‡	
Digoxin-induced dysrhythmias	Digoxin-immune Fab (digoxin antibody fragments)		

Quinidine may *inc* se mortality is these patients.
Defibrillation is the reatment of choice. Drugs are given to prevent recurrence.
Beta blockers are u d only if the dysrhythmia is symptomat

Table 48–3 PROPERTIES OF ANTIDYSRHYTHMIC DRUGS

Drug	Usual Route	Effects on the EKF	Major Antidysrhythmic Applications
Class IA			
Quinidine	PO	Widens QRS, prolongs QT	Broad spectrum: used for long-term suppression of ventricular and supraventricular dysrhythmias
Procainamide	PO	Widens QRS, prolongs QT	Broad spectrum: similar to quinidine, but toxicity makes it less desirable for long-term use
Disopyramide	PO	Widens QRS, prolongs QT	Ventricular dysrhythmias
Class IB			
Lidocaine	IV	No significant change	Ventricular dysrhythmias
Mexiletine	PO	No significant change	Ventricular dysrhythmias
Tocainide	PO	No significant change	Life-threatening ventricular dysrhythmias
Phenytoin	PO	No significant change	Digoxin-induced ventricular dysrhythmias
Class IC			
Flecainide	PO	Widens QRS, prolongs PR	Life-threatening ventricular dysrhythmias
Propafenone	PO	Widens QRS, prolongs PR	Life-threatening ventricular dysrhythmias
Other Class I			
Moricizine	PO	Widens QRS, prolongs PR	Life-threatening ventricular dysrhythmias
Class II			
Propranolol	PO	Prolongs PR, bradycardia	Dysrhythmias caused by excessive sympathetic activity; control of ventricular rate in patients with supraventricular tachydysrhythmias
Acebutolol	PO	Prolongs PR, bradycardia	Premature ventricular beats
Esmolol	IV	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Class III			
Amiodarone	PO	Widens QRS, prolongs PR and QT	Life-threatening ventricular dysrhythmias
Bretylium	IV	Prolongs QT	Life-threatening ventricular dysrhythmias
Sotalol	IV	Prolongs PR and QT, bradycardia	Life-threatening ventricular dysrhythmias
Class IV			
Verapamil	PO	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Diltiazem	IV	Prolongs PR, bradycardia	Same as verapamil
Others			
Adenosine	IV	Prolongs PR	Termination of paroxysmal supraventricular tachycardia
Digoxin	PO	Prolongs PR, depresses ST	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Ibutilide	IV	Prolongs QT	Atrial flutter, atrial fibrillation

Chapter 49: LDL Cholesterol Level Regulating Drugs

- **Coronary arterial disease (CAD) starts with development of a fatty streak in the arterial wall, followed by deposition of fibrous plaque**
  - **As plaque grows it begins to occlude artery, blocks blood flow, causes angina**
  - **May lead to formation of thrombi leading to MI**
- **Risk of CAD directly related to levels of LDL cholesterol in blood**
- **Cholesterol –**
  - **Component of all cell membranes**
  - **Required for synthesis of hormones (estrogen, progesterone, testosterone, adrenal corticosteroids)**
  - **Comes from dietary sources and liver cells**

- **Enzyme involved in cholesterol synthesis**
  - **Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase**
  - **Drugs that inhibit this enzyme are most effective at lowering cholesterol (LDL)**
  - **During night cholesterol synthesis increases: give drug at NIGHT**
  - **Dietary saturated fats increase circulating LDL (substrates for cholesterol production in liver)**
  - **Dietary cholesterol inhibits endogenous cholesterol synthesis**
- **Low-Density Lipoproteins (LDL)**
  - **Account for 60-70% of cholesterol in blood**
  - **Role of LDL is to deliver cholesterol to non-hepatic tissue**
- **High-Density Lipoproteins (HDL)**
  - **Account for 20-30% of all cholesterol in blood**
  - **Function to deliver cholesterol from peripheral tissues back to liver (promote removal of cholesterol)**

- **Role of LDLs in atherosclerosis**
  - **When cholesterol moves from arteriole lumen into space that underlies the arterial epithelium the LDLs undergo OXIDATION which causes**
    - ***Attraction of monocytes which convert into macrophages***
    - ***Inhibition of macrophage motility***
    - ***Macrophages take up cholesterol that has not been oxidized***
    - ***Macrophages become cytotoxic and damage endothelium and after inflammatory response atherosclerosis plaque develops***
- **Test for cholesterol levels every 5 years over age of 20**
- **Management of high LDL cholesterol**
  - **Diet Modification**
    - ***Reduction of LDL cholesterol –***
      - ***Lower total fat to < 30% of fat intake***
      - ***Limit saturated fats to < 10% of caloric intake***
      - ***Limit cholesterol to < 300 mg/day***
    - ***Reduction of body weight***

Table 49–2 CHOLESTEROL TESTING AND FOLLOW-UP FOR INDIVIDUALS WITHOUT CAD

Total Cholesterol

mg/dl	*Classification*	*Recommended Follow-up*
<200	Desirable blood cholesterol	For patients with HDL cholesterol ≥35 mg/dl: repeat tests of total and HDL cholesterol within 5 years For patients with HDL cholesterol <35 mg/dl: obtain lipoprotein analysis; further management based on LDL cholesterol level
200–239	Borderline high-risk blood cholesterol	For patients with HDL cholesterol ≥35 mg/dl and less than two CAD risk factor*: provide dietary information and recheck total and HDL cholesterol within 1 to 2 years For patients with HDL cholesterol <35 mg/dl or two or more CAD risk factors: obtain lipoprotein analysis; further management based on LDL cholesterol level
>240	High-risk blood cholesterol	Obtain lipoprotein analysis; further management based on LDL cholesterol level

LDL Cholesterol

mg/dl	*Classification*	*Recommended Follow-up*
<130	Desirable LDL cholesterol	Retest total and HDL cholesterol within 5 years
130–159	Borderline high-risk LDL cholesterol	For patients with less than two CAD risk factor*: recheck LDL cholesterol annually For patients with two or more CAD risk factors: institute dietary therapy to bring LDL cholesterol below 130 mg/dl
160–189	High-risk LDL cholesterol	For patients with less than two CAD risk factor: institute dietary therapy to bring LDL cholesterol below 160 mg/dl For patients with two or more risk factors; institute dietary therapy, followed by drug therapy if needed, to bring LDL cholesterol below 130 mg/dl
>190	High-risk LDL cholesterol	For patients with less than two CAD risk factor: institute dietary therapy, followed by drug therapy if needed, to bring LDL cholesterol below 160 mg/dl For patients with two or more risk factors: institute dietary therapy followed by drug therapy to bring LDL cholesterol below 130 mg/dl

*CAD risk factors: see Table 49–3.
Based on recommendations in the Summary of the Second Report of the National Cholesterol Education Program Adult Treatment Panel, published in JAMA 269:3015, 1993.

Table 49–4 RECOMMENDED DIETARY MODIFICATIONS TO LOWER SERUM CHOLESTEROL

Food Type	Recommendation: *Choose*	Recommendation: *Decrease*
Fish, chicken, turkey, and lean meats	Fish; poultry without skin; lean cuts of beef, lamb, pork, or veal; shellfish	Fatty cuts of beef, lamb, or pork; spareribs; organ meats; regular cold cuts; sausage; hot dogs
Skim and low-fat milk, cheese, yogurt, and dairy products	Skim and 1% fat milk (liquid, powdered, evaporated), buttermilk	4% fat milk (regular, evaporated, condensed), 2% fat milk, cream, half and half, imitation milk products, most nondairy creamers, whipped toppings
	Nonfat (%) or low-fat yogurt	Whole-milk yogurt
	Low-fat cottage cheese (1% or 2% fat)	Whole-milk cottage cheese (4%)
	Low-fat cheeses, farmer or pot cheeses (all of these cheeses should be no more than 2 to 6 gm of fat per ounce)	All natural cheeses (e.g., blue, Roquefort, Camembert, cheddar, Swiss)
		Cream cheese (including low-fat and "light" types), sour cream (including low-fat and "light" types)
	Sherbert, sorbet	Ice cream
Eggs	Egg whites (2 whites = 1 whole egg in recipes), cholesterol-free egg substitutes	Egg yolks*
Fruits and vegetables	Fresh, frozen, canned, and dried fruits and vegetables	Vegetables prepared in butter, cream, and other sauces
Breads and cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies	Commercial baked goods: pies, cakes, muffins, doughnuts, croissants, biscuits, high-fat crackers, high-fat cookies
	Rice, pasta	Egg noodles
	Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc.)	Breads in which eggs are a major ingredient
Fats and oils	Unsaturated vegetable oils: corn, olive, rapeseed (canola oil), safflower, sesame, soybean, sunflower	Butter, coconut oil, palm oil, palm kernel oil lard, bacon fat
	Margarine (regular or diet),* shortening made from one of the unsaturated oils listed above	
	Mayonnaise, salad dressings made with one of the unsaturated oils listed above, low-fat dressings	Dressings made with egg yolk
	Seeds and nuts	Coconut
	Baking cocoa	Chocolate

- **HMG CoA Reductase Inhibitors ("Statins")**
  - **Most effective at lowering LDL cholesterol**
  - **Few adverse side effects (muscle cramps, liver function)**
  - **Reduce LDL cholesterol by increasing number of LDL receptors on hepatocytes**
- **Bile-acid binding resins**
  - **Reduce LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes**
  - **Can form complexes with other drugs and prevent their absorption (take oral medications 1 hour before or 4 hours after bile-binding resins)**

Chapter 50: Anticoagulant, Anti-platelet and Thrombolytic Drugs

- **Hemostasis**
  - **Process by which bleeding is stopped**
    - ***Formation of platelet plug***
      - ***When platelets come in contact with collagen on surface of damaged blood vessels***
      - ***Platelets adhere, become activated and leads to platelet aggregation***
      - ***For aggregation to occur fibrinogen bridges msut be made***
      - ***Plug is unstable without fibrin reinforcement***
    - ***Reinforcement of platelet plug with fibrin (coagulation)***
      - ***Intrinsic and extrinsic systems***
      - ***Coagulatin factors VII, IX, X and prothrombin require vitamin K for synthesis***
      - ***Inactivation of clotting factors by antithrombin III***

- **Plasmin**
  - ***Enzyme that digests fibrin meshwork***
  - ***Produced through activation of precursor- plasminogen***
  - ***Thrombolytic drugs – act by promoting conversion of plasminogen into plasmin***
    - ***Streptokinase***
    - ***Urokinase***
    - ***Alteplase***
    - ***Antistreplase***
- **Thrombosis**
  - ***Blood clot formed within a blood vessel or within the heart***
  - ***Arterial thrombosis – begins with adhesion of platelets to the arterial wall***
    - ***After adhesion platelets release ADP (adenosine diphosphate) and TXA_2 (thromboxane A_2) which attract additional platelets***
    - ***Occlusion of artery occurs***
    - ***Reinforcement of clot occurs with fibrin formation***
  - ***Venous thrombus – develop at sites of slow blood flow***
    - ***Has long tail from which emboli can be released***

- **Drugs used to treat thromboembolic disorders**
  - **Anticoagulants (heparin, warfarin) – disrupt coagulation cascade and suppress production of fibrin**
  - **Antiplatelet drugs (aspirin, tirofiban) – inhibit platelet aggregation**
  - **Thrombolytic drugs (alteplase, streptokinase) – promote lysis of fibrin and cause dissolution of thrombi**
- **Heparin**
  - **Rapid acting**
  - **Administered by injection**
  - **Purified from lungs of cattle and intestines of pigs**
  - **Action –**
    - ***Helps antithrombin III inactivate thrombin, factor Xa, and others***
    - ***Suppresses formation of fibrin***
  - **Therapeutic Uses**
    - ***Useful in prophylaxis of venous thrombosis***
    - ***Pulmonary embolism***
    - ***Acute myocardial infarction***

- **Oral Anticoagulants**
  - **Used to prevent thrombosis**
  - **Have a delayed onset of action (unlike heparin) – cannot use in emergency situations!**
- **Warfarin (Coumadin)**
  - **Used to kill rats (induced bleeding and rats bled to death)**
  - **Suppresses coagulation by acting as an antagonist of vitamin K (blocks synthesis of vitamin K by liver)**
  - **Indicated for treatment in long-term prophylaxis**
    - ***Prevention of venous thrombosis and associated pulmonary embolism***
    - ***Prevention of thromboembolism in patients with prosthetic heart valves***
    - ***Prevention of thrombosis during atrial fibrillation***

- **Antiplatelet Drugs**
  - **Suppress platelet aggregation**
  - **Used to suppress formation of thrombosis in arteries (as opposed to heparin and warfarin which are used to treat thrombi in veins)**
  - **Three major groups of antiplatelet drugs:**
    - ***Aspirin***
      - ***Causes irreversible inhibition of cyclooxygenase, enzyme necessary for platelets to produce (TXA_2) thromboxane A_2***
      - ***Inhibits platelet aggregation***
      - ***TXA_2 induces: promotes platelet aggregation, vasoconstriction***
    - ***ADP receptor antagonists***
      - ***Block ADP receptors on platelet surface and prevent ADP-stimulated aggregation***
    - ***GP IIb/IIIa receptor antagonists***
      - ***Administration by IV & expensive***
      - ***Cause reversible blockade of platelet GP IIb/IIIa receptors and inhibit final step in aggregation of platelets***

- **Thrombolytic Drugs (Streptokinase)**
  - **Given to remove thrombi that have already been formed**
  - **Use of these drugs has serious risk of bleeding**
  - **Streptokinase**
    - ***First binds to plasminogen (pre-cursor to plasmin which degrades fibrin) and catalyzes its conversion into plasmin***
    - ***Plasmin also degrades fibrinogen and other clotting factors***
  - **Therapeutic Uses**
    - ***Acute coronary thrombosis (acute MMI)***
    - ***DVT***
    - ***Massive pulmonary emboli***
  - **Streptokinase is a foreign antigen that comes from the bacteria streptococci**
    - ***Can elicit allergic reaction and neutralization of streptokinase***

Chapter 51: Management of Myocardial Infarction

- **MI = necrosis of myocardium resulting from acute occlusion of a coronary artery**
  - **Risk factors**
    - ***Family history of MI***
    - ***Sedentary lilfestyle***
    - ***Obesity***
    - ***High serum cholesterol***
    - ***Hypertension***
    - ***Smoking***
    - ***Diabetes***
  - **One third of people with MI die within 20 days**

- **Diagnosis of MI**
  - **Presence of chest pain –**
    - ***must differentiate from angina (lasting longer than 30 minutes and non-responsive to nitroglycerin)***
  - **EKG changes –**
    - ***Elevation of ST segment, prominent Q wave***
    - ***Inverted T wave may occur over time***
  - **Elevated serum levels of creatine kinase and troponin**
    - ***Isozyme of creatine kinase (CK-MB) found primarily in cardiac muscle as opposed to skeletal muscle. If found means heart muscle injury (peak at 24 hours after MI)***
- **Management of MI**
  - **Acute phase management – refers to interval between onset of symptoms and discharge from the hospital (6-10 days)**
    - ***Goal is to bring oxygen supply back in balance with oxygen demand. 1st few hours are most critical***
    - ***Reperfusion therapy – restore blood flow***
    - ***Thrombolytic therapy – dissolve clots***
      - ***Drugs***
      - ***Primary Coronary Angioplasty***

Chapter 52: Drugs for Deficiency Anemias

- **Anemia- decrease in erythrocyte number, size, or hemoglobin content**
- **Causes**
  - **Blood loss**
  - **Hemolysis**
  - **Bone marrow dysfunction**
  - **Deficiencies of substances essential for RBC formatin**
    - ***Iron***
    - ***Vitamin B_{12}***
    - ***Folic acid***
  - **RBC development**
    - ***Proerythroblasts → erythroblasts (have Hb) → reticulocytes (immutrure & go into circulation) → erythrocytes (loss of nucleus)***

- **Development of RBCs involve**
  - **Healthy bone marrow**
  - **Erythropoietin**
  - **Iron (for hemoglobin synthesis)**
  - **Vitamin B_{12}**
  - **Folic acid (for DNA synthesis)**
- **Iron Deficiency**
  - **Essential for function of hemoglobin, myoglobin and many enzymes**
    - ***Uptake by mucosal cells of small intestine***
    - ***Storage within mucosal cells in form of ferritin***
    - ***Binding to transferrin for distribution around body***
      - ***Most of iron taken up by cells of bone marrow for incorporation into hemoglobin***
      - ***Some taken up by liver***
      - ***Some taken up by muscle (for production of myoglobin)***
      - ***Recycling of iron occurs***
        - ***During growth and pregnancy iron needs high***

- **Dietary sources**
  - **Liver, egg yolk, brewers yeast, wheat germ, muscle meats, fish, fowl, cereal grains, beans, green leafy vegetables**
  - **Use of iron pots can leach iron and is a good source of iron n diet**
- **Iron Deficiency**
  - **Results when there is an imbalance between uptake and demand (usually increased demand)**
    - ***Blood expansion during pregnancy coupled with RBC synthesis by developing fetus***
    - ***Blood volume expansion during infancy and early childhood***
    - ***Chronic blood loss (GI origin?)***
  - **Consequences**
    - ***Absence of iron for hemoglobin synthesis and reduced oxygen carrying capacity***
  - **Toxicity in young children**

- **Iron Preparations**
  - **Ferrous Sulfate – least expensive – Oral**
  - **Iron Dextran – Parenteral -- patients who might have intestinal disease and/or are unable to absorb iron must receive and injection**
- **Assessment**
  - **Determine cause of iron deficiency**
  - **Objective is to increase the production of hemoglobin and erythrocytes -- if successful the reticulocytes will increase w/i 4-7 days, within 1 week hemoglobin and hematocrit levels will increase**
  - **If treatment fails must determine**
    - ***Compliance***
    - ***Continued bleeding***
    - ***Inflammatory disease***
    - ***Malabsorption of iron***

- **Vitamin B_{12} Deficiency**
  - **Compounds that contain cobalt**
  - **Deficiency causes anemia and injury to nervous system (neurological damage takes a very long time to repair, or never)**
  - **Disruption of DNA synthesis (1º effect on cells that have high rate of division)**
  - **Pernicious anemia – due to lack of intrinsic factor**
  - **Causes demyelination of nerves**
  - **Megaloblastic anemia (folic acid deficiency)**
    - ***Poor diet (alcoholic) & malabsorption (intestinal disease)***

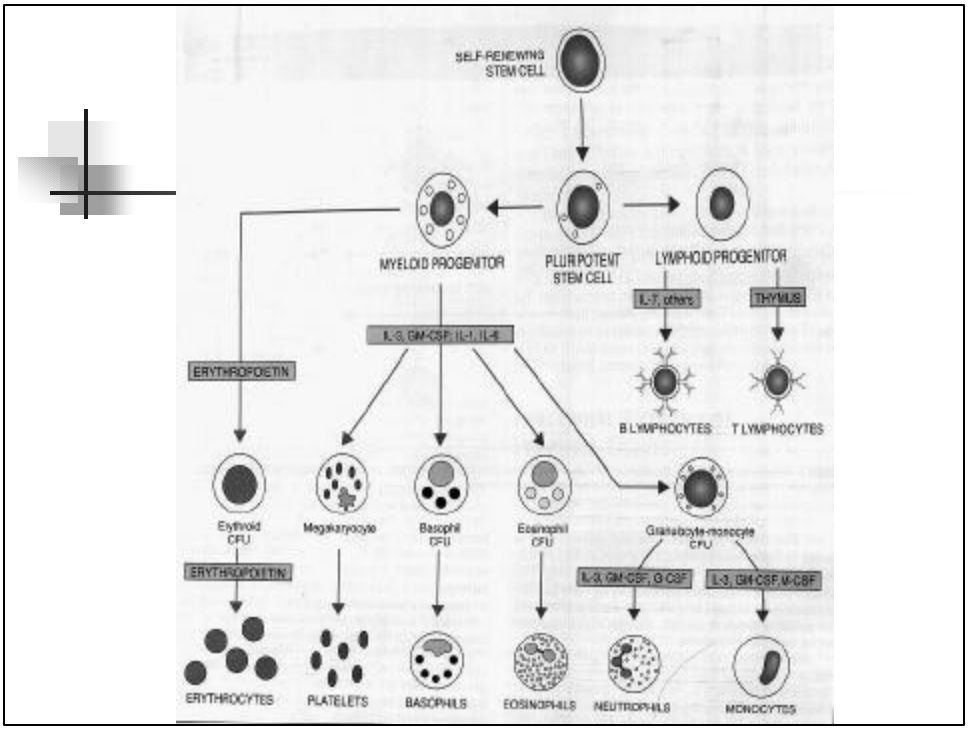
B_{12}
Folic Acid ---→ Folic Acid ---→ --→ DNA synthesis ---→
(inactive) (active)
normal maturation of RBCs

Absorption of B12 requires the presence of intrinsic factor which is secreted by parietal cells of stomach

Chapter 53: Growth Factors – Hematopoietic & Thrombopoietic

- **Hematopoietic Growth Factors**
  - **Production of new RBCs**
    - ***Erythropoietin – growth factor***
    - ***Apoetin Alfa – recombinant DNA growth factor***
      - ***(1)To maintain erythrocyte counts in patients with chronic renal failure and (2) in HIV-patients taking zidovudine (AZT) and (3) in patients with non-myeloid malignancies who have anemia secondary to chemotherapy***
    - ***Filgrastim (Granulocyte Colony-Stimulating Factor) – DNA recombination***
      - ***Increases production of granulocytes***
      - ***For patients who are undergoing cancer chemotherapy to reduce risk of infection***
      - ***For bone marrow transplant recipients***
      - ***Harvesting of Peripheral Blood Progenitor Cells prior to chemotherapy***

- **Sargramostim (Granulocyte-Macrophage Colony Stimulating Factor -- GM-CSF)**
  - ***Increase production of neutrophils, monocytes, macrophages and eosinophils***
  - ***Adjunct ot autologous bone marrow transplantation***
- **Thrombopoietic Growth Factors (Oprelvekin or IL-11)**
  - ***Recombinant DNA technology***
  - ***Given to stimulate platelet production in patients undergoing myelosuppressive chemotherapy for non-myeloid cancers (minimizes thrombocytopenia)***


SELF-RENEWING STEM CELL
MYELOID PROGENITOR
PLURIPOTENT STEM CELL
LYMPHOID PROGENITOR
IL-7, others
THYMUS
IL-3, GM-CSF, IL-1, IL-6
ERYTHROPOIETIN
B LYMPHOCYTES
T LYMPHOCYTES
Erythroid CFU
Megakaryocyte
Basophil CFU
Eosinophil CFU
Granulocyte-monocyte CFU
ERYTHROPOIETIN
IL-3, GM-CSF, G-CSF
IL-3, GM-CSF, M-CSF
ERYTHROCYTES
PLATELETS
BASOPHILS
EOSINOPHILS
NEUTROPHILS
MONOCYTES