Unit III: Chemotherapy

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(Unit III: Chemotherapy)

Pharmacology of commonly used:

- Penicillin
- Cephalosporin's
- Aminoglycocides
- Macrolide & Broad Spectrum Antibiotics
- Sulphonamides
- Quinolones
- Ant amoebic
- Antimalarial
- Antithelmintic
- Antiscabies agents
- Antiviral & Antifungal agents
- Antitubercular drugs
- Antileprosy drugs
- Anticancer drugs
- Immune-suppressants.

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TABLE 12.2 Terminology of Chemotherapy

Chemotherapeutic drug	Any chemical used in the treatment, relief, or prophylaxis of a disease
Prophylaxis	Use of a drug to prevent imminent infection of a person at risk
Antimicrobial chemotherapy	The use of chemotherapeutic drugs to control infection
Antimicrobials	All-inclusive term for any antimicrobial drug, regardless of its origin
Antibiotics	Substances produced by the natural metabolic processes of some microorganisms that can inhibit or destroy other microorganisms
Semisynthetic drugs	Drugs which are chemically modified in the laboratory after being isolated from natural sources
Synthetic drugs	The use of chemical reactions to synthesize antimicrobial compounds in the laboratory
Narrow spectrum (limited spectrum)	Antimicrobials effective against a limited array of microbial types—for example, a drug effective mainly on gram-positive bacteria
Broad spectrum (extended spectrum)	Antimicrobials effective against a wide variety of microbial types—for example, a drug effective against both gram-positive and gram-negative bacteria

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Definition
Chemotherapy & Antibiotics:

- **Chemotherapy:** Chemotherapy is the treatment of infections by substances which destroy or suppress bacteria and other microorganism. The substances / Agents used may natural synthetic or semi – synthetic in nature.
- **Antibiotics:** An antibiotic is a chemical substance produced by microorganism which prevents the growth of other microorganism or kills the other microorganism. These are natural substances

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Chemotherapy

It is a method of therapy of infectious disease and cancer with chemical agents – chemotherapeutic medicines

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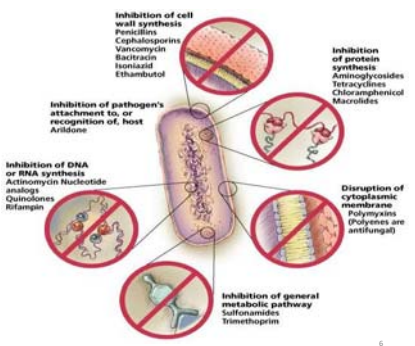
Drug Mechanisms of Action



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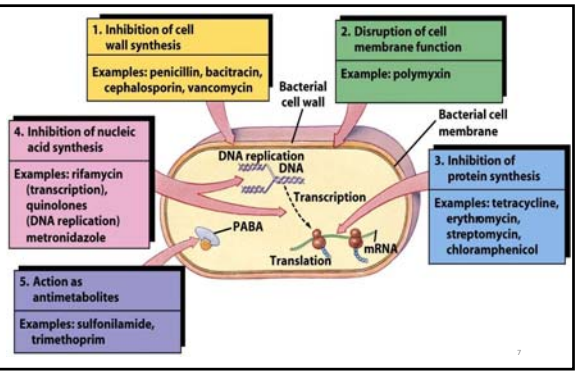

Antibiotics Classified as:

- **According to the mode of action on Bacteria:**
- **According to the type of Bacteria:**
- **According to the effectiveness against microorganism:**

According to the mode of action on Bacteria:

- **Bacteriostatic:** These antibiotics inhibit the growth & multiplication of Bacteria. Eg. Tetracycline, Chloramphenicol, Sulphonamides, Dapsone, Erythromycin, Clindamycin.
- **Bactericidal:** These antibiotics destroy or kill all the Bacteria in the process of multiplication. Eg. Penicillin, Aminoglycosides, Cephalosporin, Fluoroquinolones, Rifampicin, Metronidazole etc.

According to the type of Bacteria:

- **Gram Positive:** Some Antibiotics are effective mainly against Gram Positive Bacteria Eg. Penicillin.
- **Gram Negative:** Some Antibiotics are effective mainly against Gram Negative Bacteria Eg. Streptomycin.

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According to the effectiveness against microorganism:

- **Broad Spectrum:** The Antibiotics which acts against wide range of microorganisms. Eg. Tetracycline.
- **Narrow Spectrum:** These Antibiotics are useful against limited microorganisms. Eg. Erythromycin

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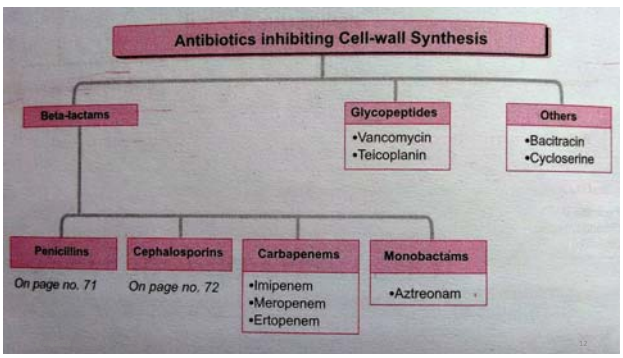

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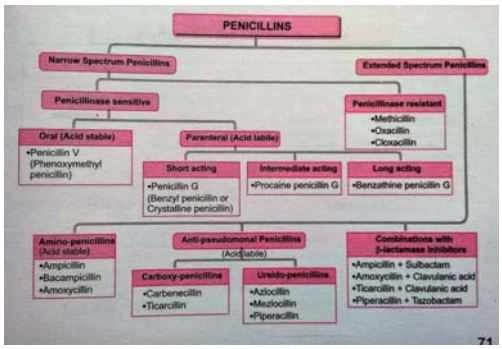
PENICILLINS
Narrow Spectrum Penicillins
Extended Spectrum Penicillins
Penicillinase sensitive
Penicillinase resistant
•Methicillin
•Oxacillin
•Cloxacillin
Oral (Acid stable)
•Penicillin V (Phenoxymethyl penicillin)
Parenteral (Acid labile)
Short acting
•Penicillin G (Benzyl penicillin or Crystalline penicillin)
Intermediate acting
•Procaine penicillin G
Long acting
•Benzathine penicillin G
Amino-penicillins (Acid stable)
•Ampicillin
•Bacampicillin
•Amoxycillin
Anti-pseudomonal Penicillins (Acid labile)
Carboxy-penicillins
•Carbenecillin
•Ticarcillin
Ureido-penicillins
•Azlocillin
•Mezlocillin
•Piperacillin
Combinations with β-lactamase inhibitors
•Ampicillin + Sulbactam
•Amoxycillin + Clavulanic acid
•Ticarcillin + Clavulanic acid
•Piperacillin + Tazobactam
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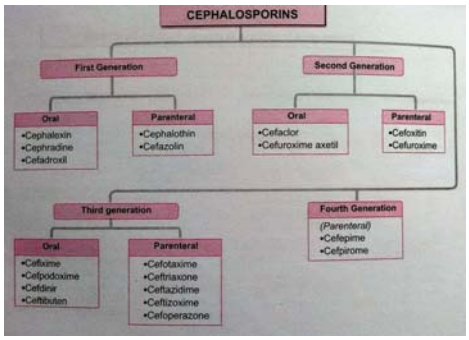
CEPHALOSPORINS
First Generation
Second Generation
Oral
•Cephalexin
•Cephradine
•Cefadroxil
Parenteral
•Cephalothin
•Cefazolin
Oral
•Cefaclor
•Cefuroxime axetil
Parenteral
•Cefoxitin
•Cefuroxime
Third generation
Fourth Generation
(Parenteral)
•Cefepime
•Cefpirome
Oral
•Cefixime
•Cefpodoxime
•Cefdinir
•Ceftibuten
Parenteral
•Cefotaxime
•Ceftriaxone
•Ceftazidime
•Ceftizoxime
•Cefoperazone
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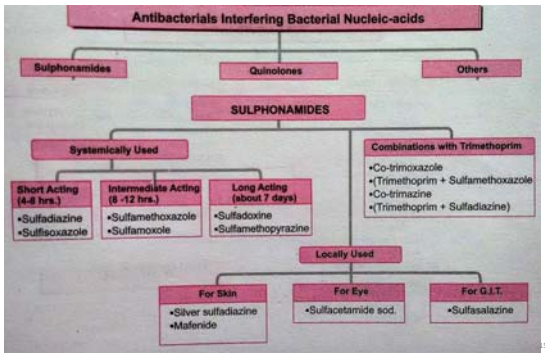
Antibacterials Interfering Bacterial Nucleic-acids
Sulphonamides
Quinolones
Others
SULPHONAMIDES
Systemically Used
Short Acting (4-8 hrs.)
•Sulfadiazine
•Sulfisoxazole
Intermediate Acting (6 -12 hrs.)
•Sulfamethoxazole
•Sulfamoxole
Long Acting (about 7 days)
•Sulfadoxine
•Sulfamethopyrazine
Combinations with Trimethoprim
•Co-trimoxazole
•(Trimethoprim + Sulfamethoxazole
•Co-trimazine
•(Trimethoprim + Sulfadiazine)
Locally Used
For Skin
•Silver sulfadiazine
•Mafenide
For Eye
•Sulfacetamide sod.
For G.I.T.
•Sulfasalazine
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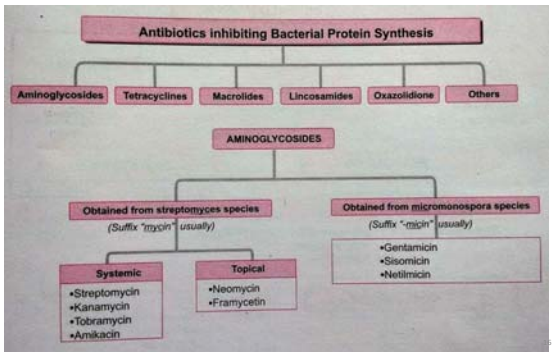

Common side effects of chemotherapeutic Agents:

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Common side effects of chemotherapeutic Agents:

- **Toxic Effects:** Gastrointestinal irritation, Nausea, Vomiting and diarrhea may occur when given by mouth.
- Skin sensitivity may develop with Penicillin or streptomycin causing rashes.
- Serious toxic effect may occur due to streptomycin on the vestibular & auditory nerve causing vertigo & deafness

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- **Drug Resistance:** Many bacteria soon develops resistance to particular drug after a period of treatment, so that the bacteria will not respond to the same drug for example tubercle bacillus develops resistance to streptomycin quickly.
- **Super infection:** The antibiotics given by mouth kill the normal bacteria inhibiting the alimentary canal and permits the over growth of other insensitive organisms which can cause serious complications. Eg. Fungus cause thrush which may go to the lungs with fatal results.

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- **Hypersensitivity Reaction:** Chemotherapeutic agents can cause Hypersensitivity reactions from mild rashes to serve anaphylactic shock. Eg. Penicillin & Sulphonamides.
- **Vitamin Deficiency:** Alteration in vitamin formation and absorption from the bowel take place . So there is deficiency of Vitamin B complex and Vitamin K.
- **Anemia:** In susceptible persons chloramphenicol may produce Aplastic anemia or agranulocytosis. (Action must be taken through proper history about previous drug reaction before administering penicillin sulphonamide and cephalosporin to the patient.

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Selection of Appropriate antimicrobial Agents

- The choice of antimicrobial agents depends on following factors: Patient factors

1. Age.
2. History or Allergy.
3. Genetic abnormalities.
4. Pregnancy.
5. Host defence.
6. Hepatic dysfunction.
7. Renal dysfunction.

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Drug factor

1. Route of administration.
2. Spectrum of antimicrobial activity.
3. Bactericidal/Bacteriostatic effect.
4. Ability to cross blood brain barrier.
5. Cost of the AMA (American Medical Association)

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Organism related factor

1. Clinical Diagnosis.
2. Bacteriological reports.
3. Resistance to AMA drugs.
4. Cross resistance.

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Pharmacology of commonly used Drugs:

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- Immune-suppressants

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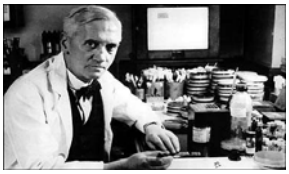
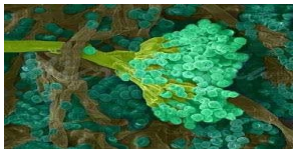
Penicillin



- It is an antibiotic, discovered by **Alexander Fleming** (1881-1955) in 1928.
- β-lactam antibiotics
- β-lactam antibiotics
- It was isolated from fungus **Penicillium *notatum***.



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Penicillin

- **Introduction:** Penicillins were the first antibiotics to be isolated and used clinically in 1941. Penicillins usually are bactericidal, they are most effective against fast growing susceptible bacteria.
- **Mechanism of Action**: Penicillin inhibit the synthesis of bacterial cell wall and causing rapid cell lysis.
- **Indication & Uses:**

1. Gram positive cocci infections.
2. Streptococcal, pneumococcal & meningococcal infection.
3. Venereal disease like gonorrhoea, syphilis.
4. Diphtheria, tetanus & Gas gangrene.

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Classification of Penicillins

Natural penicillins	β- lactamase resistant penicillins	Aminopenicillins	Carboxypenicillins	Ureidopenicillins
-Penicillin G -Penicillin V	-Methicillin -Nafacillin -Isoxazolyl Penicillins	-Ampicillin -Amoxicillin	-Ticarcillin	-Piperacillin -Mezlocillin -Azlocillin

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Cloxacillin	250 – 500 mg orally every 6hr(Max. 4gm/day)
2	Ampicillin	0.25 to 1gm daily IM/IV every 6hr.
3	Amoxicillin	0.25 to 1gm 8hrly
4	Dicloxacillin	0.25 to 1gm orally
5	Piperacillin + Tazobactum	4-5gm and 0.5gm every day 6hr.
6	Penicillin V	0.12 to 0.5gm every 6hr.
7	Penicillin G	0.12 to 0.31gm every 4hr.

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Contd

- **Contraindication & Precautions:** Contraindicated to the patient who have sensitivity to penicillin drug.
- **Adverse effect:** Nausea, vomiting, epigastric distress, Allergic reaction, phlebitis, diarrhoea, rash, pain at IM site.
- **Drug interactions:**

1) Penicillins may decrease the effect of aminoglycosides.
2) Bacterial effects of penicillin may decrease with tetracycline drugs.
3) Use of penicillin with clavulanate or sulbactum increase resistance against bacteria that produce beta – lactamase.

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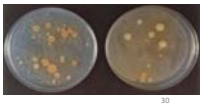
Cephalosporin

Cephalosporins are second major group of ***β-lactam*** ,broad spectrum,penicillanase resistant antibiotics

➢ They were isolated from cultures of Cephalosporium *acremonium* by italian scientist Giuseppe Brotzu in 1945.



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Cephalosporin

- **Introduction:** Cephalosporin's are clinically and pharmacologically similar to penicillin. These drugs are bactericidal
- **Mechanism of Action**: as penicillin it also inhibit the synthesis of bacterial cell wall and causing rapid cell lysis.
- **Indication & Uses:**

1. Gram positive and gram negative bacterial infection.
2. Respiratory tract infection & Septicaemia.
3. Urinary tract infection & Abdominal infections.
4. Hospital acquired infection (3rd Generation are preferred)

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CLASSFICATION OF CEPHALOSPORINS

First Generation	Second Generation	Third Generation	Fourth Generation	Fifth Generation
1.Parenteral Cephalothin Cephaloridine Cefazolin	1.Parenteral Cefamycinc Cefoxitin Cefotitan Cefmetazole	1.Parenteral Cefotaxime Ceftazidime Ceftriaxone	1.Parenteral Cefepime Cefpirome	1.Parenteral Ceftobiprole
2.Oral Cephalexin (Keflex) Cephadroxil (Durecef)	2.Oral Cefachlor Cefprozil	2.Oral Cefixime Cefdinir Ceftibuten		
3.Oral & Parenteral Cephradine				

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Cephalexin	0.25 to 1gm 6-8 hrly orally.
2	Cephalothin	1 to 2gm 6hrly IV
3	Cefuroxime	0.75 to 1.5gm I/V or I/M
4	Cefotaxime	1 to 2gm 12hrly I/V
5	Ceftriaxone	1 to 4gm daily I/V
6	Cefaclor	0.25 to 0.5gm every 8hr.
7	Cefpirome	1 to 2gm 12hrly

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Contd

- **Contraindication & Precautions:** Use cephalosporin cautiously in the patient who are allergic to penicillin.
- **Adverse effect:** cautiously with pregnant and breast feeding women, History of G.I. Disorders.
- **Drug interactions:**

✓Cephalosporin should not used with penicillins, they should be given separate site to prevent inactivation.

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Aminoglycosides

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Aminoglycosides

- **Introduction:**.
- **Mechanism of Action**: These drugs inhibit protein synthesis in the bacteria, there permeability is increased and cell contents leak out and death of cell occurs. These drugs leave bactericidal action.
- **Indication & Uses:**

1. Gram negative infection.
2. Septicaemia.
3. Post operative UTI.
4. Tuberculosis infection.
5. Infection of bones, skin, soft tissue & Joints.
6. Pelvic inflammatory disease.

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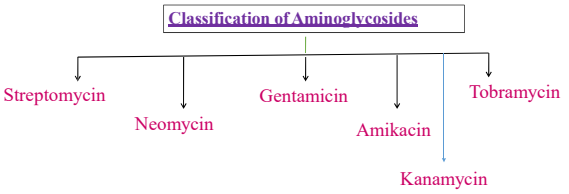

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Streptomycin	1to 2gm per day divided 12 hrly (max. 2gm/day)
2	Gentamicin	1to 1.5mg/kg IV/IM 8hrly
3	Neomycin	1gm orally 4hrly. Pediatric: 50mg/kg/day, Adult 3gm/day.
4	Kanamycin	15mg/kg/day divided 12hrly.
5	Amikacin	15mg/kg/day IM 2-3 divided doses
6	Tobramycin	3to 5 mg/kg/daily in divided dose.

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Contd

- **Contraindication & Precautions:** drug is contraindicated for pregnant and breast feeding women, it is cautiously used in patient with renal failure.
- **Adverse effect:**

1. Ototoxicity, Hypersensitivity reactions.
2. Nephrotoxicity, Hemolytic Anemia, Leukopenia.
3. Neuromuscular blockage, Thrombocytopenia.
4. Nausea/ vomiting, elevated liver enzyme.
5. Diarrhoea, Phlebitis.

- **Drug interactions:** They may cause ototoxicity use with loop diuretic or another aminoglycosides. Inactivation occurs if penicillin antibiotics mixed with aminoglycosides.

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Nursing Responsibilities

- Assess adverse effect, eg. Vertigo, hear loss.
- Monitor renal function for evidence of nephrotoxicity.
- Make sure that patient is well hydrated during therapy and encourage for fluid intake 1.2 to 2lit / day.

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Macrolide & Broad Spectrum Antibiotics

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WHAT ARE MACROLIDES?

- They are antibiotics having a macrocyclic lactone ring with attached sugars.
- THE COMMONLY USED MACROLIDES ARE:
  - Erythromycin
  - Clarithromycin
  - Roxithromycin
  - Azithromycin

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Classification of Macrolides

Older Macrolides	Newer Macrolides
➢ Erythromycin	• Roxithromycin • Clarithromycin • Azithromycin • Spiramycin

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ERYTHROMYCIN

- First isolated from Streptomyces erythreus in 1952
- Widely employed as an alternative to penicillin

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MECHANISM OF ACTION

- It is bacteriostatic at low concentration & bactericidal at high concentration
- Bactericidal property depends on the concentration, organism concerned and its rate of multiplication
- Erythromycin acts by inhibiting bacterial protein synthesis. It combines with 50s ribosome subunits and prevent translocation.

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ANTIMICROBIAL SPECTRUM

- It is a narrow spectrum antibiotic
- Spectrum is similar to Pencillin G. Mostly gram positive and few gram negative bacteria.
- Str. pyogenes , Str. Pneumonia, N. gonorrhea, Clostridium, C. Diphtheriae and Listeria
- In addition, Campylobacter, Legionella, Branhamella catarrhalis, G. vaginalis and Mycoplasma (which are not affected by pencillin are also highly susceptible to erythromycin)
- Moderately sensitive to H. influenza, B. pertussis, C. trachomatis, N. meningitidis and Rickettsiae
- Ineffective against Enterobacteriaceae, other gram negative bacilli.

Adverse Effects

1. Gastrointestinal – epigastric pain, diarrhea
2. Reversible hearing loss
3. Hypersensitivity – fever, rash

Interaction

- It inhibits hepatic oxidation of many drugs – it rises plasma level of theophylline, carbamazepine, valproate, ergotamine and warfarin

USES

- As an alternative to penicillin
  1. Streptococcal pharyngitis, tonsillitis, mastoiditis and CAP
  2. Alternative prophylaxis for RF and SABE
  3. Diphtheria
  4. Tetanus as an adjuvant to TT
  5. Syphilis and gonorrhea
  6. Leptospirosis
- As a first choice drug for
  1. Atypical pneumonia caused by Mycoplasma
  2. Whooping cough
  3. Chancroid

NEWER MACROLIDES

- ROXITHROMYCIN
- CLARITHROMYCIN
- AZITHROMYCIN
- SPIRAMYCIN

Macrolides

- THE COMMONLY USED MACROLIDES ARE:
  - Erythromycin
  - Clarithromycin
  - Roxithromycin.
  - Azithromycin.

- **Mechanism of Action**: It is bacteriostatic at low concentration & bactericidal at high concentration. Bactericidal property depends on the concentration, organism concerned and its rate of multiplication.
- **Indication & Uses: nxt slide.**

Therapeutic Uses:

- **As an alternative to penicillin**.

a) Diphtheria.
b) Tetanus.
c) Leptospirosis.
d) Syphilis and gonorrhoea.

- **As first choice of drug**.

e) Mycoplasma pneumonia.
f) Whooping cough.
g) Cancroid

- **As second choice of drug**.

a) Trachomatis infection of urogenital tract.
b) Penicillin-resistant Staphylococcal infections
c) Legionnaires' pneumonia.
d) Campylobacter enteritis.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	**Erythromycin**	250-500 mg 6 hourly (max. 4 g/day), children 30-60 mg/kg/day.
2	Roxithromycin	150-300 mg BD 30 min before meals, children 2.5-5 mg/kg/day. Syp50 mg /5 ml liquid; ROXEM 50 mg kid tab.
3	Clarithromycin	250 mg BD for 7 days; severe cases 500 mg BD up to 14 days. CLARIBID 250, 500 mg tabs, 125 mg/5 ml dry syr.
4	Azithromycin	Adult: 500 mg once daily 1 hour before or 2 hours after food (food decreases bioavailability); (children above 6 month-10 mg/kg/day for 3 days is sufficient for most infections.

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Contd

- **Contraindication & Precautions:**.
- **Adverse effect:**

1. Gastrointestinal – epigastric pain, diarrhea
2. Reversible hearing loss.
3. Hypersensitivity – fever, rash.

- **Drug interactions:** It inhibits hepatic oxidation of many drugs – it rises plasma level of theophylline, carbamazepine, valproate, ergotamine and warfarin

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Broad Spectrum Antibiotics

- **Introduction:** Tetracycline & Chloramphenicol are broad spectrum antibiotics. They are called so because of there effectiveness against a wide range of microorganism sucg as Gram positive & Gram negative bacteria Eg. Rikettsia, M pneumonia, Chlamydia, anaerobes, sirochetes, H. pylori and some protozoa (eg. Malerial parasites & Entamoeba)

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Tetracycline

- **Introduction:** Broad-Spectrum Bacteriostatic Antibiotics
- Active against many gram-positive and gram-negative bacteria, including Anaerobes, Rickettsiae, Chlamydiae, Mycoplasmas, Protozoa, e.g. amoebas **Mechanism of Action**: It inhibit bacterial protein synthesis by binding to and interfering with ribosomes.
- **Indication & Uses:** Chlamydial infections, including sexually transmitted diseases, In combination with an aminoglycoside, indicated for plague, tularemia, and brucellosis, Treatment of acne, Exacerbations of bronchitis, Community-acquired pneumonia, Lyme disease, Relapsing fever, Leptospirosis Nontuberculous mycobacterial infections (e.g., *Mycobacterium marinum*).

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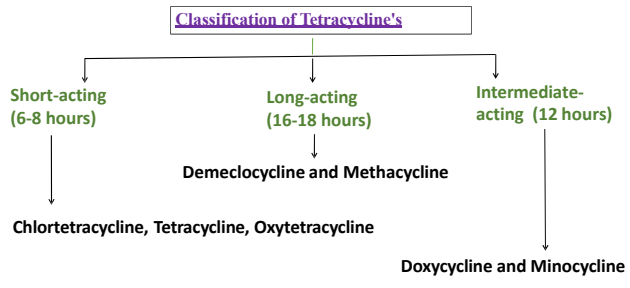

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	**Chlortetracycline,**	250 to 500mg 6hrly orally IV
2	**Oxytetracycline**	250 to 500mg 6hrly orally IV
3	**Tetracycline**	250 to 500mg 6hrly orally IV
4	**Doxycycline**	100 to 200mg daily/orally.
5	**Minocycline**	100 to 200mg daily/orally.

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Contd

- **Contraindication & Precautions:** Hypersensitivity to tetracycline drugs. Take precaution in Renal disease, Hepatic disease.
- **Adverse effect:** Mild nausea, Anorexia, Bulky and loose stool, Hepatotoxicity, Flatulence, pancreatitis.
- **Drug interactions:**

➢Milk and dairy products, Magnesium containing laxatives, antacids, calcium supplements, iron supplements reduce absorption of tetracycline's.

➢Tetracycline's decrease the effect of penicillins & Hormonal contraceptives drugs**.**

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Chloramphenicol

❖**Introduction:**Broad spectrum (aerobic, anaerobic, gram +, gram -, Rickettsiae) they closely resembles in the action to the tetracycline's

❖ Bacteriostatic (*H. influenzae, Neisseria meningitidis*)

- **Mechanism of Action**: They inhibit protein synthesis in susceptible bacteria, in presence of these drug, organism cannot multiply thus it acts as bacteriostatic drug.
- **Indication & Uses:**

1. Mainly used in typhoid fever.
2. UTI, Rickettsial, Cholera, Bacterial meningitis, Eye, Ear infections.

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Drug Examples & Doses:

- Adult & Child: PO/IV 50 to 100mg/kg/day in divided doses of Q6h not exceed to 100mg/kg/day.

Contd

- **Contraindication & Precautions:**

History of hypersensitivity or toxic reactions, Pregnancy & Lactation, spl. precaution for renal impaired and hepatic patients**.**

- **Adverse effect:** Nausea, vomiting, diarrhea, oral/vaginal candidiasis, Bone marrow depression, Hypersensitivity reaction**.**
- **Drug interactions:**

oChemical inhibits metabolism of tobutamide chorpropamide, warfarin, cyclophosphamide, and phenytoin.

oAs the bacteriostatic action of chloramphenicol can antagonize the cidal action of β lactum /aminoglycosides on certain bacteria.

Sulphonamides

-Gerhard Domagk (1870)

Sulphonamides

- **Introduction:** Sulphonamides are one of the oldest group of antimicrobial agents. These are derivatives of the parent compound para amino benzene, sulphonamide. They are mainly bacteriostatic but at very high concentrations they may have bactericidal effect. Eg. Sulfadiazine, Sulfamethoxazole, Sulfasalazine, Co-Trimoxazole.
- **Mechanism of Action**: They inhibit the enzyme folic acid synthase so folic acid is not synthesized (which is essential bacterial growth).
- **Indication & Uses:**

UTI, Ulcerative colitis, Trachoma & Conjunctivitis, Acute bacillary dysentery, cancroid, M. Meningitis.

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Classification of sulfonamides

- Short acting (4-8 h): Sulfadiazine
- Intermediate acting (8-12 h): Sulfamethoxazole
- Long acting (~ 7 days): Sulfadoxine, Sulfamethopyrazine
- Special purpose sulfonamides: Sulfacetamide sodium, Mafenide, Silver sulfadiazine, Sulfasalazine

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Cotrimoxazole	960mg twice in a day.
2	Sulfadiazime	3g followed by 1-1.5gm every 6hrs.
3	Sulfisoxazole	4-6gm /per day in divided doses
4	Sulfasalazine	1-2gm 4time in a day or 2gm/day in divided doses.
5	Sulmethazazole	160 – 800mg every 12 hrs.
6	Sulfamethazine	3-6gm every 6hrs.

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Contd

- **Contraindication & Precautions:** Children younger than 2yrs, Pregnant and breast feeding mother, Renal and hepatic diseases, Hypersensitivity to sulphonamides drug.
- **Adverse effect:** Fever, Rash, Blood Dyscrasias, Nausea/vomiting, Aplastic Anemia.
- **Drug interactions:**

1. Sulphonamides can increasing the blood thinning effect of warfarin, possibly leading to abnormal bleeding.
2. Increases blood level of potassium may occur when Sulfamethoxazole trimethoprim is combined with ACE inhibitors.
3. Sulphonamides may increase the effectiveness of oral hypoglycemics drugs.
4. Sulphonamides may increase the effectiveness of hormonal contraceptives drugs.

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Quinolones

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Anti amoebic

- **Introduction:** Amoebiasis is a protozoal disease caused by Entamoeba histolica Amoeba affect liver lung brain or other tissue and produce hepatitis and amoebic disease. The drug used to treat this kind of infection is called Antiamoebic drug.

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AMOEBIASIS

Amebiasis (also called amebic dysentry) is an infection of intestinal tract caused by Entamoeba histolytica. The disease can be acute or chronic, with the patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery (Dysentery in which the symptoms are intensely acute, leading to prostration, collapse, and often death).

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The diagnosis is established by isolating E. histolytica from fresh feces.

Therapy is aimed not only at the acutely ill patients but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infections for others.

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Protozoal infections are common among the people in underdeveloped topical and subtropical countries, where sanitary conditions, hygienic practices and control of vectors of transmission are inadequate.

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Life cycle of Entamoeba histolytica

Entamoeba histolytica exists in two forms:

1. **Cysts form** (That can survive out side the body).
2. **Trophozoites form** (That are labile and don't persist outside the body).

Life cycle

Life cycle consists 5 steps:

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1. **Ingestion of cysts**
   Cysts are ingested through feces, contaminated food or water.
2. **Formation of trophozoites**
   Cysts are passed into the lumen of intestine, where the
   Trophozoites are liberated.
3. **Penetration and multiplication of Trophozoites**
   Trophozoites are penetrated in intestinal wall and multiply within colon wall. They either invade and ulcerate the mucosa of large intestine or simply feed on intestinal bacteria.

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4. **Systemic invasion**
   Large numbers of Trophozoites within the colon wall can also lead to systemic invasion and caused liver abscess.
5. **Cysts discarded**

   The Trophozoites within the intestine are slowly carried toward the rectum, where they return to cyst form and are excreted in feces.

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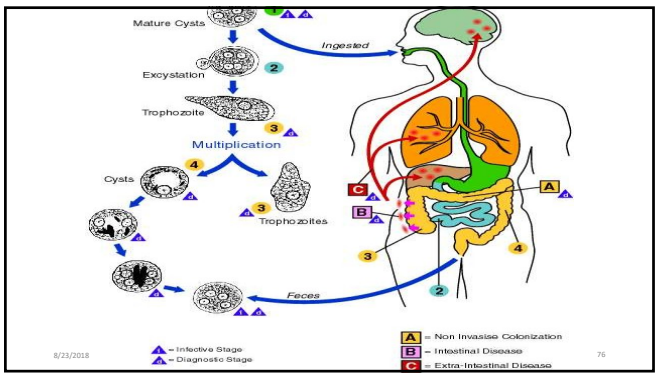

Mechanism of action

- Antiamoebic requires reductive activation of nitro group by susceptible organism. Its selective toxicity towards anaerobic and microaerophilic pathogens such as E. histolytica, G. lamblia, etc. These organisms contain electron transport components such as ferredoxin, small Fe-S proteins that have sufficiently negative redox potential to donate electrons to metronidazole.
- The single electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanisms that target DNA, resulting in cell death.

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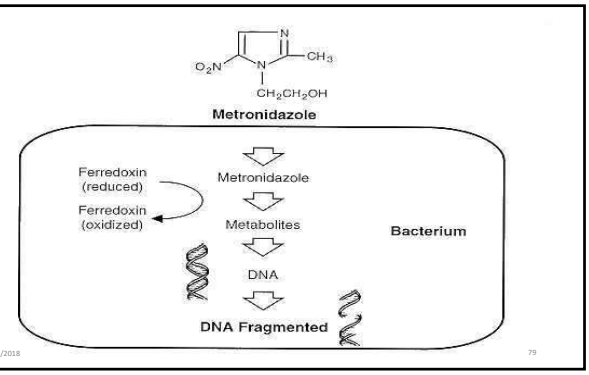

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Indication & Uses:

- **Luminal amoebicides** (Act on parasite in the lumen of bowel)
- **Systemic amoebicides** (Against aomebias in intestinal wall & liver)
- **Mixed amoebicides** (Against both the luminal
- and systemic form of diseases).

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Classification of amoebicidal Drugs

According to the site where the drug is effective, the amebicidal drugs are classified as:
- **Luminal amebicides** (Act on parasite in the lumen of bowel)
- **Systemic amebicides** (Against amebas in intestinal wall & liver)
- **Mixed amebicides** (Against both the luminal and systemic form of diseases).

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Metronidazole	400mg orally.
2	Tinidazole	500-800mg TDS
3	Secnidazole	500mg
4	Chloroquine	300mg 6-8hr
5	Antiamoebic Antibiotic Tetracycline	0.25 mg in divided doses.

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Contd

- **Contraindication & Precautions:**

✓Metronidazole's are contraindicated in neurological disorders and blood Dyscrasias.

✓Cautiously used in pregnancy and alcoholism and those have hepatic disorder.

- **Adverse effect:** Anorexia, headache, abd. Cramps, ECG changes, skin rash, vertigo, nausea & vomiting, Thrombophlebitis.
- **Drug interactions:**

➢Use of metronidazole with alcohol may cause the reaction like tachycardia, flushing, sweating, vomiting.

➢Concurrent use with warfarin may prolonged bleeding.

➢Thrombophlebitis may develop if IV infusion is not done with dilution of sterile water.

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Antimalarial

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Antimalarial

- **Introduction:** These drugs are used for prophylaxis, treatment and prevention of malaria. They acts against plasmodium (a protozoal parasite) which cause malaria.
- **Mechanism of Action**: It inhibits protein synthesis by affecting DNA & RNA functions.
- **Indication & Uses:**

Clinical cure and prophylaxis of all kinds of malaria.

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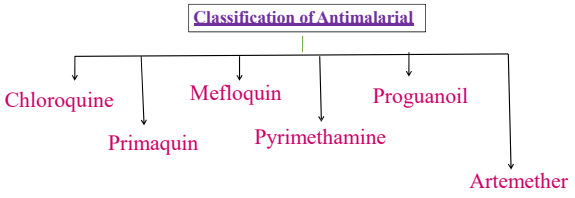

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Chloroquine	300mg at 8hrs
2	Primaquin	15mg orally for 14 days
3	Mefloquin	25mg per kg orally single
4	Pyrimethamine	25mg weekly
5	Proguanoil	100 to 200mg daily
6	Artemether	80mg daily

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Contd

- **Contraindication & Precautions:** Hypersensitivity, Retinal damage, Concurrent hepatotoxic drugs, Pregnancy & Lactation, Renal insufficiency, Known or suspected resistant P. falciparum infection.
- **Adverse effect:** Nausea & vomiting Seizures, headache, abd. Cramps, haemolysis, Ototoxicity, G.I. upset, visual disturbances like loss of accommodation, blurred vision.
- **Drug interactions:** Concurrent use of such compounds with antiarrhythmic, tricyclic antidepressants, it may increase the risk of cardiac conduction defects.

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Antithelmintic

- Drugs used to treat parasitic worm infections: helminthic infections
- Drug treatment is very specific
- It is very important to identify the causative worm
- Done by finding the parasite ova or larvae in feces, urine, blood, sputum, or tissue.

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HELMINTHS

NEMATELMINTHS (ROUND WORM)

- ROUND.W-ASCARIS.L
- HOOK W-NECATOR A
- WHIP W-TRICHURIS T
- THREAD W-STRONGYLOIDES.S
- PIN W-ENTEROBIUS V
- FILARIASIS-W BANCROFTI
- ONCHOCERCIASIS-O.VOLVULUS
- GUINEA W-DRACANCULUS M

PLATYHELMINTHS (Fluke worm)

- TREMATODES-FLUKES
- BLOOD F-SCISTOSOMIASIS
- LIVER F-CLONORCHIASIS
- INTESTINAL F-FASCIOLOPSIASIS
- LUNG F-PARAGONIMIASIS

CESTODES (Thread worm)

- BEEF TW-T.SAGINAT
- PORK TW-T.SOLIUM
- FISH TW-DIPHYLLOBOTHRIUM
- DWARF TW-HYMENOLEPIS.NANA

8/23/2018

Classification of Antithelmintic Drugs

Against Nematodes- Albendazole, Mebendazole, Pyrantel Pamoate, Levimasole, Piperazine, Ivermectin, Diethylcarbamazine, Thiabendazole, Doxycycline

Against trematodes

Metrifonate, Oxamniquine, Bithionol, Triclabendazole

Against Cestodes

Niclosamide

Against trematodes and Cestodes- Praziquantel

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Worms (helminths)	Drug of choice
Tapeworms (cestodes)	Niclosamide or Praziquantel or Albendazole
Roundworms (nematodes)	
•Enterobius vermicularis (pinworm)	Mebendazole or Pyrantel
•Ascaris lumbricoides	Mebendazole or Pyrantel
•Trichuris trichiura (whipworm)	Mebendazole or Albendazole
•Trichinella spiralis (trichinellosis)	Mebendazole and Thiabendazole
•Strongyloides stercoralis	Thiabendazole
•Necator americanus (hookworm)	Mebendazole or Pyrantel
•Ancylostoma duodenale	Mebendazole, Pyrantel, or Albendazole
•Onchocerca volvulus (Onchocercosis)	Ivermectin Diethylcarbamazine
•Wuchereria bancrofti (Elephantiasis)	
Flukes (trematodes)	
•Schistzoma (Schistozomes)	Praziquantel

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Against Nematodes

PYRANTEL PAMOATE

MOA-Blocks acetylcholine at the neuromuscular junction, resulting in paralysis of the worms, which are then expelled through the GI tract

The small amount is absorbed, so high levels are achieved in intestinal walls→ luminal anthelmintic

Uses –round w, hook w, Pin w—10mg/kg

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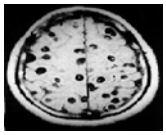
Against Nematodes

- **Benzimidazoles (ALBENDAZOLE & MEBENDAZOLE)**

It binds to beta tubulin→prevents polymerisation→ Break down of cytoplasmic microtubules→ They inhibit uptake of glucose and other nutrients, → Depletion of glycogen stores →Decrease of ATP→ Leading to autolysis and death of the parasitic worm.



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Dose: BD daily for 3 days for hookworm and roundworm infestations.

Uses:

1. Ascariasis, hook worm, pin worm infections
2. Hydatid disease-BD for 1 month
3. Neurocysticercosis- along with corticosteroids
4. Cutaneous larvae migrans-400mg for 3 days
5. Visceral larvae migrans-
6. Toxocariasis
7. Giadiasis ans tianiasis
8. Emperical treatment-Persistant eosinophilia

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Against nematodes

Thiabendazole inhibits cellular enzymes of susceptible helminths. Inhibits the helminth-specific enzyme, fumarate reductase

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LEVAMISOLE

Anthelmintic and immunomodulator belonging to a class of synthetic imidazothiazole derivatives. It is effective in infections with the common round-worm as well as hook worm. It has a nicotine-like action, stimulating and subsequently blocking the neuromuscular junctions. The paralyzed worms are then expelled in the faeces. Ova are not killed.

Uses: To treat a variety of dermatologic conditions- skin infections, leprosy, warts, lichen planus, and aphthus ulcers.

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Piperazine

It reversibly inhibits neuromuscular transmission in the worm It probably by acting like GABA/GABA-gated chloride channels in nematode muscle. The paralyzed worms are expelled alive

Uses For Ascariasis -4g * 2 days and Pin worm- 4g * 7 days

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Ivermectin

- It is highly effective broad-spectrum antiparasitic
- First choice of drug for the treatment of filarial infections and is very effective in onchocerciasis
- It kill the worm by opening glutamate-gated chloride channels (found only in invertebrates) and increasing Cl^- conductance; by binding to a novel allosteric site on the acetylcholine nicotinic receptor to cause an increase in transmission, leading to motor paralysis; or by binding to aminobutyric acid receptors.

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Ivermectin

Uses : It has also given good results against W. bancrofti, which causes elephantiasis. A single dose kills the immature microfilariae of O. volvulus- river blindness

The drug also has activity against infections with some roundworms: common roundworms, whipworms, and threadworms

It works best if repeated at 6–12-month intervals.

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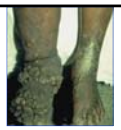
Diethylcarbamazine



Diethylcarbamazine is a piperazine derivtve

- It is active in filarial infections caused by W. bancrofti
- It mainly act by make opsonisation of worm that detected by our immune system
- It immobilizes microfilariae and alters their surface structure→ makes them susceptible for host defense
- The drug is absorbed by oral administration

Uses

chemoprophylaxis

Filariasis- 2-3mg/kg for 2-3 weeks

Tropical eosinophilia for 7 days, loiasis

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Against cestodes- NICLOSAMIDE

- Its action has been ascribed to inhibition of the parasite's mitochondrial anaerobic phosphorylation of ADP which produces usable energy
- The scolex and a proximal segment are irreversibly damaged by the drug
- The worm separates from the intestinal wall and is expelled
- There is negligible absorption of the drug from the gastrointestinal tract.

Uses-Taenia solium, the drug is given in a single dose after a light meal, followed by a purgative 2 hours

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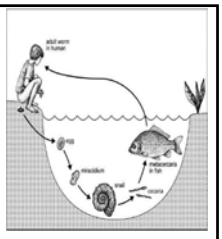

Adverse effects

Unwanted effects are few, infrequent and transient.

Drug interaction:

Enzyme inducers dexamethasone, phenytoin, and carbamazepine increase metabolism

Cimetidine, known to inhibit cytochrome P-450 isozymes, causes increased praziquantel levels.

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Against Trematodes and Cestodes-PRAZIQUANTEL

It is the drug of choice for all **forms** of schistos and for cestode infections like cysticercosis.

It make the Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the both adult worms and larvae.

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Against trematodes - **MITRIFONATE**

It is organophosphorus compound so is cholinesterase inhibitors. It is safe and cost effective for Schistosoma infection.

It has good oral absorption Orally active and time is 1/2 =1-5 hrs.

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Against trematodes: OXAMNIQUINE-

Used against Schistosoma mansoni. It is the drug of choice for all forms of schistosomiasis it is given orally.

Flukes esterifies drug to produce reactive metabolite → alkylates DNA of flukes. It intercalated with parasite DNA and inactivate it.

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Against Trematodes

BITHIONOL-orally well absorbed

For fascioliasis (sheep liver fluke) 30-50mg for 10-15 days on alternate days.

TRICLABENDAZOLE : narrow spectrum benzimidazole

For treating human fasciola hepatica

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Albendazole	10mg/kg body wt.
2	Ivermectin	6-12mg
3	Mebendazole	100mg
4	Pyrantel	10mg/kg body wt.
5	Thiabendazole	25mg/kg body wt.

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Contd

- **Contraindication & Precautions:** Hepatic disease, breast feeding women, pregnant women, use cautiously in children younger than 2yrs of age.
- **Adverse effect:** Abdominal pain, nausea, diarrhoea, vomiting, drowsiness, headache, dizziness, elevated liver enzyme level.
- **Nursing Responsibilities.**

1. **Nurse** should teach the patient and family members to wash hands well, use disposable towels to dry hands and keep hands away from mouth.
2. **Nurse** should teach the patient and family members to wash personal article including sheets and other food preparation articles, utensils etc. Use disposable towels to dry hands and keep hands away from mouth.

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Antiscabies agents

- **Sarcoptes scabiei**, otherwise known as scabies, is a highly contagious infestation of microscopic mites that affect humans and animals alike.
- Contracting scabies is more common then one may think, and occurs worldwide. No one is safe from an infestation of scabies because it can affect any race or social class. Scabies can also spread at a rapid pace, and this usually occurs in crowded areas where there is a chance of prolonged contact.

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DEFINITION

Scabies is a contagious disease caused by the mite *Sarcoptes scabiei.*

EPIDEMIOLOGY & DEMOGRAPHICS

- ❖ Mites are distributed worldwide
- ❖ affects all races and socioeconomic classes in all climates
- ❖Higher prevalence in urban areas
- ❖Greater frequency in winter than summer

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Scabies Transmission

- Direct, prolonged, skin–to-skin contact
- Sexual contact
- Exposure is most common in nursing homes, hospitals, institutions, and daycare settings; can also be spread in households
- Indirect transfer from clothing, towels and bedding
- Transmission occurs as long as person is infested and untreated, including incubation period.

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Scabies Symptoms

- Pimple-like rash or burrows between fingers, on wrist, elbows, armpits, belt line, navel, abdomen, and/or back of the hip
- Erythematous(red) skin
- Intense itching over most of the body, especially at night
- Sores on the body caused by scratching
- Sores can sometimes become infected with bacteria(usually streptococcus pyogenes or staphylococcus aureas)

Incubation period:

2-6 weeks without previous exposure
1-4 days after re-infestation (usually milder)

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LABORATORY TESTS

- **Microscopic demonstration** of the organism, feces, or eggs: a drop of mineral oil may be placed over the suspected lesion before removal; the scrapings are transferred directly to a glass slide; a drop of potassium hydroxide is added and a cover slip is applied.
- **Skin biopsy** is rarely necessary to make the diagnosis.

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Pathophysiology

- The mite, *S scabiei* spreads disease through direct and prolonged contact between hosts.
- The mite remains viable for 2-5 days on inanimate objects; therefore, transmission through for mites, such as infected bedding or clothing, is possible.
- Once bound to their host, 10-15 mites mate on the surface of the skin.

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- After mating, the male mite dies.
- The female mite burrows into the epidermis of the host using her jaws and front legs, where she lays up to 3 eggs per day for the duration of her 30-60 day lifetime.
- An affected host harbors approximately 11 adult female mites during a typical infestation. The eggs hatch in 3-4 days.
- The Larvae migrate to skin surface and burrow into the skin or hair follicles forming short burrows, called molting pouches. Larvae have 3 pairs of legs and last only 2 to 3 days before turning into nymphs.

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- Mating occurs when male mite penetrates the molting pouch of the female mite.
- Impregnated females extend their molting pouches into burrows, laying eggs in the process; survive 1-2 months in tunnels under the skin.
- A delayed type IV hypersensitivity reaction to the mites, their eggs, or scybala (packets of feces) occurs approximately 30 days after infestation.
- This reaction is responsible for the intense pruritus, which is the hallmark of the disease.

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Scabies Treatment

- Application of scabicide over entire body below head
- Cream should be reapplied to hands after routine hand washing, since hands are often infected
- Itching may continue for several weeks despite successful treatment
- In ~5% of cases, 2nd treatment may be necessary after 7-10 days.

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Sulphur

- ❑Scabies was historically treated with topical sulfur, a treatment still in use today
- ❑10% sulphur in yellow soft paraffin is safe and effective.
- ❑2.5% used for scabies in infants and young children.
- ❑Excessive or higher concentration may cause irritation.

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Lindane 1% (gamma benzene hexachloride)

- ❖Lindane is an organochloride.
- ❖A single application, washed off after 12-24h
- ❖6 hour application is equally effective

Adverse effects:

- ➢Neurological effect- seizure
- ➢Toxicity was usually the result of excessive topical application or accidental ingestion.
- ➢Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 pounds.

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Malathion

- 0.5% in aqueous base.
- For one application in an adult 100ml lotion is sufficient.
- Apply on cool, dry skin using clean paintbrush or cotton wool.
- It should be left on the skin for 24h
- If hands are washed with soap and water during the 24h, it should be reapplied to the hands.
- a second application after an interval of a week.
- Skin irritation may sometimes occur.

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Ivermectin

- Ivermectin is an **oral antiparasitic agent** approved for the treatment of worm infestations.
- Evidence suggests that oral ivermectin may be a **safe and effective treatment for scabies;**
- Oral ivermectin has been reported effective in the **treatment of crusted scabies;** its use should be considered **for patients who have failed treatment with or who cannot tolerate topical medications for the treatment of scabies.**
- The dosage of **ivermectin is 200 mcg/kg orally**. It should be taken on an empty stomach with water. A total of two or more doses **at least 7 days** apart may be necessary to eliminate a scabies infestation. The safety of ivermectin **in children weighing less than 15 kg and in pregnant women has not been established**.

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Permethrin (Elimite)

- ❖5% Dermal cream is effective.
- ❖For a single application in an adult 30-60g of cream is needed.
- ❖Applied to the whole body and left on for 8-12h before being washed off.
- ❖Second application after an interval of a week.
- ❖Can cause itching and reddening of the skin.

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TREATMENT OVERVIEW

- 5% permethrin cream: This is the most common treatment for scabies. It is safe for children as young as 1 month old and women who are pregnant.
- 25% benzyl benzoate lotion.
- 10% sulfur ointment.
- 10% crotamiton cream.
- 1% lindane lotion.

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Other treatment

Some patients need other treatment, too.

- Antihistamine: To control the itch and help you sleep.
- Pramoxine lotion: To control the itch.
- Antibiotic: To wipe out an infection.
- Steroid cream: To ease the redness, swelling, and itch.

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Antiviral & Antifungal agents

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Antiviral Agents

- **Introduction:** These agents are used to treat viral infections, the difficulty in treating viral infection is that viruses live and multiply within the cell and drug which enter the cell for not only destroy viruses but exerts bad effects on the cell also.

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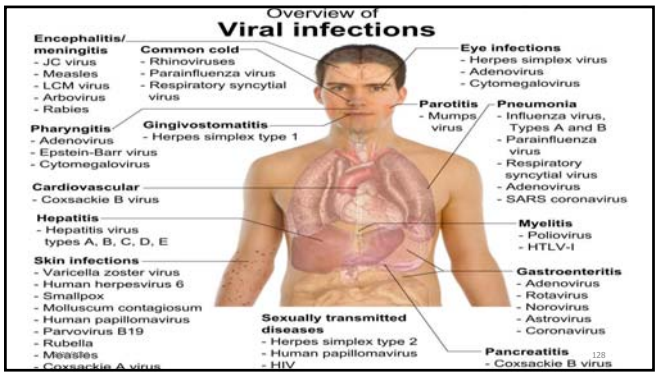

Understanding Viruses
They are different from other Microbes

Viral replication

- A virus cannot replicate on its own
- It must attach to and enter a host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA

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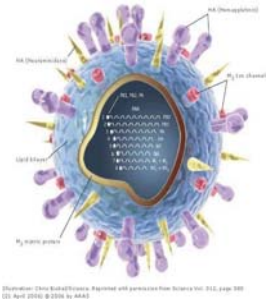
Understanding Viruses

Viruses are difficult to kill because they live inside the cells

- Any drug that kills a virus may also kill cells



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Antivirals: Available for many viral infections

Viruses controlled by current antiviral therapy

- Cytomegalovirus (CMV)
- Hepatitis viruses
- Herpes viruses
- Human immunodeficiency virus (HIV)
- Influenza viruses (the "flu")
- Respiratory syncytial virus (RSV)

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Anti-viral drugs

- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope – antigenic in nature
- Viruses are obligate intracellular parasite
- They do not have a metabolic machinery of their own – uses host enzymes

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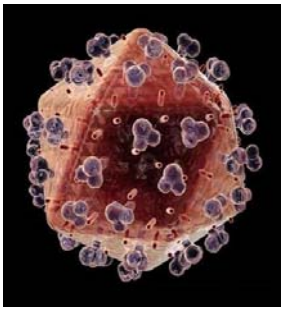
Anti-viral drugs

- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made



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Anti-Viral drugs

- Many antiviral drugs are *Purine or Pyrimidine analogs.*
- Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral agents inhibits active replication so the viral growth resumes after drug removal.

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Antivirals: Mechanism of Action.

Key characteristics of antiviral drugs

- ☐**Able to enter the cells infected with virus**
- ☐**Interfere with** viral nucleic acid **synthesis and/or regulation**
- ☐Some drugs **interfere with ability of virus to bind to cells**
- ☐Some drugs **stimulate the body's immune system**
- ☐**Best responses** to antiviral drugs are in **patients with competent immune systems**
- ☐A **healthy immune system works synergistically with the drug** to eliminate or suppress viral activity

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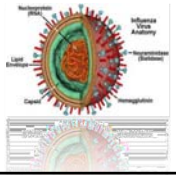
Uses: Antiviral Medications

- **Antiviral drugs**
  - Used to treat infections caused by viruses other than HIV
- **Antiretroviral drugs**
  - Used to treat infections caused by HIV, the virus that causes AIDS
- **Herpes-Simplex Viruses**
  - HSV-1 (oral herpes)
  - HSV-2 (genital herpes)
- **Varicella Zoster Virus**
  - Chickenpox
  - Shingles



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Antiviral Drugs: Non-retroviral

- **Mechanism of action**
  - Inhibit viral replication
- **Used to treat non-HIV viral infections**
  - Influenza viruses
  - HSV (herpes simplex virus), VZV (vericella zoster virus)
  - CMV (cytomegalovirus)
  - Hepatitis A, B, C (HAV, HBV, NCV)
- **Adverse Effects**
  - Vary with each drug
  - Healthy cells are often killed also, resulting in serious toxicities

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Anti-viral drugs

- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infectio.n within the infected cells.

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Anti-viral drugs

Stages of viral replication

- Cell entry – attachment
  - penetration
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release

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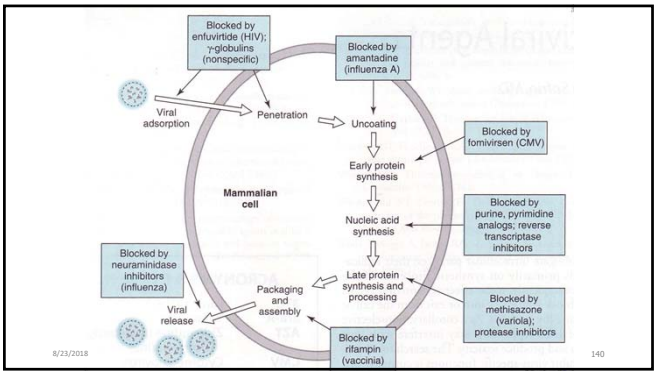

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Classification

- **DNA polymerase inhibitors**
  - **—Purine Nucleoside Analogues:**
    Acyclovir, Ganciclovir Famiciclovir
    Valacyclovir, Penciclovir Cidofovir
  - **–Pyrimidine Nucleoside Analogues:**
    Idoxuridine
  - **–Non nucloside**
    Foscarnet

- **Inhibitors of viral penetration, uncoating**
  Amantadine, Rimantadine
- **m-RNA Synthesis inhibitors**
  Ribvirin, Fomivirsen
- **Neuraminidase Inhibitors**
  Zanamivir, Oseltamivir
- **Immunomodulators**
  Immunoglobulins, Interferns, Palivizumab, Imiquimod.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Acyclovir	5mg/kg body wt. IV 8hrly/ 200-400mg orally 4hrly
2	Amantadine	100mg BD for 5days.
3	Vidarbine	100mg/kg intravenous
4	Ganciclovir	5mg/kg every 12hrs.
5	Famciclovir	250mg tds
6	Zidovudine	600mg daily in divided doses.

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Contd

- **Contraindication & Precautions:** Patient who have hypersensitivity to these drugs. Use cautiously in the patient with renal disease, dehydration, neurologic disease.
- **Adverse effect:** Leucopenia, Dizziness, Headache, Nausea/vomiting, Phlebites, sleeplessness, Thrombocytopenia, diarrhoea, Renal failure, confusion, Hallucinations, Zidovudine may cause anemia & bone marrow depression.
- **Drug interactions:** Use anticholinergic drug with may cause additive anticholinergic effects. Use of alcohol may increases risk of toxicity.

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Antifungal Agents

- These Agents used against fungal infections (superficial or systemic)
- Also called antimycotic drugs.
- Used to treat two types of fungal infection:
  - Superficial fungal infections
    - (skin or mucous membrane)
  - Systemic fungal infectons
    - (lungs or central nervous system)

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Antifungal agents

- **Introduction:** Fungi is also known as mycoses, It is very large and diverse group of microorganisms. It broken down into yeasts and molds
- **Yeast**: Single-cell fungi, Reproduce by budding, Very useful organisms
  - Baking
  - Alcoholic beverages
- **Molds**: Multicellular, Characterized by long, branching filaments called hyphae.

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Fungal infections are:

Four General Types

- **Cutaneous**
- **Subcutaneous**
- **Superficial**
- **Systemic***
  *Can be life-threatening
  *Usually occur in immunocompromised host

Candida albicans

- Due to antibiotic therapy, antineoplastics, or immunosuppressants it may result in overgrowth and systemic infections.

In the mouth:

- Oral candidiasis or thrush
- Newborn infants and immunocompromised patients

Vaginal candidiasis:

- "Yeast infection"
- Pregnancy, diabetes mellitus, oral contraceptives

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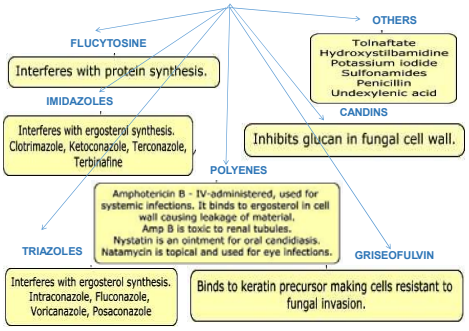
ANTI FUNGAL DRUGS MECHANISAM



CLASSIFICATION OF ANTIFUNGAL

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

- *Amphotericin B* AMBISOME
- *Anidulafungin* ERAXIS
- *Caspofungin* CANCIDAS
- *Fluconazole* DIFLUCAN
- *Flucytosine* ANCOBON
- *Itraconazole* SPORANOX
- *Ketoconazole* NIZORAL
- *Micafungin* MYCAMINE
- *Posaconazole* NOXAFIL
- *Voriconazole* VFEND

DRUGS FOR CUTANEOUS MYCOSES

- *Butenafine* LOTRIMIN ULTRA
- *Clotrimazole*, LOTRIMIN AF
- *Ciclopirox* PENLAC
- *Econazole* ECONAZOLE NITRATE
- *Griseofulvin* GRIFULVIN V, GRIS-PEG
- *Miconazole* FUNGOID, MICATIN, MONISTAT
- *Naftifine* NAFTIN
- *Nystatin* MYCOSTATIN
- *Oxiconazole* OXISTAT
- *Sertaconazole* ERTACZO
- *Sulconazole* EXELDERM
- *Terbinafine* LAMISIL
- *Terconazole* TERAZOL
- *Tioconazole* VAGISTAT-1
- *Tolnaftate* TINACTIN

Drug Examples & Doses:

S. no.	Drugs	Doses
1	Amphotericin B	0.1mg/ml(1mg/10ml) IV
2	Nystatin	4-6ml four times a day
3	Clotrimazole	100mg daily (as pessary)
4	Miconazole	2% solution
5	Ketoconazole	200-400mg daily
6	Griseofulvin	0.5 to 1gm daily.
7	Fluconazole	50mg daily/150mg single in vaginal candida or candida balanitis

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Antifungal Agents: Adverse Effects

Amphotericin B: "Shake and Bake"

fever chills headache anorexia
malaise nausea hypotension tachycardia
muscle and joint pain
lowered potassium and magnesium levels

*Renal toxicity
*Reurotoxicity: seizures and paresthesias

contd

Fluconazole

- Nausea, vomiting, diarrhea, abdominal pain,
- Increased liver function studies

Flucytosine

- Nausea, vomiting, anorexia

Griseofulvin

- Rash, urticaria, headache, nausea, vomiting, anorexia

Contd

- **Contraindication & Precautions:** Hypersensitive patients, Pregnant or breast feeding women.
- **Drug interactions:**

1. Concurrent use with nephrotoxic drugs may cause additive nephrotoxicity.
2. Ketoconazole with alcohol may increase risk of hepatotoxicity.
3. Itraconazole with antidiabetics may increase risk of hypoglycaemia.
4. Some antifungal may increase the effect of oral anticoagulants by increasing prothrombin times.

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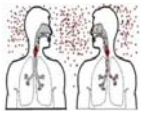
Antitubercular drugs.



Introduction: Tuberculosis.

- Gram positive , aerobic **acid fast bacilli**.
- **Resistan**t to disinfectant ,detergent & common antibiotics.
- Capable of **intracellular growth**.
- Person to person spread is by aerosol.
- **Human** are the only natural **reservoir**.
- Disease is most common in **south east asia, sub saharan region, eastern europe.**

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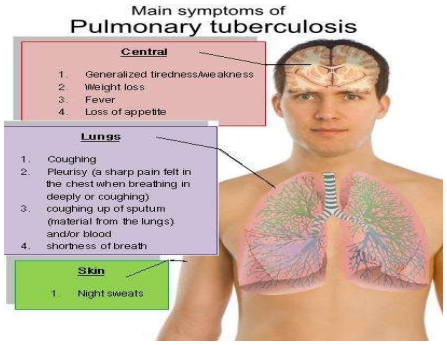
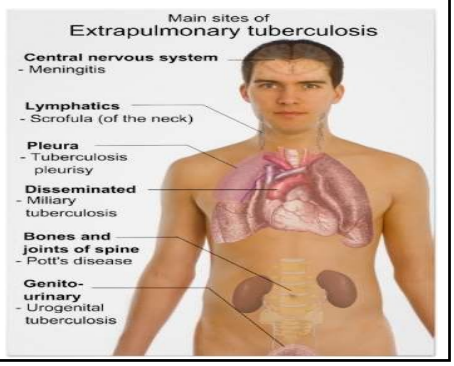
Symptoms



- Sites of extra-pulmonary tuberculosis



TUBERCULOSIS DIAGNOSIS

- Clinical (presenting symptoms, duration of symptoms, previous TB)
- Diagnostic Imaging(X-Rays, CT Scans, MRI's)
- Bacteriology (smears, cultures)
- Pathology of biopsy specimens
- Epidemiological Factors

Classification Of Anti T.B. Drugs

FIRST line drugs

- F Field defects causing drug i.e. Ethambutol [E]
- I Isoniazid (INH) [H]
- R Rifampicin [R]
- S Streptomycin [S]
- T Twice a day given drug i.e. Pyrazinamide [Z]
  (All other first line antituberculars are given once a day)

SECOND line drugs

- S Salicylates like Para-amino salicylate
- E Ethionamide
- C Cycloserine
- O Old drug: Thiacetazone
- N Newer Drugs: (Quinolones e.g. Ciprofloxacin, Levofloxacin, gatifloxacin and Moxifloxacin) &(Macrolides e.g. Clarithromycin, Azithromycin)
- D Drugs rarely used: Aminoglycosides e.g. Capreomycin, Kanamycin, Amikacin, Rifabeutin

Mechanism of Action along with Line of Regimen

First –Line Drugs:

- These drugs are used in combinations of two or more agents until bacterial conversation occurs or maximum improvement is seen.

The First-line drugs for treating tuberculosis are as follows:

- Isoniazid [INH] (Nydrazid), which affects the mycolic acid coating of the bacterium.
- Rifampin (Rifadin, RImactane), which alters DNA and RNA activity in the bacterium.
- Ethionamide (Trecator SC), which prevents cell division
- Rifapentine (Priftin), which alters DNA and RNA activity, causing cell death.

Second-line drugs :

- If the patient cannot take one or more of the first-line drugs, or if the disease continues to progress because of the emergences of a resistance strain, the second line drugs can be used.
- These drugs are used in combination with at least one other antituberculosis drug.

The Second-line drugs for treating tuberculosis are as follows:

- Ethambutol (Myambutol), which inhibits cellular metabolism.
- Pyrazinamide (generic), which is both bactericidal and bacteriostatic.

Third-line drugs: If therapeutic success is still not achieved, a third-line combination of two antituberculosis drugs can be tried.

- Using the drug in combination helps to decrease the emergence of resistant strains and to affect the bacteria at various phases during their long and slow life cycle.

The Third-line drugs for treating tuberculosis are as follows:

- Capreomycin (Capastat), whose mechanism of action is not known.
- Cycloserine (Seromycin), which inhibits cell wall synthesis and leads to cell death.

Drug name	Dosage / Route	Usual Indications
Capreomycin (Capastat)	Adult: 1g/day IM for 60-120 days, followed by 1g IM 2-3 times per week for 18024 mo; reduce dosage with renal impairment Pediatric: 15 mg/kg/day IM	Second-line drug for treatment of Mycobacterium tuberculosis
Cycloserine (Seromycin)	Adult: 250 mg PO b.i.d. for 2 wk, then 500 mg to 1 g/day PO in divided doses Pediatric: safety not established	Second-line drug for treatment of Mycobacterium tuberculosis
Ethambutol (Myambutol)	Adult: 15 mg/kg/day PO as a single dose Pediatric: not recommended for children < 13 yr.	Second-line drug for treatment of Mycobacterium tuberculosis
Ethionamide (Trecator S.C.)	Adult: 15-20 mg/kg/day PO in divided doses with pyridoxine Pediatric: 10-20 mg/kg/day PO in divided doses with pyridoxine	First-line drug for treatment of Mycobacterium tuberculosis
Isoniazid (INH) (Nydrazid)	Adult: 5 mg/kg/day PO Pediatric: 10-20 mg/kg/day PO	First-line drug for treatment of Mycobacterium tuberculosis

Pyrazinamide (Generic)	Adult and Pediatric: 15-30 mg/kg/day PO	Second-line drug for treatment of Mycobacterium tuberculosis
Rifabutin (Mycobutin)	Adult: 300 mg PO daily Pediatric: safety not established	Treatment of Mycobacterium avium-intracellulare (MAC) in patients with advance HIV infection
Rifampin (Rifadin, Rimactane)	Adult: 600 mg 2 times per week for 2 mo Pediatric: safety not established	First-line drug for treatment of M. tuberculosis
Rifapentine (Priftin)	Adult: 600 mg PO 2 times per week for 2 mo Pediatric: safety not established	First-line drug for treatment of M. tuberculosis

Contraindications and Cautions

- Antituberculosis drugs are contraindicated for patients with any known allergy to these agents
- In those with the metabolism or excretion of the drug.
- In those with severe CNS dysfunction, which could be exacerbated by the actions of the drug.
- In pregnancy because of possible adverse effects on the fetus. In an antituberculosis regimen is necessary during pregnancy, the combination of isoniazid, ethambutol and rifampin is considered the safest.

Adverse Effects

- CNS effects: neuritis, dizziness, headache, malaise, drowsiness, and hallucinations are often reported and are related to direct effects of the drugs on neurons.
- GI tract: nausea, vomiting, anorexia, stomach upset and abnormal pain.
- Rifampin, rifabutin and rifapentine cause discoloration of body fluids from urine to sweat and tears. Patients should be alerted that in many instances orange-tinged urine, sweat, and tears may stain clothing and permanently stain contact lenses. This can be frightening if the patient is not alerted that many to the possibility that it will happen.
- As with other antibiotics, there is always a possibility of hypersensitivity reactions and the patient should be monitored on a regular basis.

Drug Interactions

- When rifampin and INH are used in combination, the possibility of toxic liver reactions increases. Patients should be monitored closely.
- Increases metabolism and decreased drug effectiveness occur as a result of administration of quinidine, metoprolol, propranolol, corticosteroids, oral contraceptives, oral anticoagulants, oral antidiabetic agents, digoxin, theophylline, methadone, phenytoin, verapamil, cyclosporine or ketoconazole in combination with rifampin or rifabutin.
- Patients who are taking these drug combinations should be monitored closely and dosage adjustments made as needed.

Nursing Responsibilities.

- Check culture and sensitivity reports to ensure that this is the drug of choice for this patient and arrange repeated cultures if response is not as anticipated.
- Monitor renal and liver function test results before and periodically during therapy to arrange for dosage reduction as needed.
- Ensure that the patient receives the full course of the drugs to improve effectiveness and decrease the risk of development of resistant bacterial strains. These drugs are taken for years and often in combination. Periodic medical evaluation and re-teaching are often essentials to ensure compliance.

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Continuation….

- Discontinue the drug immediately if hypersensitivity reactions occur to avert potentially serious reactions.
- Encourage the patient to eat small, frequent meals as tolerated; perform frequent mouth care; and drink adequate fluids to ensure adequate nutrition and hydration. Monitor nutrition if GI effects become a problem.
- Encourage that the patient is instructed about the appropriate dosage regimen, use of drug combinations and possible adverse effects to enhance patient knowledge about drug therapy and to promote compliance.

The Patient should inform:

- To drink a lot of fluids to maintain nutrition (very important) even though nausea, vomiting and diarrhea may occur.
- To use barrier contraceptives and understand that oral contraceptives may not be effective if antimycobacterial drugs are being used.
- To understand that normally some of these drugs impart an orange stain to body fluids. If this occurs, the fluids may say stain clothing and tears may stain contact lenses.
- To report difficulty breathing, hallucinations, numbness and tingling, worsening of condition, fever and chills or changes in color of urine or stool to a health care provider.

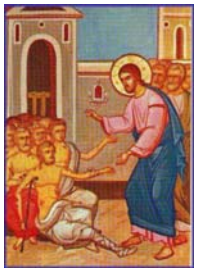
Evaluation

- Monitor patient response to the drug (resolution of mycobacterial infection).
- Monitor for adverse effects (GI effects, CNS changes and hypersensitivity reactions).
- Evaluate the effectiveness of the teaching plan (patient can name the drug, dosage, possible adverse effects to expect and specific measure to help avoid adverse effects).
- Monitor the effectiveness of comfort and safety measures and compliance with the regimen.

Antileprosy drugs

- **Leprosy** is a chronic infectious disease
- characterized of the peripheral nerve, skin, and mucus membrane of the URT(nasal mucosa).
- World's oldest recorded disease

Every year January 27 is World Leprosy Day



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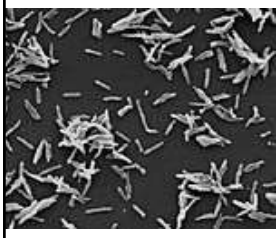
Historical aspect of leprosy

- One of the Oldest and most dreaded disease known to Mankind.
- Earliest description from India in 600BC
  - Kustha Roga & attributed to punishment or curse of God
- Al-Bukhari's Muslim Hadith (volume 1, 2.443) documented Prophet Mohammed's apparent dread of leprosy in his statement: "*Escape from the leprous the way you escape from a lion*"
- Word *leper* comes from Greek word "scaling"
- *M. leprae was* discovered by **Gerhard Henrik Armauer Hansen** in 1873 in Norway. Hence referred to as **Hansen's disease**.
- Leprosy control started with the use of chaulmoogra oil and for the last three decades, MDT has been the main tool against leprosy.

What causes it?



- *Mycobacterium leprae*
- Rod Shaped
- First bacterium disease in humans

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M. Leprae is discovered by Hansen from Norway in 1873

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- Leprosy develops slowly from **6months up to 40 yrs**
- Results in skin lesions and deformities, most often affecting the **cooler places on the body** (for example: eyes, nose, earlobes, hands, feet, and testicles) that can be very disfiguring.

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Mode of infection

- Although human-to-human transmission is the primary source of infection, three other species can carry and **(rarely)** transfer *M. leprae* to humans: **chimpanzees, mangabey monkeys, and nine-banded armadillos.**

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The nine - banded armadillo

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Mode of transmission

The exact rout of transmission is not fully known .

The spread of leprosy is believed to be via nasal discharge (Droplets infection).

Every 1 cc of nasal secretion contains 1- 2millions lepra bacilli

Other modes of transmissions

1. ***Contact through the skin (rare).***
2. ***Arthropod-born infection (rare).***
3. ***Through placenta and milk.***

Signs and Symptoms

Early signs and symptoms of leprosy are very subtle and occur slowly (usually over years).

- **First symptoms** :
  - Numbness and loss of temperature sensation (cannot sense very hot or cold temperatures)
- **As the disease progresses** :
  - The sensations of touch, then pain, and eventually deep pressure are decreased or lost.

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Long-term developing sequence of events :

- Relatively painless ulcers, skin lesions of **hypopigmented macules** (flat, pale areas of skin), and eye damage (dryness, reduced blinking)
- Late stage: **large ulcerations, loss of digits, and facial disfigurement**. **(for example, hands, feet, face, and knees).**

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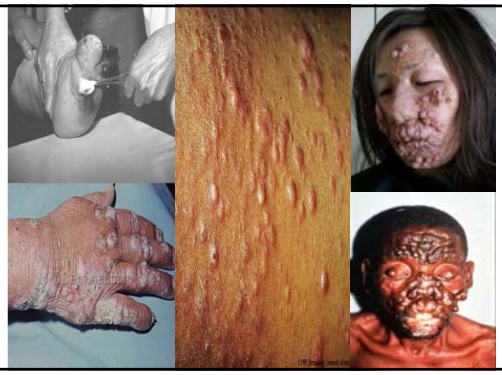

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Predisposing or risk factors

1. Residence in an **endemic area**.
2. **Poverty** (malnutrition).
3. Contact with affected **armadillo.**
4. **Immunity**

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(cont.)

- The incubation period range from **3 -5 years. Males** appear to be **twice** common than females.
- Bimodal age (10-14years & 35-44 years).
- Children are more susceptible to disease.
- Genetic factors, e.g. **HLA markers** may determine the type of leprosy which the patient develops .

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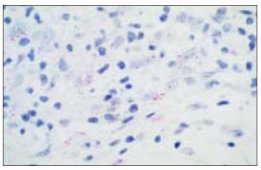
Slit Skin Smear (Reporting the smear).



(Ridley's logarithmic scale)Bacteriological index

0 – no bacilli in 100 fields

1+: 1-10 bacilli in 100 fields

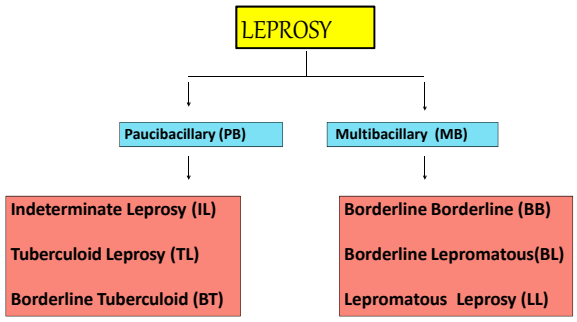
2+: 1-10 bacilli in 10 fields

3+: 1-10 bacilli in 1 field

4+: 10-100 bacilli in 1 field

5+: 100-1000 in 1 field

6+: >1000 bacilli field (globi).



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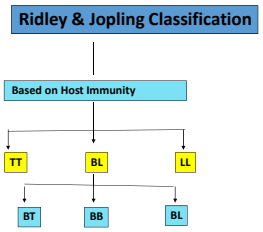
Classification & Clinical Presentation



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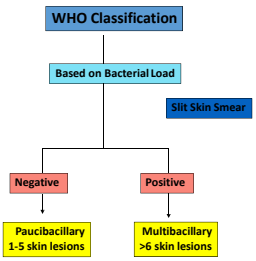
Classification & Clinical Presentation



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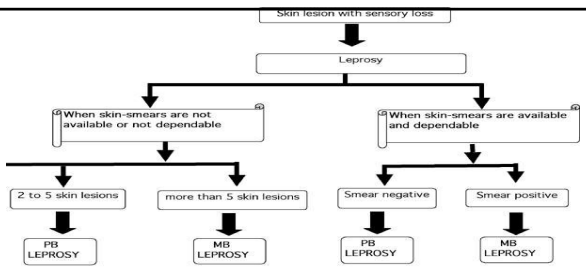

Flowchart of Diagnosis and Classification

7th WHO Expert Committee on Leprosy, June 1997

Today, the diagnosis and treatment of leprosy is **easy** and most endemic countries are striving to fully **integrate leprosy services into existing general health services.**

HISTORY OF TREATMENT

- In 1941, **promin**, a sulfone drug, showed efficacy but required many painful injections.
- **Dapsone** pills were found to be effective in the 1950s
- But soon (1960s-1970s), *M. leprae* **developed resistance** to dapsone.
- . In the early 1960s, Rifampicin and clofazimine, the other two components of MDT, were discovered.
- This **multi-drug treatment (MDT)** was recommended by the WHO in **1981** and remains, with minor changes, the therapy of choice.
- Since **1995, WHO provides free MDT** for all patients in the world
- NB: MDT, however, **does not alter the damage** done to an individual by *M. leprae* before MDT is started.

LEPROSY IS A CURABLE DISEASE

Drugs used in Leprosy treatment

What are the three commonly used drugs?

1. **Dapson.**
2. **Rifampicine.**
3. **Clofazimine.**

The combination of these three drugs is known as Multi Drug Therapy (MDT)

Treatment method with dose:

1. **Multibacillary** – Duration(12months) It treat with combination of three drugs:

a) Dapsone 100mg daily.

b) Rifampicin 600mg daily once a month.

c) Clofazimine initially 100mg for 14days then 50mg daily; 300mg once a month; supervised daily 50mg daily set of administered.

2. **Paucibacillary Leprosy**: These are combination of two drugs for this treatment:

a) Dapsone 100mg daily.

b) Rifampicin 600mg once a month.

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ADVERVE EFFECT OF ANTI-LEPROTIC DRUGS:

DRUGS	MINOR	MAJOR
1. RIFAMPICIN	RED URINE	JAUNDICE
	GIT UPSET	HEPATITIS
	FLU LIKE SYNDROME	SHOCK
2. DAPSONE	GIT UPSET	DAPSONE SYNDROME
	DRUG RASH	AGRANULOCYTOSIS
	ANAEMIA	HEMOLYTIC ANAEMIA
3. CLOFAZIMINE	GIT UPSET	ACUTE PAIN ABDOMEN
	DISCOLOURATION OF SKIN	
	ICHTHYOSIS	

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Antileprotic Agents

- **Mechanism of Action**: Bacteriostatic Dapsone is similar to sulphonamides and has the same mechanism of action. It inhibit PABA (**P**ara **A**mino **B**enzoic **A**cid – It is precursor of folic acid which is essential for the growth & multiplication of bacteria). Clofazamine interfering DNA functions. It is also anti – inflammatory property.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Dapsone	100mg orally OD
2	Rifampicin	600mg monthly
3	Clofazimine	50 – 100mg daily.
4	Ethionamide	250mg OD
5	Ofloxacin	400mg OD
6	Clarithromycin	500mg OD

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Contd

- **Contraindication & Precautions:**
- Dapsone should not be used for patient with Anemia and those showing hypersensitivity reaction.
- Clofazimine avoided during early pregnancy and the patient with kidney and liver diseases.

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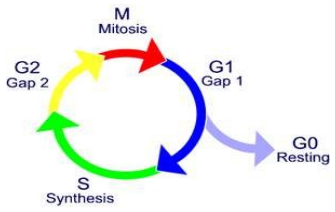
Anticancer drugs: Introduction

- **Introduction:** Cancer is a disease of cells characterised by progressive, Persistent, perverted (abnormal) Purposeless and uncontrolled proliferation of tissue.
- **Cell cycle**: Five Phases.

CANCER: A group of disease involving abnormal cell growth with the potential to invade or spread to other part of the body.



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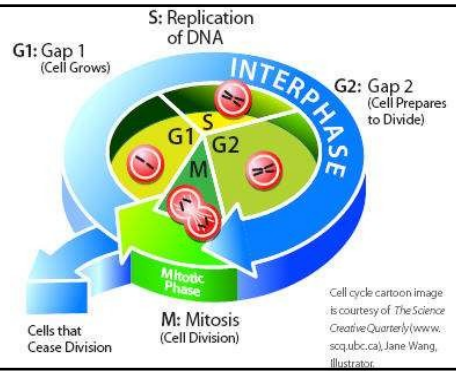

- **CELL CYCLE**

Understanding the cell cycle is necessary in cancer chemotherapy

It is a series of events that takes place in a proliferating cell (normal and malignant) leading to its division and duplication.

Phases of cell cycle

- **G_0 Phase(*resting phase*)**
  - The cell has ***not started*** diving.
  - They spend ***much of their lives*** in this phase.
  - When the cell get **a signal to reproduce**, they move into the G_1 Phase.
  - ***Limitation to successful eradication*** of many tumors by chemotherapy. They re-enter the cycle after therapy.

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- **G_1 PHASE(*Pre-synthetic phase*)**
  - The cell starts to produce ***proteins and enzymes*** necessary for DNA synthesis.
  - During this phase, ***RNA synthesis*** occurs.
  - This phase last about ***18 to 30 hours***.
- **S-PHASE(synthetic phase)**
  - **DNA synthesis**
  - Cellular DNA is **duplicated** in preparation in preparation for cellular division.
  - Length of time S phase is approximately 18-30hrs.
  - A **weak link**, and large number of anticancer agent act.

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- **G_2 Phase (*pre-mitotic phase*)**
  - the cell checks the DNA
  - Gets ready to start splitting into 2 cells.
  - Here both **protein, RNA,** and the precursors to the **mitotic spindle** apparatus are produced.
  - This phase is very short **1-2hrs**.
- **MITOTIC PHASE**
  - In this phase, which last only 30-60min, the cell actually split into 2 new cells.

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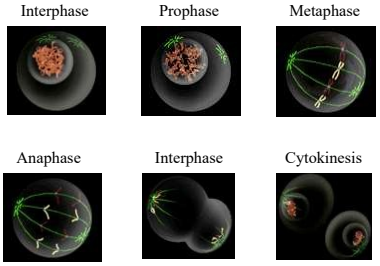
STAGES OF MITOSIS:



History:

- **No Treatment:** Before 1940
- **Surgery:** before 1955
- **Radiotherapy:** 1955~1965
- **Chemotherapy:** after 1965
- **Immunotherapy and Gene therapy**

Goals of Therapy

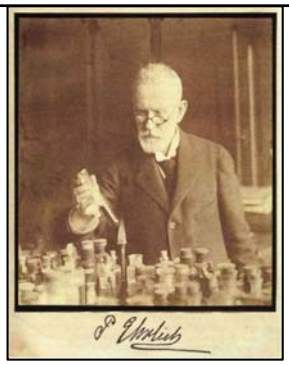
- **Cure** or induce prolonged 'remission' so that all macroscopic and microscopic features of the cancer disappear, though disease is known to persist - Acute Lymphoblastic Leukaemia, Wilm`s tumor, Ewing`s sarcoma etc. in children, Hodgekin`s lymphoma, testicular teratoma and choriocarcinoma
- **Palliation:** Shrinkage of evident tumour, alleviation of symptoms and prolongation of life - Breast cancer, ovarian cancer, endometrial carcinoma, CLL, CML, small cell cancer of lung and Non-Hodgekin lymphoma
- **Insensitive** or less sensitive but life may be prolonged - Cancer esophagus, cancer stomach, sq. cell carcinoma of lung, melanoma, pancreatic cancer, myeloma, colorectal cancer

MODALITIES OF TREATMENT

- **1-Local therapy**:
  - -surgery.
  - -radiation therapy.
- **2-Systemic treatment**:
  - *Chemotherapy.*
  - *Hormonal therapy.*
  - *Monoclonal antibodies.*
  - Radioactive material.
- **3-Supportive care**.
- **4-Non-conventional therapy.**

Cancer Chemotherapy – 5 years survival rate

Childhood Acute Lymphoblastic Leukemia	50 - 80%
Acute Adult Lymphoblastic Leukemia	20 - 60%
Childhood Acute Myeloblastic Leukemia	20 - 60%
Adult Acute Myeloblastic Leukemia	10 - 20%
Breast Cancer	5 - 20%
Hodgkin's lymphoma	40 - 80%



Paul Ehrlich 1854 - 1915

Father of Chemotherapy

- Initiated Treatment of Syphilis
- Nobel Prize 1908
- "Magic Bullet Concept"

HISTORICAL PERSPECTIVE

- Nitrogen mustards were a product of the secret war gas programs in both world wars
- In World War II, an explosion at Bar Harbor exposed seamen to mustard gas - they developed severe marrow and lymphoid hypoplasia
- Led to the use of these agents to treat Hodgkins and non-Hodgkins lymphomas at Yale in 1943.

HISTORICAL PERSPECTIVE

- In the 1950's, folic acid was shown to accelerate the progression of childhood leukemias; led to development of folic acid antagonists
- In the 1960's, combination chemotherapy for childhood leukemias and Hodgkins lymphoma began to be used.

INTRODUCTION: DEFINATIONS

- CHEMOTHERAPY: The term chemotherapy is describe as the use of chemicals or drugs to treat cancer.
- CYTOTOXIC DRUG: Lysis both normal and cancer cells

CHEMOTHERAPY

- Systemic chemotherapy is the main treatment available for disseminated malignant diseases.
- Progress in chemotherapy resulted in cure for several tumors.
- Chemotherapy usually require multiple cycles.

MODES OF CHEMOTHERAPY

- **PRIMARY CHEMOTHERAPY** - chemotherapy is used as the sole anti-cancer treatment in a highly sensitive tumor types
  - Example – CHOP for Non-Hodgkins lymphoma
- **ADJUVANT CHEMOTHERAPY** – treatment is given **after surgery** to "mop up" microscopic residual disease
  - Example – Adriamycin, cyclophosphamide for breast cancer
- **NEOADJUVANT CHEMOTHERAPY** – treatment is given **before surgery** to shrink tumor and increase chance of successful resection
  - Example – Adriamycin, ifosfamide for osteosarcoma

MODES OF CHEMOTHERAPY

- CONCURRENT CHEMOTHERAPY – treatment is given **simultaneous to radiation** to increase sensitivity of cancer cells to radiation.
- Example – Cisplatin, 5-fluourouracil, XRT for head and neck tumors.

COMPLICATION OF CHEMOTHERAPY

- Every chemotherapeutic will have some deleterious side effect on normal tissue .
- E.G; Myelosuppression, nausea & vomiting,

Stomatitis, and alopecia are the most frequently observed side effects.

SIDE EFFECTS OF CHEMOTHERAPY

Mucositis

Nausea/vomiting

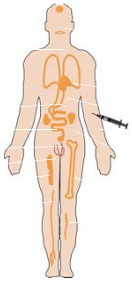
Diarrhea

Cystitis

Sterility

Myalgia

Neuropathy



CRITERIA USED TO DESCRIBE RESPONSE ARE:

- ***Complete response*** (complete remission)is the disappearance of all detectable malignant disease.
- ***Partial response*** : is decrease by more than 50% in the sum of the products of the perpendicular diameters of all measurable lesions.
- ***Stable disease*** : no increase in size of any lesion nor the appearance of any new lesions.
- ***Progressive disease*** : means an increase by at least 25% in the sum of the products of the perpendicular diameters of measurable lesion or the appearance of new lesions.

ENDOCRINE THERAPY

- Many hormonal antitumor agents are functional agonist or antagonist of the steroid hormone family.
- Adrenocorticoids:
- Antiandrogen:
- Estrogen:
- Antiestrogen:
- Progestins
- Aromatase inhibitor:
- Gonadotropin-releasing hormone agonists:
- Somatostatin analogues:

BIOLOGIC THERAPY

- Immunotherapy:
- Cytokines:
- Cellular therapy:
- Tumor vaccine:
- Hematopoietic growth factors.

Anticancer drugs: Drugs used in Cancer

- The drugs which are used to destroy cancer cell and normal tissue is known as antineoplastic agents. Combination therapy is usually used to kill as many as cancer cells.
- **Drug Classification**: These drugs mainly classified as:

1. **Alkylating Drugs**: they inhibit the synthesis of DNA.
2. **Antitumor Antibiotics**: They act as interfere with DNA & RNA synthesis.
3. **Antimetabolites**: A metabolite is a chemical substance which takes part in cellular metabolic reaction. It blocks a metabolic reaction.

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Mechanism of Action

- According to chemical structure and sources of drugs
  - Alkylating Agents, Antimetabolite, Antibiotics, Plant Extracts, Hormones and Others
- According to the cycle or phase specificity of the drug:
  - Cell cycle nonspecific agents (CCNSA) & Cell cycle specific agents (CCSA).

Mechanism of Anticancer Drugs

- According to biochemistry mechanisms of anticancer action:

✓Block nucleic acid (DNA, RNA) biosynthesis

✓Directly destroy DNA and inhibit DNA reproduction

✓Interfere transcription and block RNA synthesis

✓Interfere protein synthesis and function

✓Influence hormone homeostasis.

Block nucleic acid (DNA, RNA) biosynthesis

Antimetabolites:

- **Folic Acid Antagonist:** inhibit dihydrofolate reductase (methotrexate)
- **Pyrimidine Antagonist:** inhibit thymidylate synthetase (fluorouracil) ; inhibit DNA polymerase (cytarabine)
- **Purine Antagonist:** inhibit interconversion of purine nucleotide (6-mercaptopurine and 6-Thioguanine)
- **Ribonucleoside Diphosphate Reductase Antagonist:** (hydroxyurea)

Influence the Structure and Function of DNA

- **Alkylating Agent:** mechlorethamine, cyclophosphamide, ifosfamide, chlorambucil, Mephalan, Busulfan, Nitrosoureas and Thio-TEPA
- **Platinum:** cis-platinium, carboplatin and imatinib
- **Antibiotic:** bleomycin and mitomycin C
- **Topoismerase inhibitor:** camptothecin analogues and podophyllotoxin and antibiotics like actinomycin D, daunorubicin and doxorubicin

Interfere Protein Synthesis

- **Antitubulin: vinca alkaloids (vincristine and vinblastin)** and **taxanes (paclitaxel and docetaxel)**

Bind tubulin, destroy spindle to produce mitotic arrest

- **Influence amino acid supply: L-asparaginase**.

Influence hormone homeostasis

These drugs bind to hormone receptors to block the actions of the sex hormones which results in inhibition of tumor growth

- Estrogens and estrogen antagonistic drug (EE, SERM-tamoxifene)
- Androgens and androgen antagonistic drug (flutamide and bicalutamide)
- Progestogen drug (hydroxyprogesterone)
- Glucocorticoid drug (prednisolone and others)
- Gonadotropin-releasing hormone inhibitor: nafarelin, triptorelin
- aromatase inhibitor: Letrozole and anastrazole.

CHEMOTHERAPUETIC AGENT	MECHANISM OF ACTION	SIDE EFFECT
ALKYLATING AGENT Cyclophosphamide, chlorambucil, thiothepa, melphalan etc	Interferes with cross linkage of DNA	Myelosupression **Hemorrhagic cystitis** Skin rash Flu-like syndrome
ANTIMETABOLITES • **Folic acid antagonist** e.g methotraxate • **Purine antagonist** e.g 6-mercaptopurine, • **Pyrimidine antagonist** e.g 5-fluorouracil	Interfere with nucleic acid synthesis because they are analogues of normal metabolites	Mucositis, Nephropathy, Hepato-toxicity & Hand & foot syndrome
VINCA ALKALOID- vincristin, vimblastin	Cause mitotic arrest via spindle fiber inhibition	**Neuropathy**, constipation, Mucositis & myelosuppresion
ANTITUMOUR ANTIBIOTIC e.g adramycin, daunorubicin, actinomycin D, bleomycin	Bind to DNA to block RNA production	**cardio toxicity**, pulmonary toxicity & myelosuppresion

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CHEMOTHERAPEUTIC AGENT	MECHANISM OF ACTION	SIDE EFFECT
TAXANES e.g paclitaxel, docetaxel	Bind to tubulin. Stop disassembly of mitotic spindle	neuropathy skin rash & myelosuppresion
MISCELLANEOUS L-Asparaginase Nitrosourea Cis-platinium		

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IMMUNO-THERAPUETIC AGENTS	MECHANISM OF ACTION	CLINICAL USE
Levamisole (antihelmenthic)	immunomodulator	Adjuvant in colonic cancer in combination with 5-FU
Interleukin-2(IL-2)	Enhances NK-cells and tumour specific T-cells	Melanoma Renal cell ca Neuroblastoma NHL
Interferon	Enhance NK-cells Re-expression of HLA gene	Kaposi's sarcoma Multiple myeloma Leukemia
BCG	Stimulate immune response	CIS of the bladder,

TARGET THERAPY	MECHANISM OF ACTION	CILNICAL USES
SMALL MOLECULES Gefitinib Erlotinib	Inhibits EGFR tyrosine kinase thereby inhibiting growth of cancer cells	Non-small cell cancer of the lungs
MONOCLONAL ANTIBODIES Trastuzumab(Herceptin) Rituximab(mabthera) Bevacizumab cetuximab	Selectively kill tumour cells expressing certain receptors	Trastuzumab is use Her-2 positive breast cancer

HORMONE	CLINCAL USES
ANTI-ANDROGENS ***Flutamide*** oestrogen	Use with gosereline in the treatment of metastatic prostate cancer
ANTI-ESTROGEN Tamoxifen Pure anti-oestrogen (fasodex)	Breast cancer
SELECTIVE AROMATASE INHIBITORS Anastrozole	2nd line in ER/PR +ve breast ca
AMINOGLUTETHIMIDE	Breast and adrenal ca
PROGETINS Medroxyprogesterone acetate	Breast and endometrial
LHRH analogue Goserelin	Prostate and breast ca
CORTICOSTEROIDS Dexamethasone prenisolone	Breast ca as acombination, treatment of hypercalcemia, raise ICP from brain metastesis

ADMINISTRATION OF DRUG depend on:

- *Choice of agents*
- *Type of cancer*
- *The stage*
- *Age*
- *Clinical state of patient*
- *Co-morbidities*
- *Treatment in the past*
- *Drug interactions*

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ROUTES OF DRUG ADMINISTRATION

- *ROUTES OF ADMINSTRATION*
  - *Oral*
  - *Intravenous*
    - *Bolus*
    - *Infusion*
  - *Arterial infusion*
  - *Extracorporeal limb perfusion*
  - *Intracavitory*
  - *Intrathecal*
  - *Subcutaneous*
  - *intramuscular*
  - *Topical*

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Alkylating Drugs:

- **Contraindications:** Pregnant women, Blood cell suppression patients, Renal & Liver failure, Buscofan not useful in lymphatic and acute leukaemia.
- **Adverse effect:** Nausea, vomiting, Bone marrow depression, Ototoxicity, Nephrotoxicity, Gonadal suppression, Stomatitis, Hyperuricemia, Tinnitus, Alopecia (Cyclophosphamide), Hepatotoxicity.
- **Drug interaction:**

1. Use with other nephrotoxic & ototoxic drugs may cause additive ototoxicity.
2. Use of these drugs with anticoagulants, Asprin, NSAID's may increase risk of bleeding.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Cicplastin	10mg/day. IV
2	Cyclophosphamide	2-6mg/kg/ weekly in divided doses
3	Chorambucil	200mcg/kg body wt/day
4	Streptozocin	600mg/metre square/day (IV)

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Antitumor Antibiotics:

- **Contraindications:** Pregnancy, Chicken pox or Herpes infection, Use cautiously in pt with renal or liver dysfunction.
- **Adverse effect:** Nausea, vomiting, Anorexia, Heart failure, Cardiomyopathy, Bladder pain, UTI, Incontinence, Gonadal suppression, Stomatitis, Alopecia (Cyclophosphamide), Myocardial toxicity, Phlebitis at IV site.
- **Drug interaction:**

1. Digoxin level may decrease with use of these drugs.
2. Concurrent use with cyclophosphamide may increase cardio toxicity.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Mitomycin	6-8wk internal 20mg/meter square IV single dose.
2	Bleomycin	15,000IU once or twice a wk.
3	Dactinomycin	15mcg/kg/day.
4	Plicamycin	15-25mcg of body wt IV
5	Doxorubicin	20mg/meter square IV

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Antimetabolites

- **Contraindications:** Renal & Liver intoxicity, Bone marrow depression, Pregnant women.
- **Adverse effect:** Leukopenia, Megaloblastic Anemia, Intestinal obstruction, Stomatitis, UTI, G.I. disturbances, Hepatotoxicity, Hyperuricemia, Alopecia due to damage of hair follicle, fever, Hyperbilirubinemia, Thrombocytopenia, Photosensitivity, dermatitis, Hepatotoxicity, Renal failure, Diarrhoea. thrombophlebitis.
- **Drug interaction:** Methotrexate toxicity may increase if use this drug with tetracycline, chloramphenicol, oral hypoglycemics, phenytoin's, salicylates.

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Drug Examples & Doses:

S. no.	Drugs	Doses
1	Methotrexate	10-25mg daily
2	Pentostatin	4mg/metre square q wk IV
3	Fludarabine	40mg/metre square daily
4	Fluorouracil	15mg/kg once weekly
5	Hydroxyurea.	80mg/kg single dose q3rd day.

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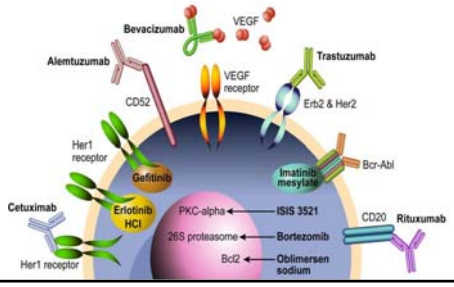
"TARGETED" THERAPIES

Definition: New technology and drugs that allow the cancer treatment to "target" a certain cancer cell by interfering with the natural functions of tumor growth

How they work: They "target" specific parts of a cancer cell or its actions.

What it means in cancer treatment: Potentially fewer side effects

Targeted Therapies



TARGETED THERAPIES

- **Monoclonal antibodies**: proteins that trigger the body's pathways involved in cancer growth to fight cancer more effectively.
- **EGFR**: family of receptors found on surface of normal and cancer cells that bind with an epidermal growth factor (EGF) causing cells to divide.
- **Tyrosine Kinase Inhibitors**: Part of the cell that signals it to divide and multiply; enhances cell growth. Still investigational

CONCLUSIONS

- People with cancer are living longer
- The focus is on quality of life in addition to quantity
- People surviving cancer want to live normal lives
- New treatments of various kinds are available and there is no need to suffer

FUTURE TRENDS

- **Tumour vaccine-** stimulate the body to produce CD4 cells which suppresses tumour cells **e.g sipuleucel-T**, **prostate G-vax** still under investigations
- **Gene therapy.**

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Cell and macromolecules

Engage: Cell History

- ***Cytology-*** study of cells
- 1665 English Scientist Robert Hooke
- Used a microscope to examine cork (plant)
- Hooke called what he saw "Cells"

Robert Hooke
(1635-1703)

Cell History

- Robert Brown
  - discovered the nucleus in 1833.
- Matthias Schleiden
  - German Botanist Matthias Schleiden
  - 1838
  - ALL PLANTS "ARE COMPOSED OF CELLS".
- Theodor Schwann
  - Also in 1838,
  - discovered that animals were made of cells

Cell History

- Rudolf Virchow
  - 1855, German Physician
  - " THAT CELLS ONLY COME FROM OTHER CELLS"
- His statement debunked "**Theory of Spontaneous Generation**"

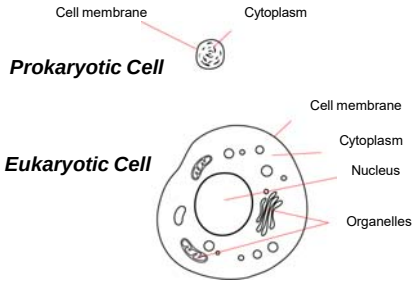
Cell Theory

- The COMBINED work of Schleiden, Schwann, and Virchow make up the modern **CELL THEORY**.

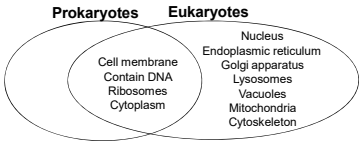
The Cell Theory states that:

1. All living things are composed of a cell or cells.
2. Cells are the basic unit of life.
3. All cells come from preexisting cells.

Internal Organization

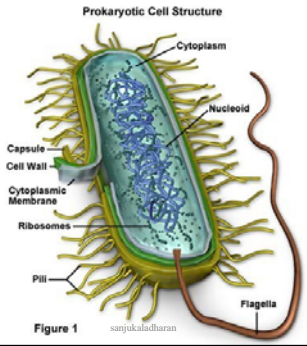


Compare and Contrast



Prokaryotic Examples

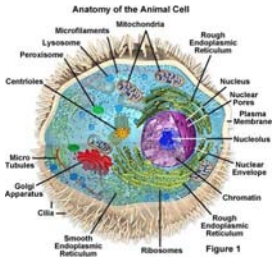
ONLY Bacteria

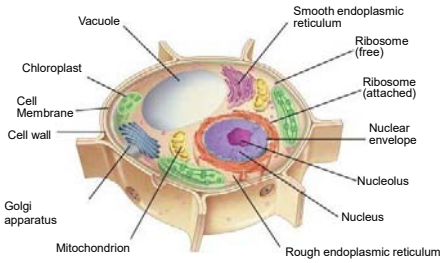


EUKARYOTIC CELLS

Two Kinds:
Plant and Animal

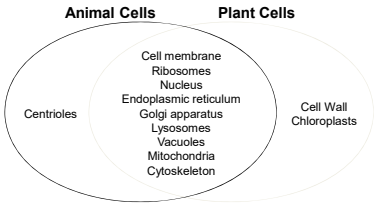
Eukaryotic Example



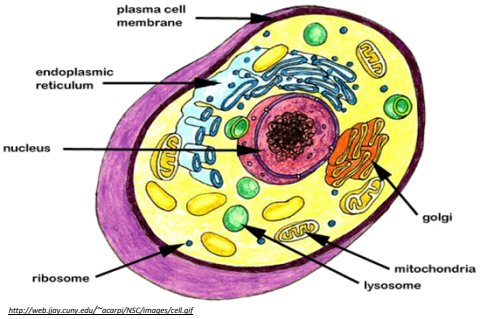


Plant Cell

Compare and Contrast

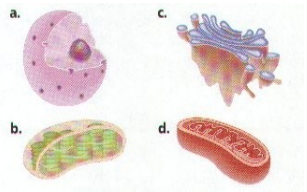


"Typical" Animal Cell



http://web.jjay.cuny.edu/~acarpi/NSC/images/cell.gif

Internal Organization



- Cells contain **ORGANELLES**.
- Cell Components that PERFORMS SPECIFIC FUNCTIONS FOR THE CELL.

Cellular Organelles

- **The Plasma membrane**
  - The boundary of the cell.
  - Composed of three distinct layers.
  - Two layers of fat and one layer of protein.

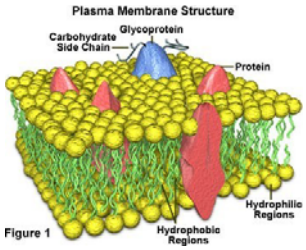


Figure 1

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- it is composed mainly of a lipid bilayer of phospholipid molecules, but with large numbers of protein molecules protruding through the layer.
- Two types of proteins occur: *integral proteins that protrude* all the way through the membrane, and *peripheral proteins* that are attached only to one surface of the membrane and do not penetrate all the way through.
- Also, carbohydrate moieties are attached to the protein molecules on the outside of the membrane and to additional protein molecules on the inside.

The Nucleus

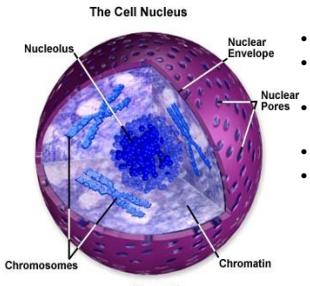

Figure 1

- Brain of Cell
- Bordered by a porous membrane - nuclear envelope.
- Contains thin fibers of DNA and protein called Chromatin.
- Rod Shaped Chromosomes
- Contains a small round nucleolus
  - produces ribosomal RNA which makes ribosomes.

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Nucleoli

- The nuclei of most cells contain one or more highly staining structures called *nucleoli.*
- it is simply an accumulation of large amounts of RNA and proteins of the types found in ribosomes.
- The nucleolus becomes considerably enlarged when the cell is actively synthesizing proteins.

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Ribosomes

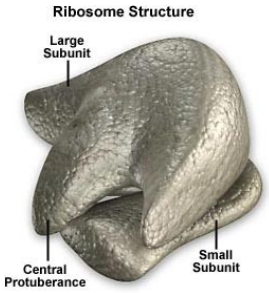

Figure 1

- Small **non-membrane** bound organelles.
- Contain two sub units
- Site of protein synthesis.
- Protein factory of the cell
- Either free floating or attached to the Endoplasmic Reticulum.

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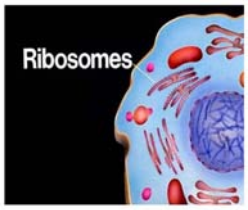
RIBOSOMES

- Structure
  - Made of proteins and RNA
  - No membrane
  - Most numerous organelle
  - Made in nucleus (specifically in nucleolus)
- Function
  - Aids in protein synthesis
  - Free ribosomes make proteins used by the cell
  - Ribosomes on rER make proteins for export to other cells
- Cell Type
  - Prokaryotic and Eukaryotic Cells
  - Plant and Animal Cells



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Endoplasmic Reticulum

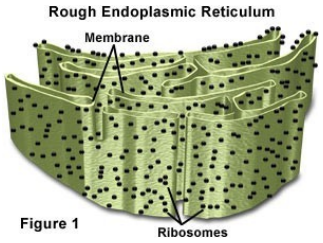

Figure 1

- Complex network of transport channels.
- Two types:

1. **Smooth**- ribosome free and functions in poison detoxification.
2. **Rough** - contains ribosomes and releases newly made protein from the cell.

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Endoplasmic Reticulum

- A system of membrane channels and saccules (flattened vesicles) continuous with the outer membrane of the nuclear envelope
- **Rough ER**
  - Studded with ribosomes on cytoplasmic side
  - Protein anabolism
    - Synthesizes proteins
    - Modifies and processes proteins
      - Adds sugar to protein
      - Results in glycoproteins
- **Smooth ER**
  - No ribosomes
  - Synthesis of lipids
  - Site of various synthetic processes, detoxification, and storage
  - Forms **transport vesicles**

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Golgi Apparatus

- A series of flattened sacs that modifies, packages, stores, and transports materials out of the cell.
- Works with the ribosomes and Endoplasmic Reticulum.

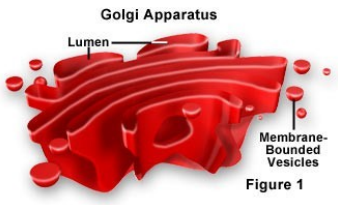

Figure 1

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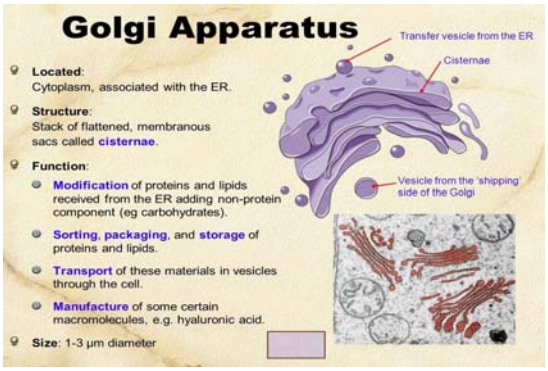
Golgi Apparatus



- **Located**: Cytoplasm, associated with the ER.
- **Structure**: Stack of flattened, membranous sacs called **cisternae**.
- **Function**:
  - **Modification** of proteins and lipids received from the ER adding non-protein component (eg carbohydrates).
  - **Sorting**, **packaging**, and **storage** of proteins and lipids.
  - **Transport** of these materials in vesicles through the cell.
  - **Manufacture** of some certain macromolecules, e.g. hyaluronic acid.
- **Size**: 1-3 µm diameter

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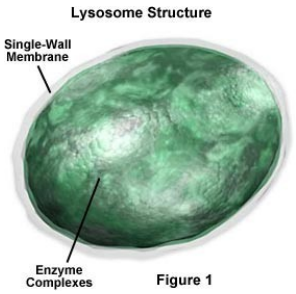
Lysosomes



- Recycling Center
  - Recycle cellular debris
- Membrane bound organelle containing a variety of enzymes.
- Internal pH is 5.
- Help digest food particles inside or out side the cell.

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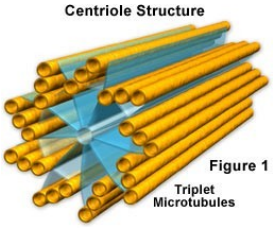
Centrioles

- Found **only** in animal cells
- Paired organelles found together near the nucleus, at right angles to each other.
- Role in building cilia and flagella
- Play a role in cellular reproduction



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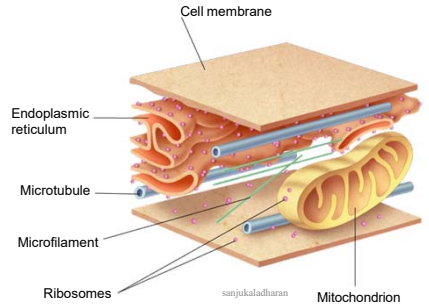
Cytoskeleton

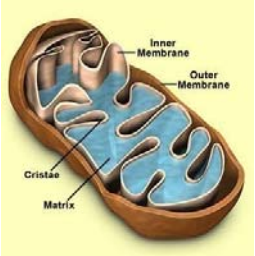


Cytoskeleton

- Framework of the cell
- Contains small microfilaments and larger microtubules.
- They support the cell, giving it its shape and help with the movement of its organelles.
- The fibrillar proteins of the cell are usually organized into filaments or tubules.
- These originate as precursor protein molecules synthesized by ribosomes in the cytoplasm.
- The precursor molecules then polymerize to form *filaments.*
- *Eg microtubules*

Mitochondrion

- Double Membranous
- It's the size of a bacterium
- Contains its own DNA; mDNA
- Produces high energy compound ATP



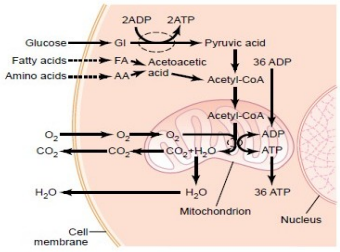


Figure 2–14

Formation of adenosine triphosphate (ATP) in the cell, showing that most of the ATP is formed in the mitochondria. ADP, adenosine diphosphate.

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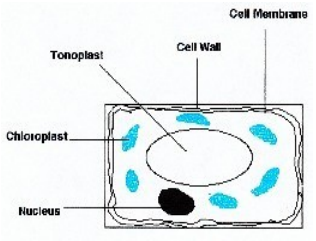
The Vacuole

- Sacs that help in food digestion or helping the cell maintain its water balance.
- Found mostly in plants and protists.
- Smaller one in animal cell



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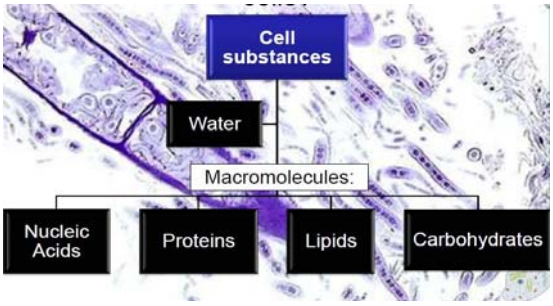
7.12D Cell Organelle Structure vs Function

Organelle	**Structure** – physical properties, like shape, color, and location	**Function** – job or role an organelle does for the cell	**Kind of cell found in?**
Cell Membrane (Plasma Membrane)	Surrounds the cytoplasm and other organelles	Allows things to enter and exit the cell; gets rid of waste	Both plant and animal cells
Cell Wall	Rigid; surrounds plant cells	provides support, protection	Plant cells only
Nucleus	Houses chromosomes / DNA – the genetic code (heredity material)	Control center, tells other organelles what to do	Both plant and animal cells
Cytoplasm	Gel-like liquid that fills the cell	Provides suspension to organelles so they move around easier	Both plant and animal cells
Mitochondrion (Mitochondria)	Double membrane organelle with inner folds	Converts glucose molecules into energy	Both plant and animal cells
Chloroplast	Filled with chlorophyll; Contains stacks of discs	Site of photosynthesis – which makes food for plant cells	Plant cells only
Vacuole	Much larger in plant cells than animal cells	Storage site of water, nutrients, and waste	Plant - large, central animal -small
Lysosome	Small, circular organelle that contains enzymes	Digest old cells parts; Aids with removal of waste	Animal cells only

The FOUR Classes of Large Biomolecules

- All living things are made up of four classes of large biological molecules:
  - Carbohydrates
  - Lipids
  - Protein
  - Nucleic Acids
- **Macromolecules** are large molecules composed of thousands of *covalently* bonded atoms
- Molecular structure and function are inseparable

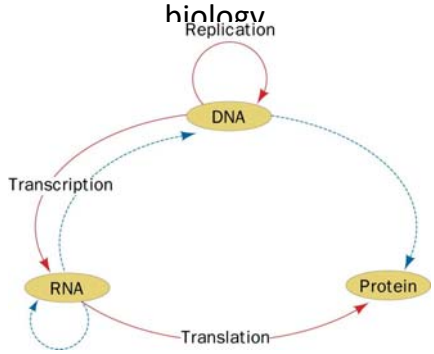
Macromolecules



		Macromolecules			
	Water	Nucleic Acids	Proteins	Lipids	Carbohydrates
Definition	Water makes up ___% of a cell's volume	Long chains of nucleotides	Long chains of Amino acids	Large macromolecule that does not dissolve in water	Sugar molecules (1, 2, or long chain)
Examples		DNA RNA	enzymes hair (horns, feathers)	fats oils	sugars starch cellulose
Importance to the cell	• dissolves substances • insulates	• carry hereditary Information • used to make proteins	• regulate cell Processes • provide structural support	• store large amounts of Energy • form Protective barrier around Cells & cell parts	• supply energy for cell processes • provide structural support

Nucleic acid

The central dogma of molecular biology



28.11 Nucleic Acids and Heredity

- Processes in the transfer of genetic information:
- Replication: identical copies of DNA are made
- Transcription: genetic messages are read and carried out of the cell nucleus to the ribosomes, where protein synthesis occurs.
- Translation: genetic messages are decoded to make proteins.

Definitions

- Nucleic acids are polymers of nucleotides
  - Nucleotides are carbon ring structures containing nitrogen linked to a 5-carbon sugar (a ribose)
  - 5-carbon sugar is either a ribose or a deoxy-ribose making the nucleotide either a ribonucleotide or a deoxyribonucleotide
- In eukaryotic cells nucleic acids are either:
  - Deoxyribose nucleic acids (DNA)
  - Ribose nucleic acids (RNA)
    - Messenger RNA (mRNA)
      Transfer RNA (tRNA)
      Ribosomal RNA (tRNA)

Nucleic Acid Function

DNA

- Genetic material - sequence of nucleotides encodes different amino aci

RNA

- Involved in the transcription/translation of genetic material (DNA)
- Genetic material of some viruses

Nucleotide Structure

- Despite the complexity and diversity of life the structure of DNA is dependent on only 4 different nucleotides
- Diversity is dependent on the nucleotide sequence
- All nucleotides are 2 ring structures composed of:
  - **5-carbon sugar :** β-D-ribose (RNA)
    β-D-deoxyribose (DNA)
  - **Base** **Purine**
    Pyrimidine
  - **Phosphate group** A nucleotide **WITHOUT** a phosphate group is a **NUCLEOSIDE**

TABLE 8–1 Nucleotide and Nucleic Acid Nomenclature

Base	Nucleoside	Nucleotide	Nucleic acid
Purines			
Adenine	Adenosine Deoxyadenosine	Adenylate Deoxyadenylate	RNA DNA
Guanine	Guanosine Deoxyguanosine	Guanylate Deoxyguanylate	RNA DNA
Pyrimidines			
Cytosine	Cytidine Deoxycytidine	Cytidylate Deoxycytidylate	RNA DNA
Thymine	Thymidine or deoxythymidine	Thymidylate or deoxythymidylate	DNA
Uracil	Uridine	Uridylate	RNA

Note: "Nucleoside" and "nucleotide" are generic terms that include both ribo- and deoxyribo- forms. Also, ribonucleosides and ribonucleotides are here designated simply as nucleosides and nucleotides (e.g., riboadenosine as adenosine), and deoxyribonucleosides and deoxyribonucleotides as deoxynucleosides and deoxynucleotides (e.g., deoxyriboadenosine as deoxyadenosine). Both forms of naming are acceptable, but the shortened names are more commonly used. Thymine is an exception; "ribothymidine" is used to describe its unusual occurrence in RNA.

Table 8-1
Lehninger Principles of Biochemistry, Fifth Edition

Names of Nucleosides and Nucleotides

Base	Nucleosides	Nucleotides
RNA		
Adenine (A)	Adenosine (A)	Adenosine 5'-monophosphate (AMP)
Guanine (G)	Guanosine (G)	Guanosine 5'-monophosphate (GMP)
Cytosine (C)	Cytidine (C)	Cytidine 5'-monophosphate (CMP)
Uracil (U)	Uridine (U)	Uridine 5'-monophosphate (UMP)
DNA		
Adenine (A)	Deoxyadenosine (A)	Deoxyadenosine 5'-monophosphate (dAMP)
Guanine (G)	Deoxyguanosine (G)	Deoxyguanosine 5'-monophosphate (dGMP)
Cytosine (C)	Deoxycytidine (C)	Deoxycytidine 5'-monophosphate (dCMP)
Thymine (T)	Deoxythymidine (T)	Deoxythymidine 5'-monophosphate (dTMP)

base (purine 、 pyrimdine)
+ribose （deoxyribos

↓ N-glycosyl linkage

nucleoside+phosphate

↓ phosphoester linkage

nucleotide

↓ phosphodiester linkage

Functions of Nucleotides and Nucleic Acids

- Nucleotide Functions:
  - Energy for metabolism (ATP)
  - Enzyme cofactors (NAD^+)
  - Signal transduction (cAMP)
- Nucleic Acid Functions:
  - Storage of genetic info (DNA)
  - Transmission of genetic info (mRNA)
  - Processing of genetic information (ribozymes)
  - Protein synthesis (tRNA and rRNA)

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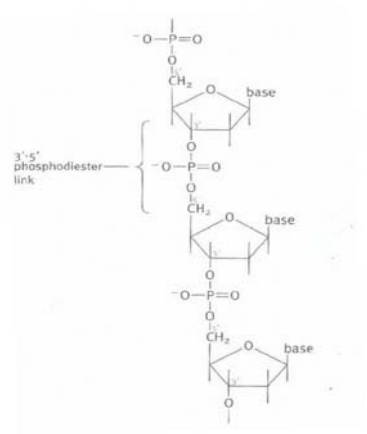
28.10 Base Pairing in DNA: The Watson–Crick Model

- In 1953 Watson and Crick noted that DNA consists of two polynucleotide strands, running in opposite directions and coiled around each other in a double helix
- Strands are held together by hydrogen bonds between specific pairs of bases
- Adenine (A) and thymine (T) form strong hydrogen bonds to each other but not to C or G
- (G) and cytosine (C) form strong hydrogen bonds to each other but not to A or T

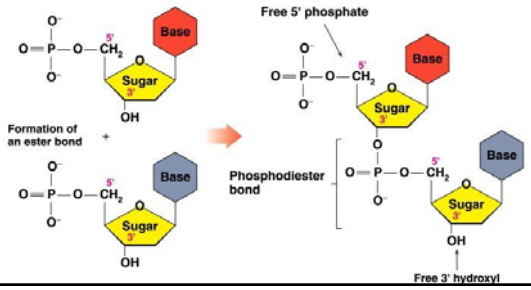
The Difference in the Strands

- The strands of DNA are complementary because of H-bonding
- Whenever a G occurs in one strand, a C occurs opposite it in the other strand
- When an A occurs in one strand, a T occurs in the other

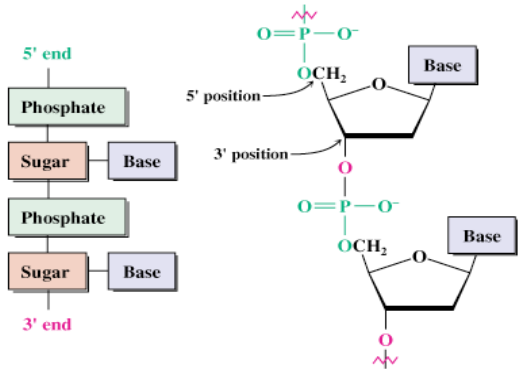


Primary Structure of Nucleic Acids

- The **primary structure** of a nucleic acid is the nucleotide sequence
- The nucleotides in nucleic acids are joined by phosphodiester bonds
- The 3'-OH group of the sugar in one nucleotide forms an ester bond to the phosphate group on the 5'-carbon of the sugar of the next nucleotide

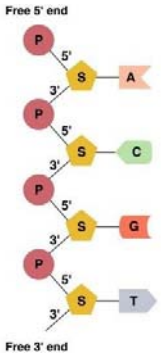


Generalized Structure of DNA

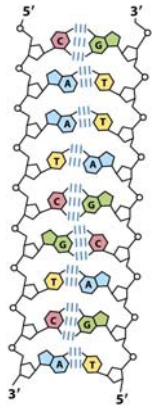


Reading Primary Structure

- A nucleic acid polymer has a free 5′-phosphate group at one end and a free 3′-OH group at the other end
- The sequence is read from the free 5′-end using the letters of the bases
- This example reads 5′—A—C—G—T—3′



Properties of a DNA double helix



The strands of DNA are antiparallel

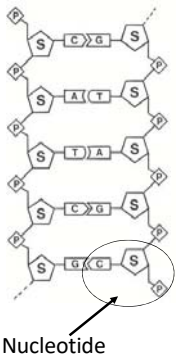
The strands are complimentary

There are Hydrogen bond forces

There are base stacking interactions

There are 10 base pairs per turn

Untwisted it looks like this:



- The **sides** of the ladder are:
  P = **phosphate**
  S = **sugar** molecule
- The **steps** of the ladder are C, G, T, A = **nitrogenous bases**
  (Nitrogenous means containing the element **nitrogen**.)

A = **Adenine** **(Apples are Tasty)**
T = **Thymine**
A always pairs with T in DNA

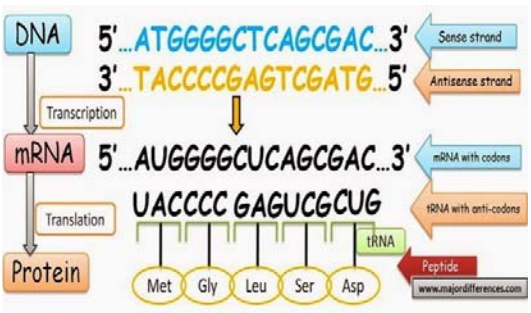
C = **Cytosine** **(Cookies are Good)**
G = **Guanine**
C always pairs with G in DNA

Secondary Structure: DNA Double Helix

- In DNA there are two strands of nucleotides that wind together in a **double helix**
  - the strands run in opposite directions
  - the bases are are arranged in step-like pairs
  - the **base pairs** are held together by hydrogen bonding
- The pairing of the bases from the two strands is very specific
- The **complimentary base pairs** are **A-T** and **G-C**
  - two hydrogen bonds form between A and T
  - three hydrogen bonds form between G and C
- Each pair consists of a purine and a pyrimidine, so they are the same width, keeping the two strands at equal distances from each other

Sense vs. Antisense DNA strands

- The DNA double helix has two strands
- Only one of them is transcribed
- The **transcribed** strand is the **antisense** strand
- The **non transcribed** strand is the **sense** strand
- ***mRNA is complementary to the anitsense strand***



5'- A T G C A T G C -3' Sense (Partner)
| | | | | | | |
3'- T A C G T A C G -5' Template (Antisense)
| | | | | | | |
5'- A U G C A U G C -3' Messenger RNA

Ribonucleic Acid (RNA)

- RNA is much more abundant than DNA
- There are several important differences between RNA and DNA:
  - the pentose sugar in RNA is ribose, in DNA it's deoxyribose
  - in RNA, uracil replaces the base thymine (U pairs with A)
  - RNA is single stranded while DNA is double stranded
  -RNA molecules are much smaller than DNA molecules
- There are three main types of RNA:
  - ribosomal (rRNA), messenger (mRNA) and transfer (tRNA)

Types of RNA

Table 22.3 Types of RNA Molecules

Type	Abbreviation	Percentage of Total RNA	Function in the Cell
Ribosomal RNA	rRNA	75	Major component of the ribosomes
Messenger RNA	mRNA	5–10	Carries information for protein synthesis from the DNA in the nucleus to the ribosomes
Transfer RNA	tRNA	10–15	Brings amino acids to the ribosomes for protein synthesis

Messenger RNA (mRNA)

- Its sequence is copied from genetic DNA
- It travels to ribsosomes, small granular particles in the cytoplasm of a cell where protein synthesis takes place

Ribosomal RNA (rRNA)

- Ribosomes are a complex of proteins and rRNA
- The synthesis of proteins from amino acids and ATP occurs in the ribosome
- The rRNA provides both structure and catalysis

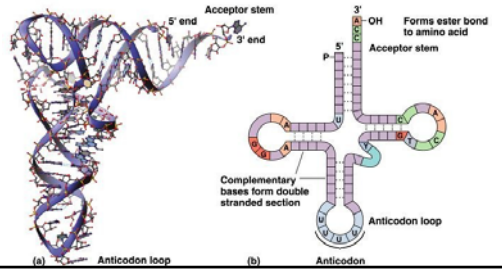
Transfer RNA (tRNA)

- Transports amino acids to the ribosomes where they are joined together to make proteins
- There is a specific tRNA for each amino acid
- Recognition of the tRNA at the anti-codon communicates which amino acid is attached

Transfer RNA

- **Transfer RNA** translates the genetic code from the messenger RNA and brings specific amino acids to the ribosome for protein synthesis
- Each amino acid is recognized by one or more specific tRNA
- tRNA has a tertiary structure that is L-shaped

  - one end attaches to the amino acid and the other binds to the mRNA by a 3-base complimentary sequence



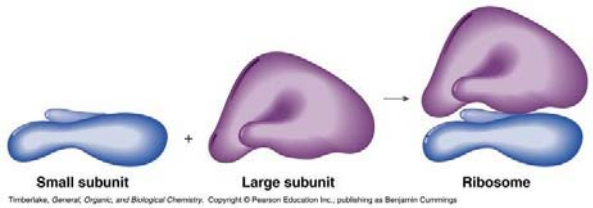
Ribosomal RNA and Messenger RNA

- **Ribosomes** are the sites of protein synthesis

  - they consist of **ribosomal DNA** (65%) and proteins (35%)

  - they have two subunits, a large one and a small one
- **Messenger RNA** carries the genetic code to the ribosomes

  -they are strands of RNA that are complementary to the DNA of the gene for the protein to be synthesized



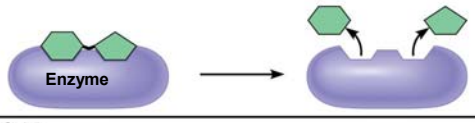
Proteins

Proteins Come In Many Varieties!

- Proteins include a diversity of structures, resulting in a wide range of functions
- Proteins account for more than 50% of the *dry* mass of most cells
- Protein functions include structural support, storage, transport, cellular communications, movement, and defense against foreign substances

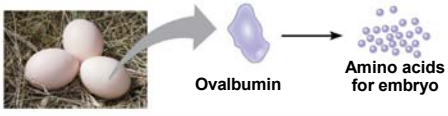
Enzymatic proteins

Function: Selective acceleration of chemical reactions
Example: Digestive enzymes catalyze the hydrolysis of bonds in food molecules.



Storage proteins

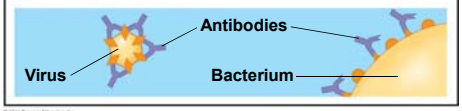
Function: Storage of amino acids
Examples: Casein, the protein of milk, is the major source of amino acids for baby mammals. Plants have storage proteins in their seeds. Ovalbumin is the protein of egg white, used as an amino acid source for the developing embryo.



Defensive proteins

Function: Protection against disease

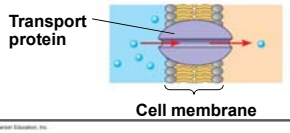
Example: Antibodies inactivate and help destroy viruses and bacteria.



Transport proteins

Function: Transport of substances

Examples: Hemoglobin, the iron-containing protein of vertebrate blood, transports oxygen from the lungs to other parts of the body. Other proteins transport molecules across cell membranes.



Hormonal proteins

Function: Coordination of an organism's activities

Example: Insulin, a hormone secreted by the pancreas, causes other tissues to take up glucose, thus regulating blood sugar concentration.

Receptor proteins

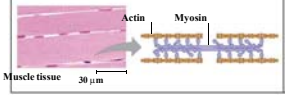
Function: Response of cell to chemical stimuli

Example: Receptors built into the membrane of a nerve cell detect signaling molecules released by other nerve cells.

Contractile and motor proteins

Function: Movement

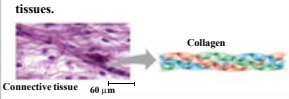
Examples: Motor proteins are responsible for the undulations of cilia and flagella. Actin and myosin proteins are responsible for the contraction of muscles.



Structural proteins

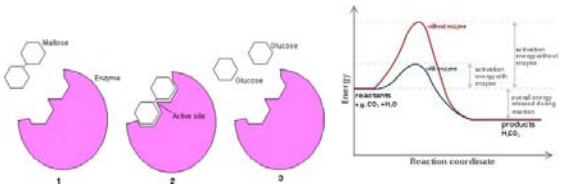
Function: Support

Examples: Keratin is the protein of hair, horns, feathers, and other skin appendages. Insects and spiders use silk fibers to make their cocoons and webs, respectively. Collagen and elastin proteins provide a fibrous framework in animal connective tissues.



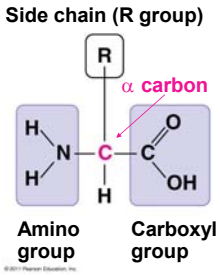
More About Enzymes

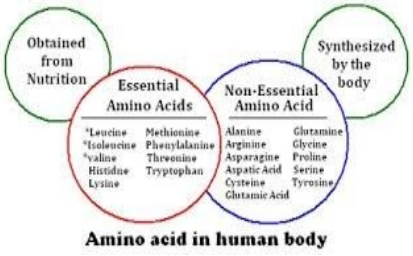
- **Enzymes** are a type of protein that acts as a **catalyst** to speed up chemical reactions
- Enzymes can perform their functions repeatedly, functioning as workhorses that carry out the processes of life



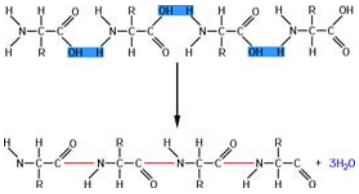
Amino Acids: Yet Another Monomer

- **Amino acids** are organic molecules with carboxyl and amino groups
- Amino acids differ in their properties due to differing side chains, called R groups

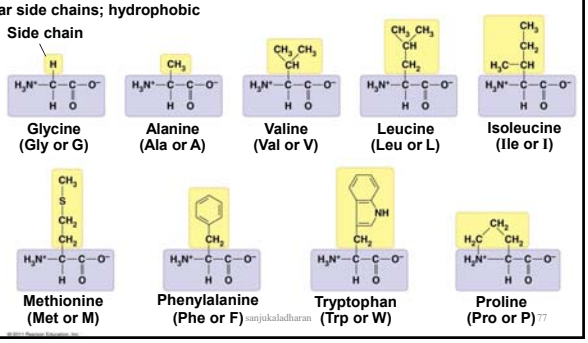




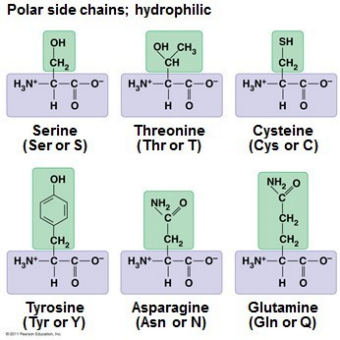
- **Polypeptides** are unbranched polymers built from the same set of 20 amino acids
- A **protein** is a biologically functional molecule that consists of one or more polypeptides

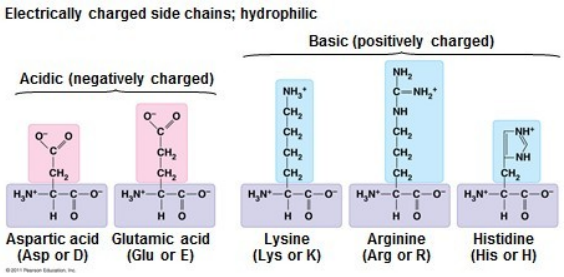


polar side chains; hydrophobic



Polar side chains; hydrophilic

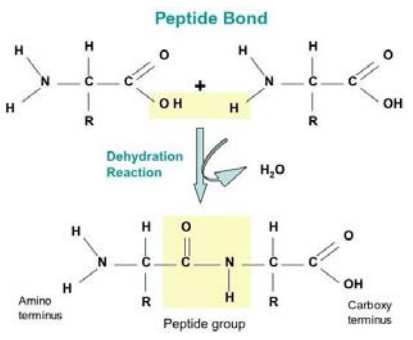




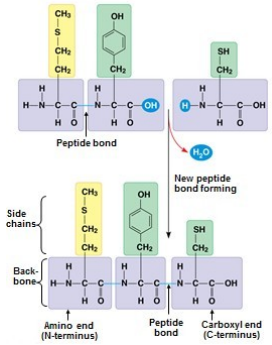
Peptide Bonds

- Amino acids are linked by **peptide bonds**
- A polypeptide is a polymer of amino acids
- Polypeptides range in length from a few to more than a thousand monomers (Yikes!)
- Each polypeptide has a unique linear sequence of amino acids, with a carboxyl end (C-terminus) and an amino end (N-terminus)

Peptide Bonds



Peptide Bonds



Protein Structure & Function

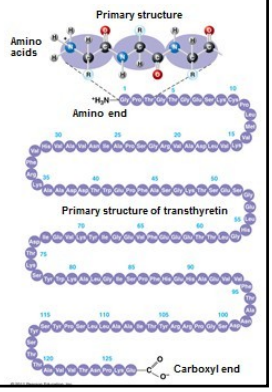
- At first, all we have is a string of AA's bound with peptide bonds.
- Once the string of AA's interacts with itself and its environment (often aqueous), then we have a functional protein that consists of one or more polypeptides precisely twisted, folded, and coiled into a unique shape
- The sequence of amino acids determines a protein's three-dimensional structure
- A protein's structure determines its function

Protein Structure: 4 Levels

- P*rimary* structure consists of its unique sequence of amino acids
- *Secondary* structure, found in most proteins, consists of coils and folds in the polypeptide chain
- *Tertiary* structure is determined by interactions among various side chains (R groups)
- *Quaternary* structure results when a protein consists of multiple polypeptide chains

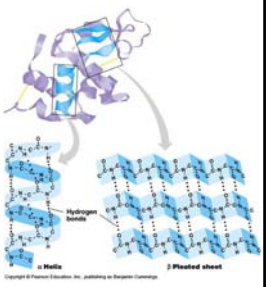
Primary Structure

- **Primary structure**, the sequence of amino acids in a protein, is like the order of letters in a long word
- Primary structure is determined by inherited genetic information

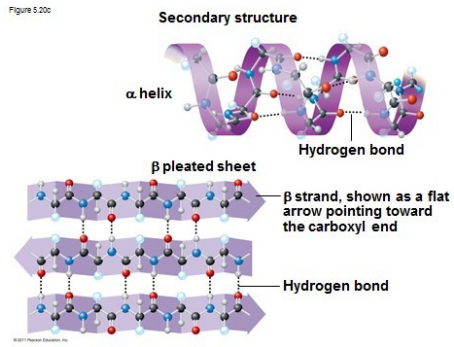


Secondary Structure

- The coils and folds of **secondary structure** result from hydrogen bonds between repeating constituents of the polypeptide backbone
- Typical secondary structures are a coil called an α **helix** and a folded structure called a β **pleated sheet**



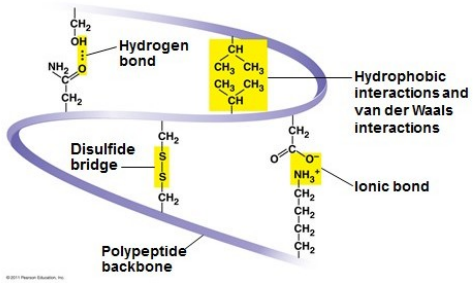
Secondary Structure



Tertiary Structure

- **Tertiary structure** is determined by interactions between R groups, rather than interactions between backbone constituents
- These interactions between R groups include actual *ionic bonds and* strong *covalent bonds* called **disulfide bridges** which may *reinforce* the protein's structure.
- **IMFs** such as London dispersion forces (LDFs a.k.a. and van der Waals interactions), hydrogen bonds (IMFs), and **hydrophobic interactions** (IMFs) may *affect* the protein's structure

Tertiary Structure

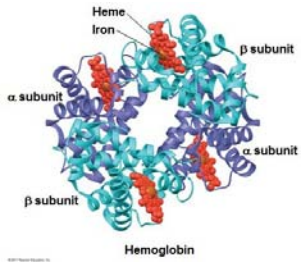


Quaternary Structure

- **Quaternary structure** results when two or more polypeptide chains form one macromolecule
- Collagen is a fibrous protein consisting of three polypeptides coiled like a rope

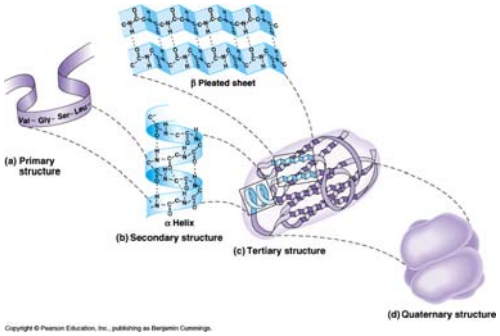
Quaternary Structure

- Hemoglobin is a globular protein consisting of four polypeptides: two alpha and two beta chains



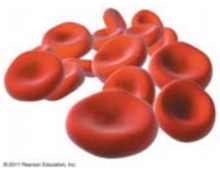
Hemoglobin

Four Levels of Protein Structure Revisited



Sickle-Cell Disease: A change in Primary Structure

- A slight change in primary structure can affect a protein's structure and ability to function
- **Sickle-cell disease**, an inherited blood disorder, results from a single amino acid substitution in the protein hemoglobin


"Normal" Red Blood Cells

Sickle-Cell Disease: A change in Primary Structure

- A slight change in primary structure can affect a protein's structure and ability to function
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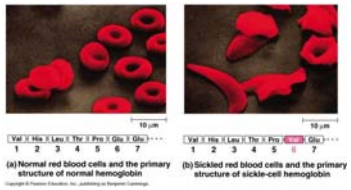
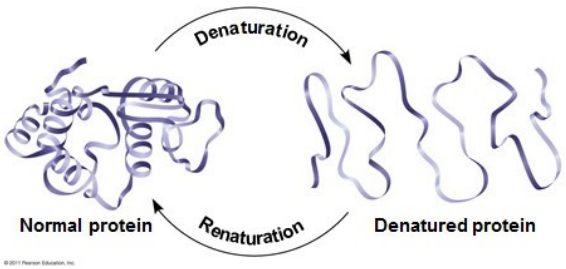


What Determines Protein Structure?

- In addition to primary structure, physical and chemical conditions can affect structure
- Alterations in pH, salt concentration, temperature, or other environmental factors can cause a protein to unravel
- This loss of a protein's native structure is called **denaturation**
- A denatured protein is biologically inactive

Denature: Break Bonds or Disrupt IMFs



carbohydrates

Carbohydrates serve as fuel and building material

- **Carbohydrates** include sugars and the polymers of sugars
- The simplest carbohydrates are monosaccharides, or single sugars
- Carbohydrate macromolecules are polysaccharides, polymers composed of many sugar building blocks

Sugars

- **Monosaccharides** have molecular formulas that are usually multiples of CH_2O
- Glucose ($C_6H_{12}O_6$) is the most common monosaccharide
- Monosaccharides are classified by
  - The location of the carbonyl group (as aldose or ketose)
  - The number of carbons in the carbon skeleton

Figure 5.3

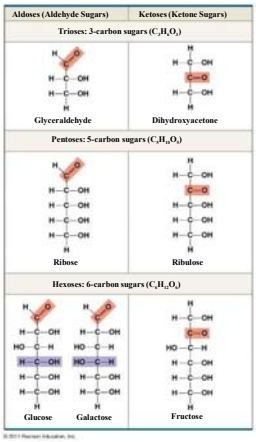


Figure 5.3a

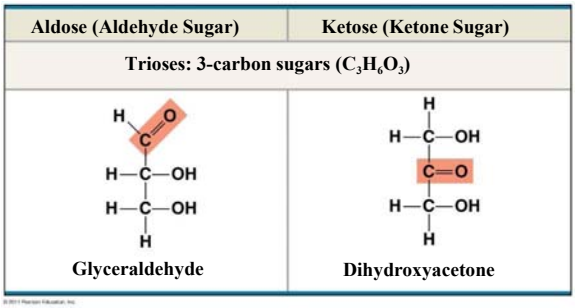


Figure 5.3b

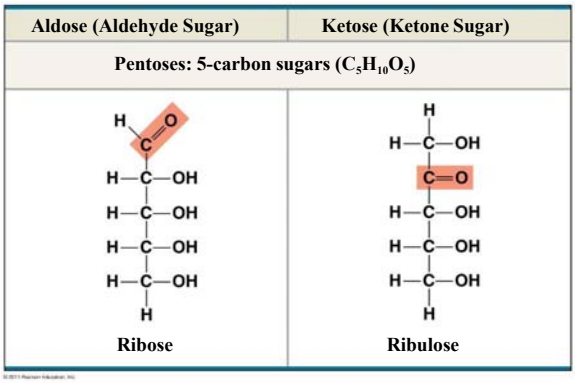
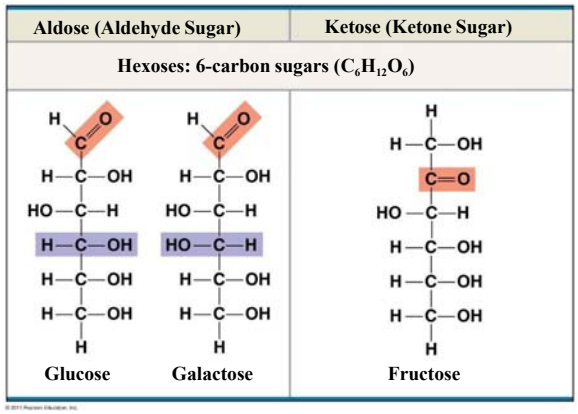
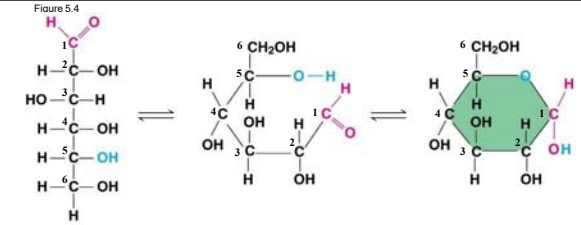


Figure 5.3c

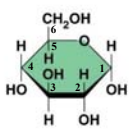


- Though often drawn as linear skeletons, in aqueous solutions many sugars form rings
- Monosaccharides serve as a major fuel for cells and as raw material for building molecules

Figure 5.4



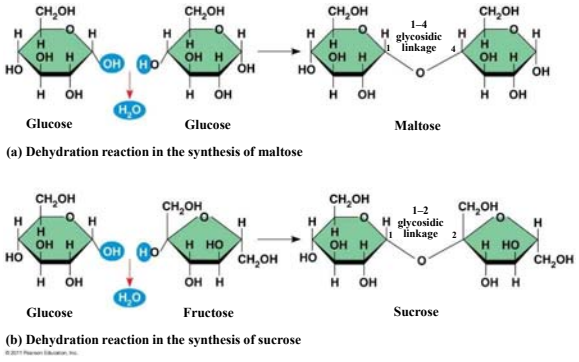
(a) Linear and ring forms



(b) Abbreviated ring structure

- A **disaccharide** is formed when a dehydration reaction joins two monosaccharides
- This covalent bond is called a **glycosidic linkage**

Figure 5.5



Polysaccharides

- **Polysaccharides**, the polymers of sugars, have storage and structural roles
- The structure and function of a polysaccharide are determined by its sugar monomers and the positions of glycosidic linkages

Storage Polysaccharides

- **Starch**, a storage polysaccharide of plants, consists entirely of glucose monomers
- Plants store surplus starch as granules within chloroplasts and other plastids
- The simplest form of starch is amylose

Figure 5.6

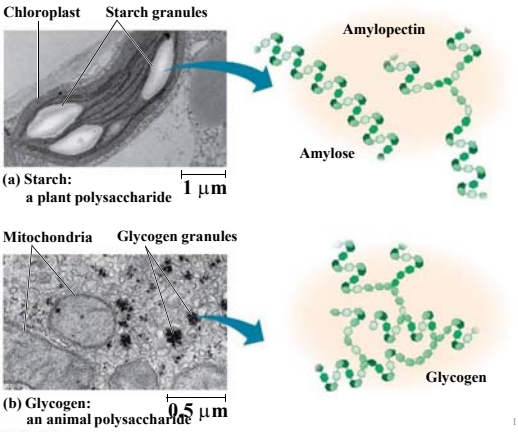


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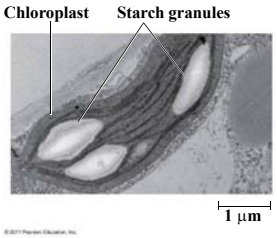
Figure 5.6a



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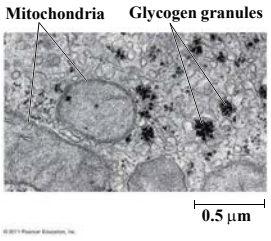
- **Glycogen** is a storage polysaccharide in animals
- Humans and other vertebrates store glycogen mainly in liver and muscle cells

112

Figure 5.6b



113

Structural Polysaccharides

- The polysaccharide **cellulose** is a major component of the tough wall of plant cells
- Like starch, cellulose is a polymer of glucose, but the glycosidic linkages differ
- The difference is based on two ring forms for glucose: alpha (α) and beta (β)

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Figure 5.7

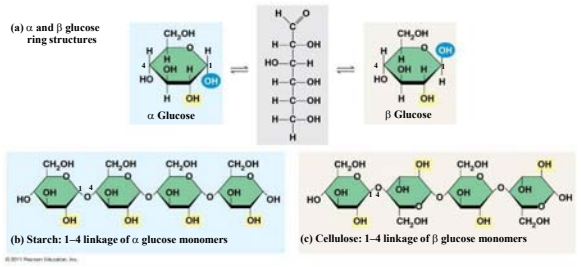


Figure 5.7a

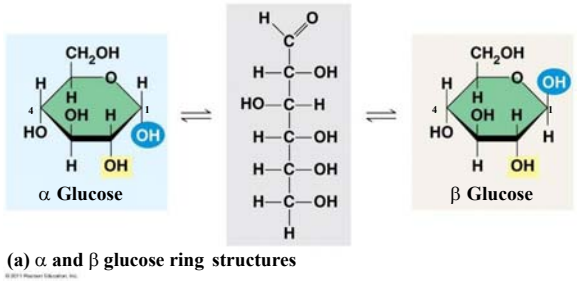
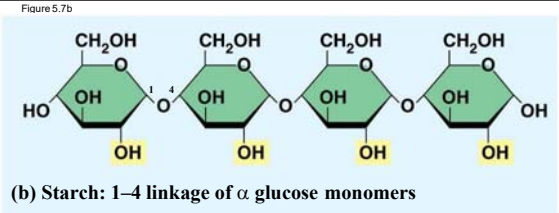
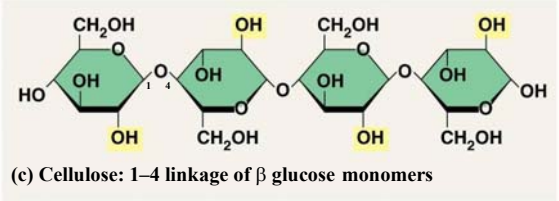
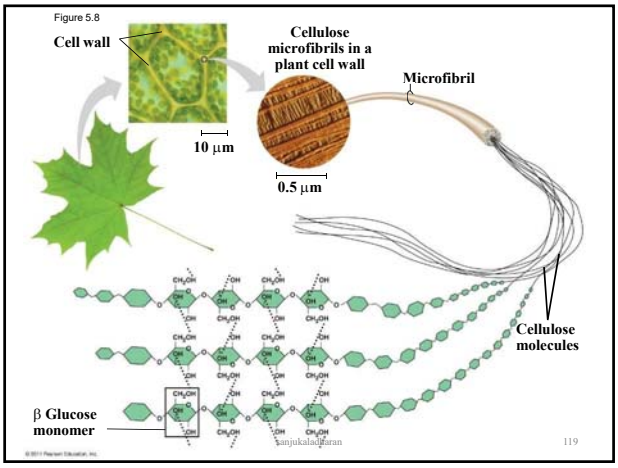


Figure 5.7b





- Polymers with α glucose are helical
- Polymers with β glucose are straight
- In straight structures, H atoms on one strand can bond with OH groups on other strands
- Parallel cellulose molecules held together this way are grouped into microfibrils, which form strong building materials for plants



- Enzymes that digest starch by hydrolyzing α linkages can't hydrolyze β linkages in cellulose
- Cellulose in human food passes through the digestive tract as insoluble fiber
- Some microbes use enzymes to digest cellulose
- Many herbivores, from cows to termites, have symbiotic relationships with these microbes

- **Chitin**, another structural polysaccharide, is found in the exoskeleton of arthropods
- Chitin also provides structural support for the cell walls of many fungi

LIPIDS

Lipids Overview

- Variety of compounds that do not dissolve in water
- Fats - solid at room temperature
  - saturated fats - animal
- Oils - liquid at room temp.
  - unsaturated fats - plants
- Triglycerides - storage form
- Phospholipids - polar and non-polar, form cell membranes
- Lipoproteins - carriers for fats in blood

Lipids are a diverse group of hydrophobic molecules

- **Lipids** are the one class of large biological molecules that do not form polymers
- The unifying feature of lipids is having little or no affinity for water
- Lipids are hydrophobic because they consist mostly of hydrocarbons, which form nonpolar covalent bonds
- The most biologically important lipids are fats, phospholipids, and steroids

Fats

- **Fats** are constructed from two types of smaller molecules: glycerol and fatty acids
- Glycerol is a three-carbon alcohol with a hydroxyl group attached to each carbon
- A **fatty acid** consists of a carboxyl group attached to a long carbon skeleton

Figure 5.10

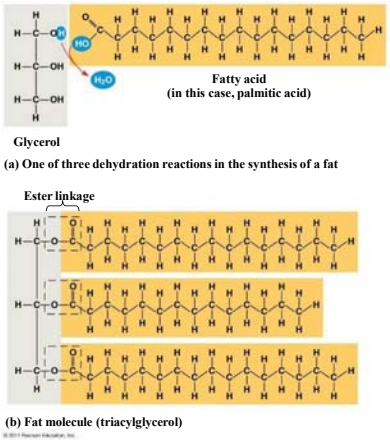
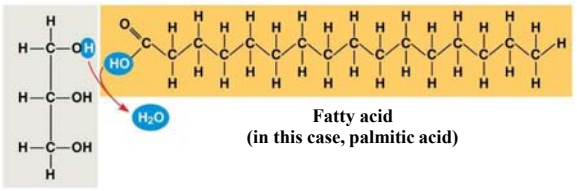


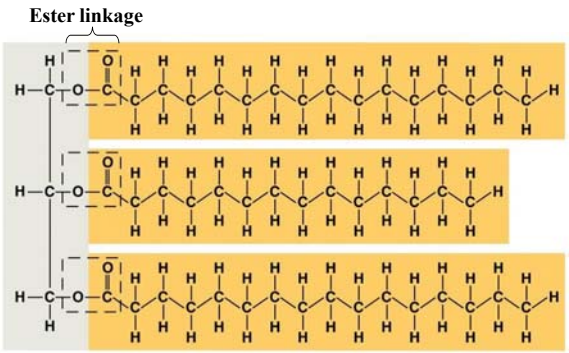
Figure 5.10a



(a) One of three dehydration reactions in the synthesis of a fat

- Fats separate from water because water molecules form hydrogen bonds with each other and exclude the fats
- In a fat, three fatty acids are joined to glycerol by an ester linkage, creating a **triacylglycerol**, or triglyceride

Figure 5.10b



(b) Fat molecule (triacylglycerol)

- Fatty acids vary in length (number of carbons) and in the number and locations of double bonds
- **Saturated fatty acids** have the maximum number of hydrogen atoms possible and no double bonds
- **Unsaturated fatty acids** have one or more double bonds

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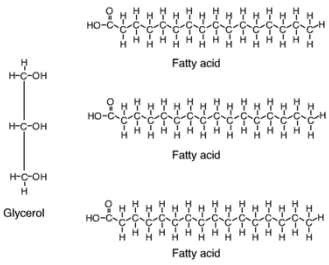

Animation: Fats
Right-click slide / select "Play"

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Figure 5.11

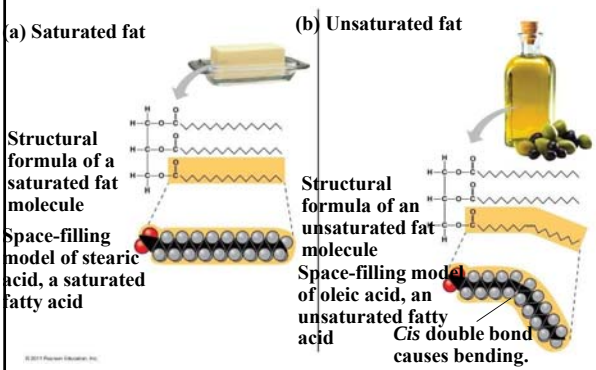


Figure 5.11a

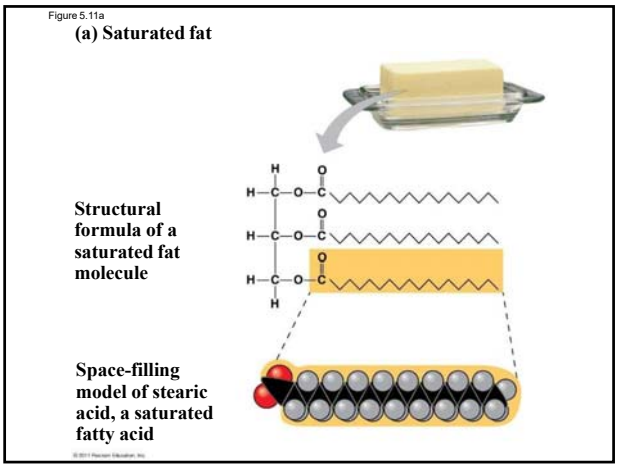
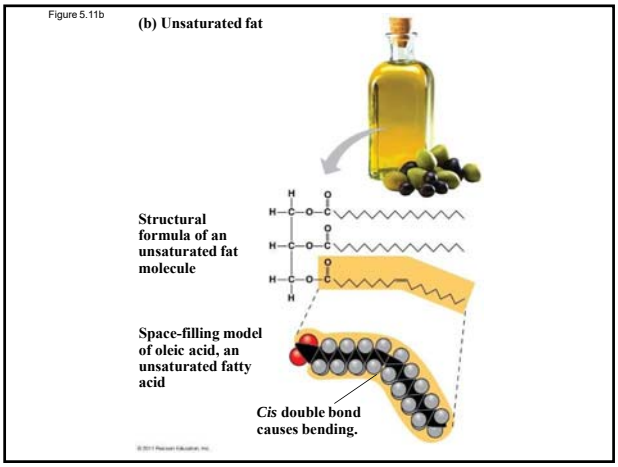


Figure 5.11b



- Fats made from saturated fatty acids are called saturated fats, and are solid at room temperature
- Most animal fats are saturated
- Fats made from unsaturated fatty acids are called unsaturated fats or oils, and are liquid at room temperature
- Plant fats and fish fats are usually unsaturated

- A diet rich in saturated fats may contribute to cardiovascular disease through plaque deposits
- Hydrogenation is the process of converting unsaturated fats to saturated fats by adding hydrogen
- Hydrogenating vegetable oils also creates unsaturated fats with *trans* double bonds
- These ***trans* fats** may contribute more than saturated fats to cardiovascular disease

- Certain unsaturated fatty acids are not synthesized in the human body
- These must be supplied in the diet
- These essential fatty acids include the omega-3 fatty acids, required for normal growth, and thought to provide protection against cardiovascular disease

- The major function of fats is energy storage
- Humans and other mammals store their fat in adipose cells
- Adipose tissue also cushions vital organs and insulates the body

Phospholipids

- In a **phospholipid**, two fatty acids and a phosphate group are attached to glycerol
- The two fatty acid tails are hydrophobic, but the phosphate group and its attachments form a hydrophilic head

Figure 5.12

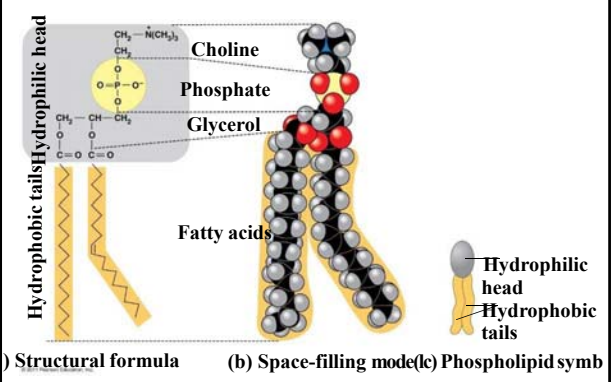
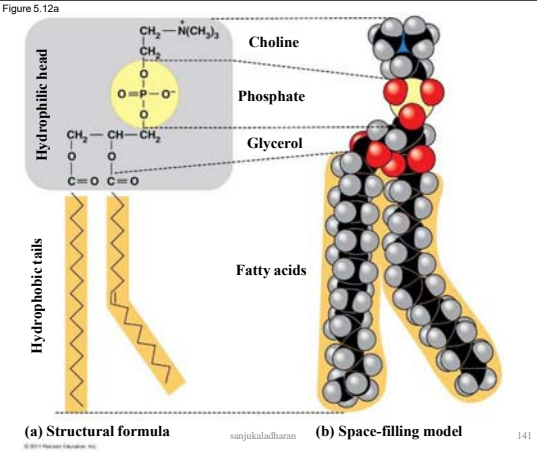
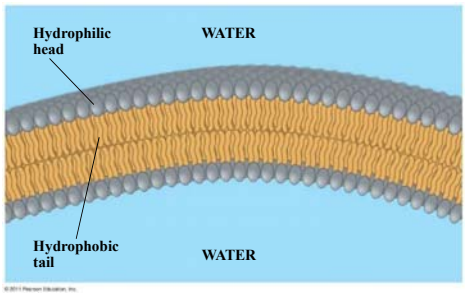


Figure 5.12a



- When phospholipids are added to water, they self-assemble into a bilayer, with the hydrophobic tails pointing toward the interior
- The structure of phospholipids results in a bilayer arrangement found in cell membranes
- Phospholipids are the major component of all cell membranes

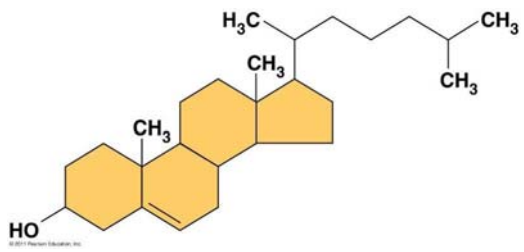
Figure 5.13



Steroids

- **Steroids** are lipids characterized by a carbon skeleton consisting of four fused rings
- **Cholesterol**, an important steroid, is a component in animal cell membranes
- Although cholesterol is essential in animals, high levels in the blood may contribute to cardiovascular disease

Figure 5.14



Macromolecular assembly (MA)

- The term **macromolecular assembly** (MA) refers to massive chemical structures such as viruses and non-biologicnanoparticles cellular organelles and membranes and ribosomes, etc. that are complex mixtures of polypeptide, polynucleotide, polysaccharide or other polymeric molecules.
- They are generally of more than one of these types, and the mixtures are defined spatially (i.e., with regard to their chemical shape), and with regard to their underlying chemical composition and structure.

Bacterial Ribosomes (and mitochondrial/chloroplast)

A ribosome is composed of structures called the large and small subunits

Each subunit is formed from the assembly of Proteins + rRNA

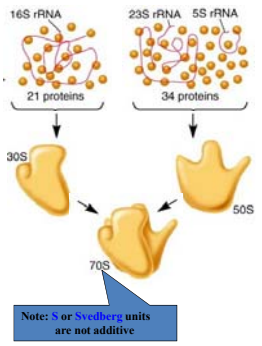


Figure 13.13

Eukaryotic Ribosomes

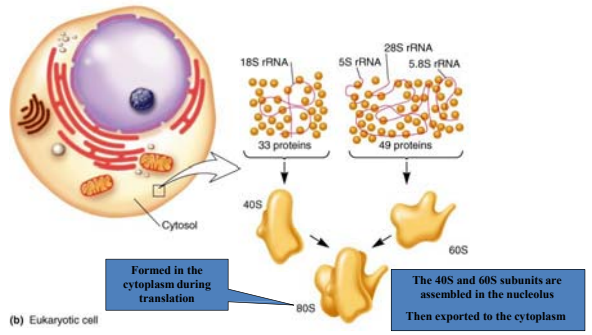


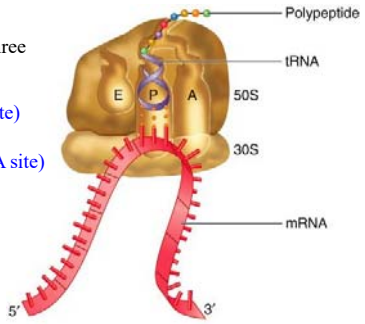
Figure 13.13

Ribosomes contain three discrete sites:

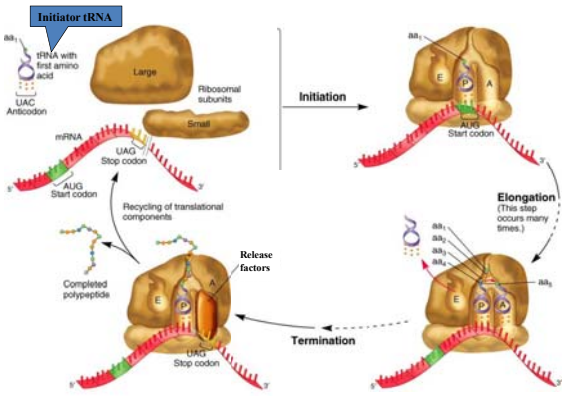
Peptidyl site (P site)

Aminoacyl site (A site)

Exit site (E site)



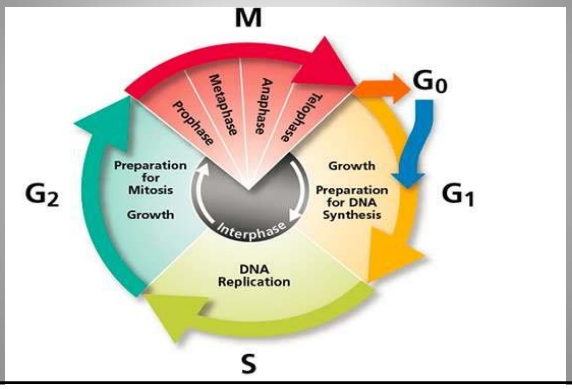
Three Stages: Initiation → Elongation → Termination



THANK YOU

CELL CYCLE

CELL CYCLE



PHASES OF CELL CYCLE

- G0 Phase
- Interphase (90% of cell cycle)
  - Gap 1 (G1)
  - Synthetic phase (S)
  - Gap 2 (G2)
- Mitosis (10% of cell cycle)

G0

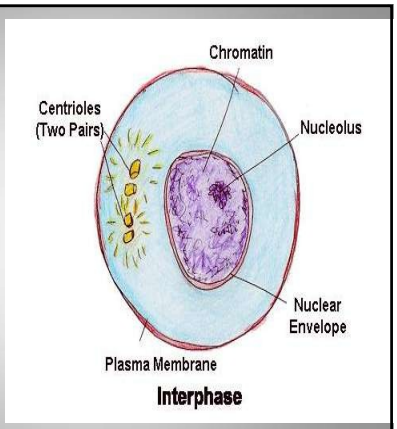
- Resting phase
- Cell leaves the cell cycle and stops dividing

Interphase

•Preparation before entering into cell division

•Series of changes take place in a newly formed cell and its nucleus

•Also k/a preparatory phase or inter mitosis



G1

- From end of previous M phase to beginning of DNA synthesis
- Also k/a growth phase
- Biosynthesis of protein , enzymes required for S phase needed for DNA replication
- Under control of p53 gene

S phase

- Starts when DNA replication starts
- Completes when all chromosomes have been replicated and each chromosome has sister chromatids

G2

- Gap between DNA synthesis and mitosis
- Cell grows
- Checked everything is ready to enter the mitosis phase

Mitosis

- Divided into following phases:
  - Prophase
  - Prometaphase
  - Metaphase
  - Anaphase
  - Telophase

Prophase

- Internal membranous compartments of the cell including nucleus are disassembled and dispersed
- Chromatids condense
- Protein synthesis ceases

prometaphase

- Bivalent attachment of chromosomes to spindle dragging them to equator

Metaphase

- Proper equatorial alignment of chromosomes on spindle

Anaphase

- Centromere divide
- Sister chromatids separate and lose cohesion and pulled towards opposite poles

Telophase

- Chromatids reach the opposite poles
- Nuclei and other membrane structures reassemble
- Chromosomes recondense
- Karyokinesis is followed by cytokinesis

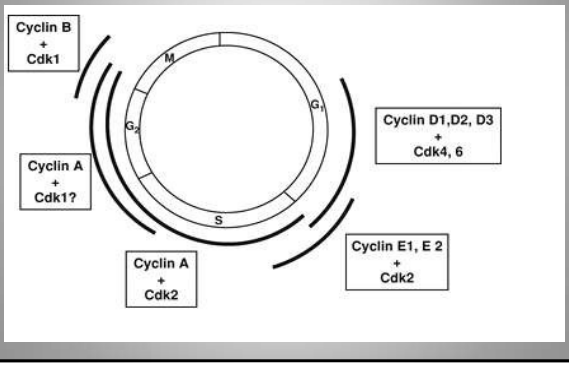
Regulation of cell cycle

- Regulation of entry and exit from proliferation mode
- Co-ordination of cell cycle events
- Specialised responses that increase the probability of environmental and internally generated insults

Cyclin Dependent Kinase

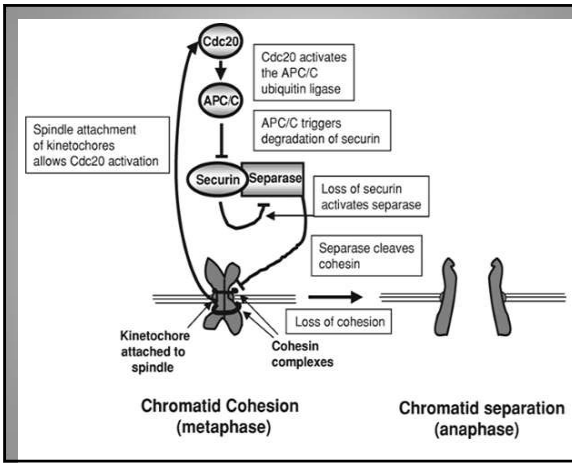
- Proline directed serine threonine specific protein kinase
- 2 subunits:
  - Catalytic (CDK)
  - Positive regulatory (Cyclin)

CDK function in cell cycle



Cell-Cycle Phase Transitions

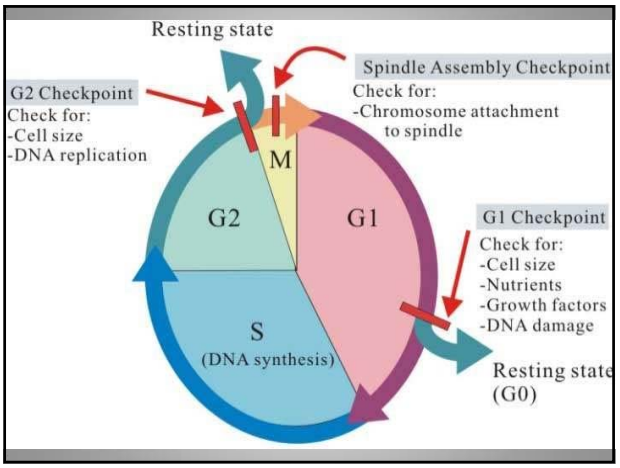
- between G_1 and S phase: cyclin A and E dependent
- between G_2 and M phase: Cyclin B and CDK1 dependent
- within M phase that is between metaphase and anaphase to preserve genomic integrity



Checkpoints in cell cycle

- Damaged molecules make necessary repairs
- Harmful cell cycle progression delayed

- DNA damage check points
- Replication check points
- Spindle integrity check points



DNA damage check points

- G1 and G2 checkpoints are p53 dependent while intra S phase DNA damage checkpoint is not.

Replication checkpoints

- Functions like G2 DNA damage checkpoint but through different pathway
- Mitotic entry blocked by inhibiting CDC25C via action of chk1, preventing action of CDK1

Spindle Integrity Checkpoint

- Mechanism of delay at prometaphase or metaphase in response to spindle defects or improper chromosome attachment
- Sensors of the defect are APC/C cofactor, CDC20
- Cells are prevented from initiating anaphase

Restriction point

- A point in mid G1
- Cells deprived of essential nutrients or growth factor are blocked

Senescence

- Loss of capacity of proliferation
- Protective phenomenon against malignancy
- Accumulation of high levels of CDK inhibitors leading to permanent G1 arrest

- Lack of enzyme telomerase

Progressive shortening of telomere of chromosome

Discontinuity of telomere

Chronic check point responses

Permanent cell cycle arrest

Cell Cycle and Cancer

- Cancer is a disease of uncontrolled proliferation

Alterations in Pathways

- Growth and Proliferation Signaling Pathways:
  - Overexpression of receptors
  - eg.Her-2/neu in ca breast

- Cell cycle machinery:
  - Increased synthesis of cyclin D
  - Increased degradation of CDK inhibitors
  - Activation of CDK4/6
  - Inactivation of tumour supression gene

- Senescence:
  - mutations in gene encoding for DNA checkpoints signaling elements most commonly p53,
  - Telomerase expression

Genetic and genomic instability

- Tumour supressor gene:
  - mutation leading to loss of function gives rise to cancer. Eg. p53, Rb , BRCA-1/2
  - have recessive mutation i.e both alleles of the chromosome need to be mutated
- Proto-oncogene:
  - mutation leading to enhanced function gives rise to cancer. Eg. RAS ,SRC kinase
  - have dominant mutation i.e single allele mutation.

- Stress Responses:
  - Abnormal growth provokes stress response leading to cell cycle arrest or cell death
  - Eg. p53 required for DNA damage checkpoint response as well as key effector of stress response
  - Mutation in p53 can lead to cancer by both ways

Application of cell cycle in treatment of cancer

- Radiotherapy
  - Cells are most radiosensitive in mitotic phase and least sensitive in S phase of cell cycle.

Chemotherapy and cell cycle

- G1 phase:
  - L-Asparaginase
- S phase:
  - Antimetabolites: 5-FU, Capecitabine,Methotrexate,Gemcitabine
  - Topoisomerase inhibitors:Etoposide, Irinotecan

- G2 phase:
  - Bleomycin (Anti-tumor antibiotics)
- M phase:
  - Taxanes: Paclitaxel, Docetaxel
  - Plant alkaloids: : Vincristine, vinblastine

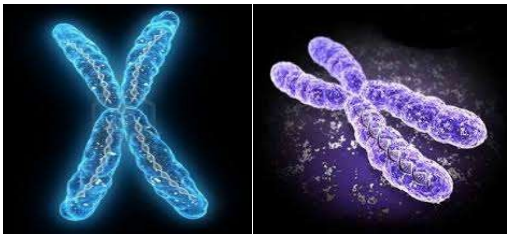
- Cell cycle phase non-specific:
  - Alkylating agents: Cyclophosphamide, ifosphamide
  - Anthracyclins: Doxorubicin, Epirubicin
  - Platinum: Cisplatin, Carboplatin
  - Antitumor antibiotics: Dactinomycin, Mitomycin

Conclusion

- Cancer is a disease of alteration in cell cycle and the knowledge of cell cycle can be used in the treatment of cancer.

CHROMOSOMES

STRUCTURE AND FUCTION



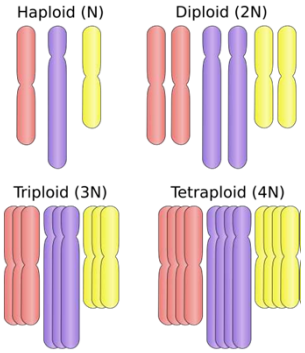
INTRODUCTION

- E. Strasburger in 1875 first discovered thread-like structures which appeared during cell division.
- These thread like structures were called chromosomes due to their affinity for basic dyes.
- The term chromosome is derived from two Greek words; chrom = colour, soma=body.
- This term was first used by Waldeyer in 1888.
- Chromosomes contributed to the division of cells and they are of prime importance as they carry the genes which are the hereditary material.

CHROMOSOME NUMBER

- ✓ The number of chromosomes in a given species is generally **constant**.
- ✓ All the members of the species ordinarily have definite and generally a constant **somatic** and **gametic** chromosome number.
- ✓ Somatic chromosome number is the number of chromosomes found in **somatic cells** of a species and is represented by **2n**.
- ✓ Generally somatic cells contain **two** copies of each chromosome except the *sex chromosomes*.
- ✓ Both the copies are ordinarily identical in morphology, gene content and gene order and hence known as **homologous chromosomes**.
- ✓ **Gametic** chromosome number is exactly half of somatic chromosome number and is represented by **n**.
- ✓ It denotes the number of chromosomes found in gametes of a species.

CHROMOSOME NUMBER



CHROMOSOME SIZE

- The size of the chromosome shows a remarkable variation depending upon the stage of cell division.
- longest and thinnest during interphase and hence not visible under light microscope.
- smallest and thickest during mitotic metaphase.
- Chromosome size is not proportional to the number of genes present on the chromosome.

CHROMOSOME MORPHOLOGY

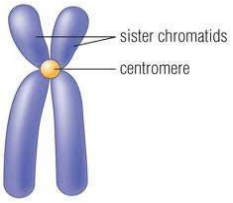
- The outer covering or sheath of a chromosome is known as pellicle, which encloses the matrix.
- Within the matrix lies the chromatin.
- Flemming introduced the term chromatin in 1879.
- The chromosome morphology changes during cell division and mitotic metaphase is the most suitable stage for studies on chromosome morphology.

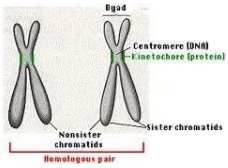
✓ In mitotic metaphase chromosomes, the following structural features can be seen under the light microscope.

1. **Chromatid**
2. **Centromere**
3. **Telomere**
4. **Secondary constriction**
5. **Chromomere**
6. **Chromonema**
7. **Matrix**

Chromatid

- Each metaphase chromosome appears to be longitudinally divided into two identical parts each of which is called chromatid.
- Chromatids of a chromosome appear to be joined together at a point known as centromere.
- Two chromatids making up a chromosome are referred to as sister chromatids.
- The chromatids of homologous chromosomes are known as non-sister chromatids.





Centromere:

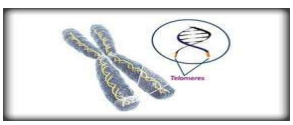
- The region where two sister chromatids appear to be joined during mitotic metaphase is known as centromere
- It generally appears as constriction and hence called primary constriction.
- helps in the movement of the chromosomes to opposite poles during anaphase of cell division.
- The centromere consists of two disk shaped bodies called kinetochores.
- Normally chromosomes are monocentric having one centromere each.

Depending on position of the centromeres, chromosomes can be grouped as:

a) **Metacentric:** Centromere is located exactly at the centre of chromosome, Such chromosomes assume 'V' shape at anaphase.
b) **Submetacentric:** The centromere is located on one side of the centre point such that one arm is longer than the other. These chromosomes become 'J' or 'L' shaped at anaphase.
c) **Acrocentric:** Centromere is located close to one end of the chromosome and thus giving a very short arm and a very long arm. These chromosomes acquire ' J' shape or rod shape during anaphase.
d) **Telocentric:** Centromere is located at one end of the chromosome so that the chromosome has only one arm. These chromosomes are 'I" shaped or rod shaped.

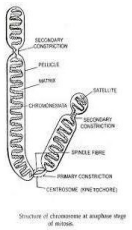
Telomere

- The two ends of chromosomes are known as telomeres.
- They are highly stable and do not fuse or unite with telomeres of other chromosomes due to polarity effect.
- Any broken end of a chromosome is unstable and can join with a piece of any other chromosome.
- But the telomeres impart stability to the chromosome, which retains its identity and individuality through cell cycle and for many cell generations.



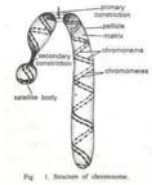
Secondary constriction

- The constricted or narrow region other than that of centromere is called secondary constriction.
- The chromosomes having secondary constriction are known as satellite chromosomes or sat chromosomes.
- Chromosome may possess secondary constriction in one or both arms of it.
- Chromosomal end distal to the secondary constriction is known as satellite.
- Production of nucleolus is associated with secondary constriction and therefore it is also called nucleolus organizer region.
- Satellite chromosomes are often referred to as nucleolus organizer chromosomes.



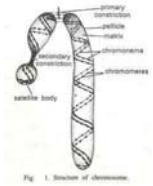
Chromomere

- In some species like maize, rye etc. chromosomes in pachytene stage of meiosis show small bead like structures called chromomeres.
- The distribution of chromomeres in chromosomes is highly characteristic and constant.
- The pattern of distribution being different for different chromosomes.
- They are clearly visible as dark staining bands in the giant salivary gland chromosomes.
- Chromomeres are regions of tightly folded DNA.



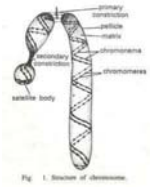
Chromonema

- A chromosome consists of two chromatids and each chromatid consists of thread like coiled structures called chromonema (plural chromonemata).
- The term chromonema was coined by **Vejdovsky** in **1912**.
- The chromonemata form the gene bearing portion of chromosomes.



Matrix

- The mass of acromatic material which surrounds the chromonemata is called matrix.
- The matrix is enclosed in a sheath which is known as pellicle.
- Both matrix and pellicle are non genetic materials and appear only at metaphase, when the nucleolus disappears.



Composition of chromosomes

- The material of which chromosomes are composed is called chromatin.
- N.Fleming introduced the term chromatin in 1879.
- Chromatin was classified into two groups by cytologists on the basis of its affinity to basic dyes like acetocarmine or feulgen (basic fuchsin) reagent at prophase.
- The darkly stained regions were called heterochromatin, while lightly stained regions were called euchromatin.
- This differential staining capacity of different parts of a chromosomes is known as 'heteropycnosis'
- Heterochromatin is further classified into two groups:
- **a) Constitutive :-** It is present in all cells at identical positions on both homologous chromosomes of a pair.
- **b)Facultative:-** It varies in state in different cell types, at different stages or sometimes, from one homologous chromosome to another.

Composition of chromosomes

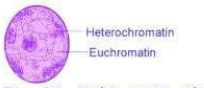
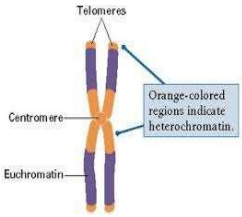


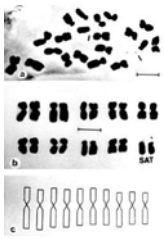
Fig. 6.1 Nuclei consist of chromatin strands as tightly packed heterochromatin or loosely packed euchromatin.

constitutive HC	facultative HC
stable	reversible
contains satellite DNA	enriched in LINES sequences
polymorphism +	polymorphism -
C bands+	C bands -



Karyotype and Ideogram

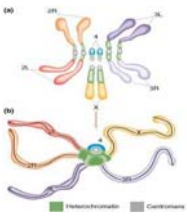
- "the characteristic features by which a set of chromosomes of a species is identified".
- Generally, karyotype is represented by arranging the chromosomes in descending order of size, keeping their centromeres in the same line.
- The karyotype of a species can be represented diagrammatically showing all the morphological features of chromosomes.
- Such a diagram is known as ideogram or ideotype.



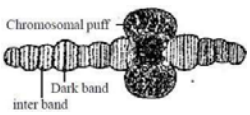
SPECIAL TYPES OF CHROMOSOMES

- Some tissues of certain organisms contain chromosomes which differ significantly from normal chromosomes in terms of either morphology or function.
- Such chromosomes are referred to as special chromosomes.
- The following are included under this category:
- **1. Giant chromosomes or polytene chromosomes:-** These were first discovered by **E. G. Balbiani** in **1882** in *Dipteran salivary glands* and hence commonly called salivary gland chromosomes.
- These chromosomes replicate repeatedly but the daughter chromatids do not separate from one another and the cell also does not divide.
- This phenomenon is known as endomitosis or endoreduplication.
- It results in the formation of many stranded giant chromosomes known as polytene chromosomes and the condition is known as polyteny.
- Their size is 200 times or more than the normal somatic chromosomes (autosomes) and very thick.
- Hence they are known as giant chromosomes.

SPECIAL TYPES OF CHROMOSOMES



GIANT CHROMOSOME



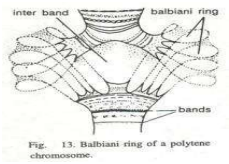
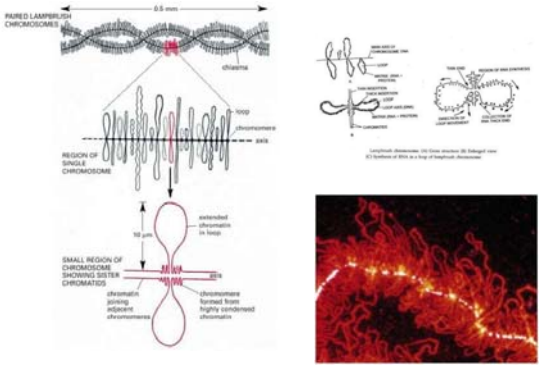


Fig. 13. Balbiani ring of a polytene chromosome.

SPECIAL TYPES OF CHROMOSOMES

2. **Lamp brush chromosomes:-** These were first observed by W. Flemming in 1882 and were described in detail in oocytes of sharks by Rukert in 1892.
- They occur at diplotene stage of meiotic prophase in oocytes of all animal species.
- Since they are found in meiotic prophase, they are present in the form of bivalents in which the maternal and paternal chromosomes are held together by chiasmata at those sites where crossing over has previously occurred.
- Each bivalent has four chromatids, two in each homologue.
- The axis of each homologue consists of a row of granules or chromomeres, each of which have two loop like lateral extensions, one for each chromatid.
- Thus each loop represents one chromatid of a chromosome and is composed of one DNA double helix.
- One end of each loop is thinner than other which is known as thickend.
- There is extensive RNA synthesis at thin ends of the loop while there is little or no RNA synthesis at the thick ends.

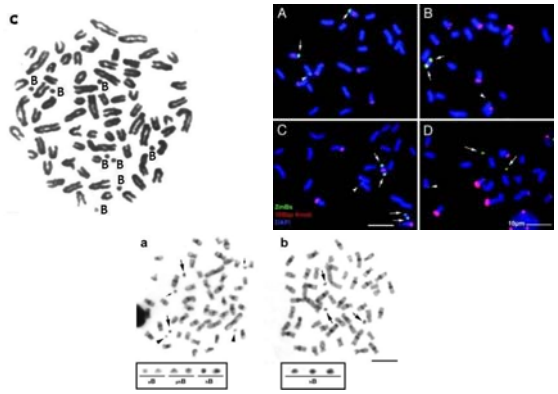
SPECIAL TYPES OF CHROMOSOMES



SPECIAL TYPES OF CHROMOSOMES

3. **Accessory chromosomes:-** In many species some chromosomes are found in addition to normal somatic chromosomes.
- These extra chromosomes are called accessory chromosomes or B-chromosomes or supernumerary chromosomes.
- These chromosomes are broadly similar to normal somatic chromosomes in their morphology, but have some peculiar functional aspects.
- For instance, presence of several such chromosomes often leads to reduction in vigour and fertility in males.
- These chromosomes are generally smaller in size than the normal somatic complement.
- They are believed to be generally inactive genetically.
- Origin of these chromosomes in most species is unknown.

SPECIAL TYPES OF CHROMOSOMES

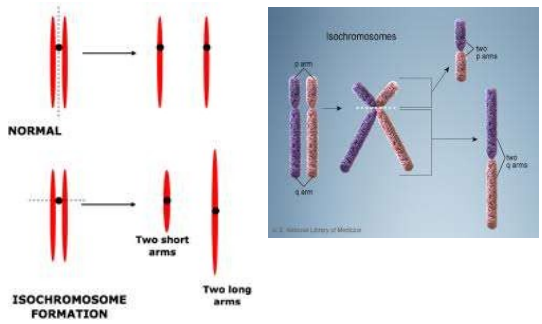


SPECIAL TYPES OF CHROMOSOMES

4. **Isochromosomes:-** An isochromosome is the one in which two arms are identical with each other in gene content and morphology.

- Such a chromosome is in assense a reverse duplication with entromeres separating the two arms.
- Every isochromosome is metacentric. The attached 'x' chromosome of *Drosophila is a classical example of an* isochromosome. However its origin is uncertain.
- There is no evidence that isochromosomes had any evolutionary significane.

SPECIAL TYPES OF CHROMOSOMES



SPECIAL TYPES OF CHROMOSOMES

5. **Allosomes / sex chromosomes:-** Chromosomes differing in morphology and number in male and female are called allosomes.

- They are responsible for determination of sex.
- Eg: X and Y chromosomes in human beings and *Drosophila*.
- Chromosomes which have no relation with determination of sex and contain genes which determine somatic characters of individuals are called autosomes and are represented by letter 'A'.

SPECIAL TYPES OF CHROMOSOMES