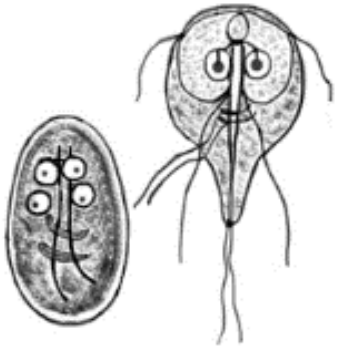
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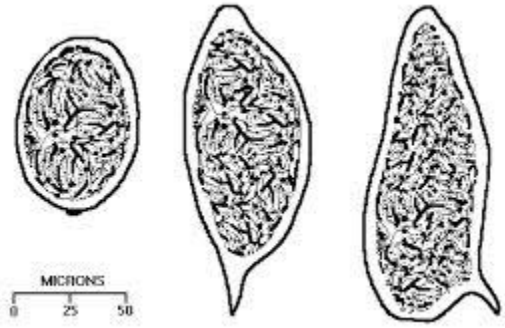
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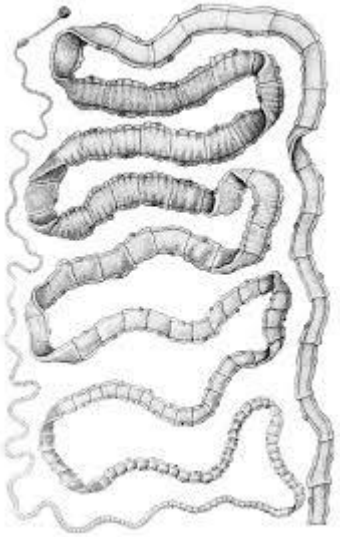
Clinical Parasitology Sheet





Protozoology

Helminthology



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Batch 89 (2011)

2014-15

Preface

- These Notes are gathered from different sources:
  - Lecture notes
  - Amjad Notes
  - Hassanain's Notes
  - Levinson 12th Ed.
  - Jawetz 26th Edition
  - Sherris 4th Ed.
  - Internet (CDC, Wikipedia)

- Any mistakes in this notes, are not intentional
- Studying Malaria and Leishmania from here, is not recommended because they contain a lot of extra information, that doesn't show up on exams frequently.

Thanks to all my friends who supported me all the way, without whom such a work couldn't have been made.

Special Thanks to Hazim Eldirdiri for his great efforts in this sheet.

Dedicated to my mother, the reason behind all my successes, the one who made me who I am today.

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Amoebiasis

- Defined as infection with ***Entamoeba histolytica.***
- New cases worldwide (480 million/year).
- 89% are asymptomatic cyst passers (carriers).
- With disease (amebic dysentery & amebic liver abscess): 34-50 millions.
- Deaths: 40000-110000 / year.
- Worldwide, this organism is thought to produce more deaths than any other parasite, except those that cause malaria and schistosomiasis.

- Five species of Entamoeba :
    1. ***E.Histolytica*** **(the only pathogenic one).**
    2. E.dispar.
    3. E.coli.
    4. E.hartamanni.
    5. E.gingivalis.

- Morphological characteristic :
  Different forms: **Trophozoite & cyst (1, 2, 4 nuclei)**

    - **Trophozoite (active form) :**

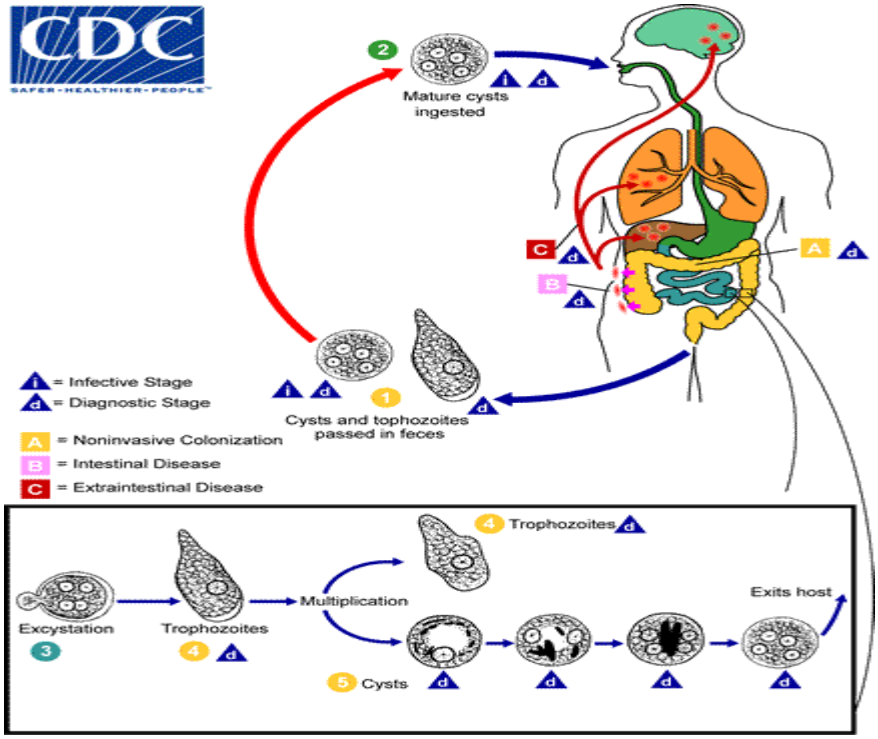
1. Size: 10-40 micrometers.
2. Pseudo podium (ectoplasmic protrusion): broad or finger-like, thrust out quickly, firstly formed with ectoplasm & secondly endoplasm flows into it, motility is progressive & directional.
3. Endoplasm: **RBCs maybe found in it (diagnostic).**
4. Nucleus (vesicular type).

- **Cyst (non-motile) :**

1. Size: 10-20 micrometer. Spherical in shape.
2. 1-2 nuclei (immature cyst) or **4 nuclei (mature cyst, infective stage).**
3. Inclusions: become smaller & smaller as the cyst ages.
4. Glycogen vacuole appears as a clear space (food reservoir).
5. Chromatin body: dark, blue rods or dots, unknown function.

- *Transmission :*
    1. Food or drink contaminated with feces containing the E.Histolytica (fecal-oral).
    2. Use of human feces (night soil) for soil fertilizers.
    3. Contamination of food stuffs by flies.

- *Life cycle :*
  - **Infective stage:** mature cyst.
  - **Access:** mouth.
  - **Ecological niches:** large intestine, liver, lung & other organs.
  - **Pathological stage:** Trophozoite.
  - **Diagnostic Stage:** Trophozoite & cyst.



- *Pathogenesis :*
  - Cyst ingested with food.
  - Cyst excystation in the small intestine (Trophozoite).
  - Trophozoite Move to the large intestine & start reproduction (binary fission). Invade the sub mucosa causing ulceration **(flask-shape ulcer).**
  - Then the Trophozoite can either pass through. The large intestine, undergo encystation & pass in feces. Or move to other organs thro. Blood vessels causing extra intestinal amebiasis.
  - So, after adherence Trophozoites invade the colonic epithelium to produce the ulcerative lesions typical of flask-shape ulcers thro. Catalytic enzymes & pseudopodia invasion of colonic tissue.
  - May cause amebic liver abscess, bleeding, perforation, peritonitis.
  - Spread to the liver occurs by mesenteric vein (portal blood).
  - Trophozoites ascend the portal veins to produce **liver abscess** filled with acellular proteinaceous debris. This material has the **appearance of anchovy paste.**

- **[Note:]**
    - Invasiveness correlates well with endocytic capacity, the production of extracellular proteinases capable of activating complement and degrading collagen, the presence of a galactose-specific lectin apparently capable of mediating attachment of the organism to colonic mucosa, and perhaps most importantly, the capacity to lyse host cells on contact.
    - The latter phenomenon is initiated by the galactose-specific lectin-mediated adherence of the trophozoite to a target cell. Following adherence, the ameba releases a pore-forming protein that polymerizes in the target cell membrane, forming large tubular lesions. Cytolysis rapidly follows.
    - Colonic flora may also enhance invasiveness.
- *Pathology :*
    - Ameba's contact and lyse colonic epithelial cells, producing small mucosal ulcerations. There is little inflammatory response other than edema and hyperemia, and the mucosa between ulcers appears normal.
    - Trophozoites are present in large numbers at the junction between necrotic and viable tissue.
    - Once the lesion penetrates below the superficial epithelium, it meets the resistance of the colonic musculature and spreads laterally in the submucosa, producing a flask-like lesion with a narrow mucosal neck and a large submucosal body.
    - It eventually compromises the blood supply of the overlying mucosa, resulting in sloughing and a large necrotic ulcer.
    - Extensive ulceration leads to secondary bacterial infection, formation of granulation tissue, and fibrotic thickening of the colon.
    - In approximately 1% of patients, the granulation tissue is organized into large, tumor-like masses known as ameboma.
    - The major sites of involvement, in order of frequency, are the cecum, ascending colon, rectum, sigmoid, appendix, and terminal ileum.
    - Ameba's may also enter the portal circulation and be carried to the liver or, more rarely, to the lung, brain, or spleen. In these organs, liquefaction necrosis leads to the formation of abscess cavities.
- **Immunity :**
    - Patients with invasive disease are known to produce high levels of circulating antibodies.
    - Nevertheless, there is no correlation between the presence or concentration of such antibodies and protective immunity, possibly because pathogenic E. histolytica trophozoites have the capacity to aggregate and shed attached antibodies and are resistant to the lytic action of complement.
    - Pathogenic E. histolytica strains produce a lectin-like substance that is mitogenic for lymphocytes.
    - It has been suggested that this substance could stimulate viral replication of human immunodeficiency virus–infected lymphocytes as does another mitogen, phytohemagglutinin.

- *Clinical manifestations :*
  - **I.P:** 1-4 weeks.
  - Clinical forms :

1. Acute typical form: asymptomatic form (90% of pts.) or mild form or fulminant form.
2. Chronic form.

- *Outcomes of intestinal amebiasis :*

1. Amebic colitis (dysentery) :

- **Gradual onset**, with symptoms presenting over 1-2 weeks.
- Diarrhoea is the most common symptom, other symptoms include cramping abdominal pain, watery or bloody diarrhoea (with mucous) & weight loss.
- The diarrhea is intermittent, alternating with episodes of normality or constipation over a period of months to years. Typically, the stool consists of one to four loose to watery, foul-smelling passages that contain mucus and blood.
- Fever is noted in 10% of pts.
  - Differences between amebic dysentery & bacillary dysentery :

Bacillary Dysentery	Amebic Dysentery
Acute Onset	Gradual Onset
High grade fever	Fever is absent or low grade
Pus (Leukocytes) in stool	No Pus in stool (There is ova)
usually starts watery then becomes bloody	usually starts bloody
Stool is Alkaline	Stool is Acidic
The pt. passes stool 10-15 times / day	, pt. passes stool few times /day
There is no role of serology.	serology is very important

2. Fulminant amebic colitis :

- Rare complication of amebic dysentery (0.5%).
- Presents with rapid onset of severe bloody diarrhoea, severe abdominal pain & high grade fever.
- Children younger than 2 years are at increased risk.
- Intestinal perforation is common.
- Most commonly, abscesses occur singly and are localized to the upper outer quadrant of the right lobe of the liver. This localization results in the development of point tenderness overlying the cavity and elevation of the right diaphragm.
- Has a mortality rate of more than 50%.

3. Toxic Megacolon :
   - Typically associated with use of corticosteroids. D.D of toxic Megacolon is Cl.difficile.
4. Chronic amebic colitis :
   - Recurrent episodes of bloody diarrhoea & vague abdominal discomfort.

5. Ameboma :

   - Results from formation of colonic granulation tissue in response to the infective ameba.
   - Presents as right lower quadrant abdominal mass which may be mistaken for Carcinoma, Tb, Chron's disease or lymphoma.
   - Biopsy findings assist in establishing the correct diagnosis.

- *Extra intestinal amebiasis :*

1. Hepatic :
- Acute, non-suppurative.
- Liver abscess (right upper quadrant pain referred to the right shoulder, tender).
2. Pulmonary.
3. Brain.
4. Skin, perianal infection.

1. Amebic liver abscess:

- **The most common form of extra intestinal amebiasis.**
- Results from spread of the organisms from the intestinal submucosa to the liver via the portal system.
- Approximately 40% of pts. Who have amebic liver abscess have a history of prior bowel symptoms.
- 5% of pts. With symptomatic intestinal amebiasis.
- 10 times as frequent in men as in women.
- Presents with **fever & a constant, dull, upper right abdominal or epigastric pain.**
- **Involvement of the diaphragmatic surface of the liver may lead to right sided pleuritic pain or referred shoulder pain.**
- Associated GI symptoms occur in 10-35% of pts. And include nausea, vomiting, abdominal distension, diarrhoea, constipation. May present with vague abdominal discomfort, weight loss & anemia.

[Extra]

2. Pleuropulmonary amebiasis :

   - Is most commonly the result of contagious spread from a liver abscess rupturing through the right diaphragm, Cough, pleuritic pain & dyspnea are common symptoms.

3. Hepatobronchial fistula :

   - Expectoration of sputum resembling anchovy paste.
   - Trophozoites may be found in sputum samples.

4. Amebic peritonitis :

   - Is generally secondary to a ruptured liver abscess.
   - Left lobe liver abscesses are more likely to rupture.
   - Pt. presents with fever & rigid distended abdomen.

5. Amebic pericarditis :

   - Caused by a rupture of the left liver lobe abscess.
   - Presents with chest pain & CHF.
   - Extension of an abscess from the left lobe of the liver to the pericardium is the single most dangerous complication. It may produce rapid cardiac compression (tamponade) and death or, more commonly, a chronic pericardial disease that may be confused with congestive cardiomyopathy or tuberculous pericarditis.

6. Cerebral amebiasis :

   - Abrupt onset & rapid progression to death in 12-72 hours.
   - Presents with altered consciousness & focal neurological signs.
   - CT scanning reveals irregular lesions without a surrounding capsule.
   - Tissue biopsy: Trophozoites.

7. Genitourinary involvement :

   - May cause painful genital ulcers or Fallopian tube amebiasis.

- **Note :**
- **D.D of amebic dysentery :**
  1. Bacillary dysentery.
  2. Enterohemorrhagic E.coli (O: 157 H: 7) & Enteroinvasive E.coli.
  3. Campylobacter.
  4. Salmonella.
  5. Y.Enterocolitica.

- **D.D of amebic liver abscess :**
  1. Pyogenic liver abscess.
  2. Necrotic hepatoma.
  3. Echinococcal cyst (Hydatid cyst).

- *Diagnosis :*

  1. Microscopy:

  - Fresh stool.
  - Trophozoites that contain ingested RBCs are diagnostic.
  - 3 stool samples over 10 days.
  - Also we can see cysts. No fecal leukocytes.
  - So, If you found a Trophozoite = amebic dysentery, and If you found a cyst = chronic intestinal amebiasis or carrier.
  - E.dispar should be differentiated. E. histolytica trophozoites can be differentiated from those of E. dispar only by the presence of ingested erythrocytes in the former; the cysts appear identical.

2. **Culture:**

- Techniqually difficult, not usually done.

3. **Stool Ag. Detection**

- ELISA used in stool samples < 7 days. Specific for E.Histolytica.
- Nowadays we use *Rapid Diagnostic Tests (RDT).*

4. **Serum Ag. Detection.**

- E.Histolytica galactose lectin Ag. Is detectable by ELISA in 75% of serum from pts. With Amebic Liver Abscess (ALA).
- RDT.

5. **Antibody detection :**

- Method used: EIA & IHA (Indirect Hemagglutination).
- EIA detects Abs. specific to E.Histolytica in 95% of pts. With extra intestinal amebiasis, 70% of pts. With active intestinal Amebiasis & 10% of asymptomatic pts.
- Persists for 6-12 months following eradication.

6. **Nucleic acid detection :**

- PCR / RT-PCR / LAMP.
- Stool / liver aspirate.
- Methods of choice for discriminating between the pathogenic species (E.Histolytica) and the nonpathogenic species (e.g. E.dispar).

7. **Diagnosis of ALA :**

- Clinical signs & symptoms.
- Usually strongly positive serology.
- ALA pts. With –ve serology (3-7 days after onset of symptoms).
- Seroconverted during treatment, abscesses rapidly developing but completely gone in 50 days.
- Aspiration from the liver abscess => anchovy paste.
- Imaging & other tests (chest radiograph, ultra sound, CT & MRI, LFTs).

Note:

- Amoebic dysentery is diagnosed mainly by serology, while in bacillary dysentery there is no role of serology.

- *Treatment :*
- **Medical care :**
  1. **Luminal agents** (e.g. Paromomycin, Iodoquinol, Diloxanide furoate) are best for noninvasive disease. First choice is **Paromomycin.**
  2. **Nitroimidazoles:**

- Are **tissue amebicidal**. E.g. *Metronidazole* is the main stay of therapy for invasive amebiasis.

- Tinidazole & other nitroimidazoles with longer half-lives e.g. Secnidazole, ornidazole are used.
- Nitroimidazole therapy should be followed by treatment with a luminal agent to prevent relapse.

- **Surgical intervention :**
  - In Perforated amebic colitis, massive GI bleeding or Toxic Megacolon.
- **ALA Treatment :**
  - Metronidazole or Tinidazole (alone in USA)
  - Metronidazole or Tinidazole + Chloroquine phosphate or Emetine. Followed by a luminal drug.
- **Indications for abscess drainage :**
  - Presence of left lobe abscess (> 10 CM in diameter).
  - Rupture.
  - Abscess that doesn't respond to medical therapy within 3-5 days.

  <u>(So in summary):</u>

  - **Asymptomatic cyst carriers:** Paromomycin or Iodoquinol.
  - **Diarrhoea / Dysentery / Extra intestinal amebiasis:** Metronidazole + Paromomycin or Iodoquinol.
  - **ALA:** Metronidazole + Chloroquine phosphate or Emetine + luminal agent.

Giardia intestinalis
(Giardia duodenalis, giardia lamblia)

- Most common protozoal intestinal parasite, in summer, occurs more commonly in children (which become carriers). Causes Giardiasis

- *Morphology :*
  - Diagnosis is very easy.
  - **Trophozoites:** Are binucleated, Move by flagella, Median body (adhesion disk) (suction disk).
  - **Cyst:** Rounded with 4 nuclei give 2 Trophozoites. There is axonemes (support), 2 bars.

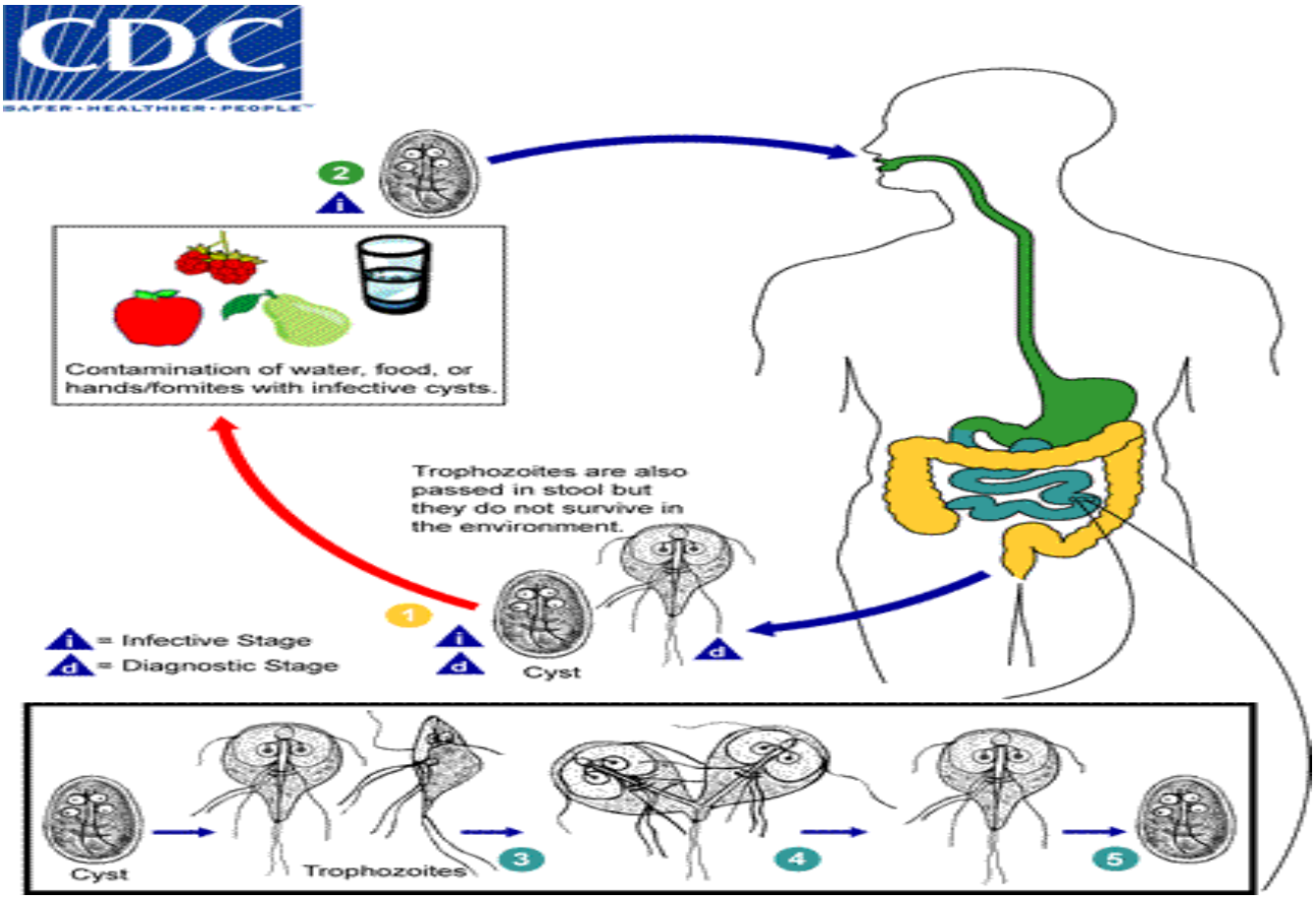
- *Transmission :*
  1. Waterborne (outbreaks)
  2. Homosexual anal-oral contact
  3. From person to person by food.

  - Giardiasis is a common among attendees of day-care centers. Attack rates of over 90% have been seen in the ambulatory non–toilet-trained population (age, 1 to 2 years) of these institutions, suggesting direct person-to-person transmission of the parasite
  - **G.Intestinalis is easily transmitted :**

1. Infective dose is very small (~10 cysts).
2. Resistant cyst (resistant to chlorine and other disinfectants).

- *Life cycle :*

  - After ingestion, it undergoes excystation in the small intestine to form trophozoites which pass to the large intestine, where bile salts trigger formation of the cyst.



- *Pathogenesis :*
  1. Attachment to the intestinal surface by adhesive disk.
  2. Mechanical blockade of the intestinal mucosa by large numbers of Giardia (forming a barrier that interferes with enterocytes) resulting in loss of epithelial function & increase in intestinal permeability.
  3. Damage to the brush border of the microvilli by the parasite's sucking disc resulting in **villus atrophy** & destruction of brush border enzymes.
  4. **Disaccharidase deficiency with lactose intolerance**, altered levels of intestinal peptidases, and decreased vitamin B12 absorption have been demonstrated. This results in malabsorption of Glucose, water & Sodium causing osmotic diarrhoea.
  5. There is also hypersecretion of Cl resulting in **watery diarrhea.**
  6. The parasite may also interfere with bile salt metabolism (causes **deconjugation of bile salts**).
  7. Moreover, Giardiasis can cause immune inhibition, possibly by **consuming Arginine**, the precursor of NO.

- *Immunity :*
  - Children with immunoglobulin deficiencies are more likely to acquire the flagellate, possibly because of a deficiency in intestinal immunoglobulin A.
  - Predisposing factors include hypochlorhydria and being immunocompromised.

- *Clinical manifestations :*
  - **I.P:** 1-3 weeks.
  - 60-80% asymptomatic infections.
  - **Symptomatic Infection:** typically include diarrhea, which is sudden in onset and explosive in character.
  - The stool is **foul smelling, greasy in appearance, and floats on water. It is devoid of blood or mucus. Upper abdominal cramping is common.**
  - Large quantities of intestinal gas produce abdominal distention, sulfuric eructation, and abundant flatus.
  - Nausea, vomiting, and low-grade fever may be present.
  - The acute illness generally resolves in 1 to 4 weeks; in children, however, it may persist for months, leading to significant *malabsorption, weight loss, and malnutrition.*
  - In many adults, the acute phase is often followed by a subacute or chronic phase characterized by *intermittent bouts of mushy stools, flatulence, and "heartburn" and weight loss that persist for weeks or months.*
  - At times, patients presenting in this fashion deny having experienced the acute syndrome described previously.
  - In the majority, symptoms and organisms eventually *disappear spontaneously.*
  - It is not uncommon for lactose intolerance to persist after eradication of the organisms. This condition may be confused with an ongoing infection, and the patient may be subjected to unnecessary treatment.

- So, symptomatic infection include: Diarrhea, foul smelling faeces, Malaise, Flatulence, Anorexia, mild fever, weight loss. Sleep disorders & mental depression may occur.

- Note: Unlike the typical bacterial diarrhea syndrome seen in travelers, the diarrhea begins late in the course of travel and may persist for several weeks.

- **D.D of Traveler's diarrhoea :**

1. Enterotoxigenic E.coli (watery diarrhoea).
2. Campylobacter (bloody diarrhoea).
3. Giardia intestinalis (watery, foul-smelling diarrhoea).

- *Complications :*
    1. Disaccharides deficiency.
    2. Malabsorption.
    3. Weight loss.
    4. Growth retardation in children.

- *Diagnosis :*
    1. **Light microscopy: best method.**
    2. **String test (entero test)** which consists of swallowing a weighted piece of string until it reaches the duodenum, should be performed. The trophozoites adhere to the string and can be visualized after withdrawal of the string.
    3. **Aspiration or biopsy (villus atrophy):** Pts. With IgA deficiency & hypogammaglobulinemia with giardiasis may demonstrate various degrees of villus atrophy.
    4. **Serology :**
    - Direct fluorescence antibody staining of cysts: useful for screening.
    - Abs. are not very helpful (helpful only in screening).
    5. **Antigen detection:** ELISA, slightly less sensitive than DFA, detect Ag. In stool **(GA65).**
    6. **PCR**.

- *Treatment :*
    - **Metronidazole** is the drug of choice. Tinidazole is slightly more effective. Nitazoxanide has recently been licensed for treatment.
- Note :
    - Because of the disulfiram-like activity of metronidazole, alcohol consumption should be suspended during treatment.
    - The drug should never be used during the first trimester of pregnancy because of its potential teratogenic activity.
    - Use in the last two trimesters is unlikely to be hazardous but should be reserved for patients whose symptoms cannot be adequately controlled with local therapies.
    - **Paromomycin is the drug of choice for pregnant women.**

Cryptosporidium

- *C.Parvum* causes Cryptosporidiosis, one of the most common causes of waterborne illness with AIDS patients.

- *Life cycle :*

- Infective oocysts are excreted in the stool of the parasitized animal. Unlike those of Toxoplasma, cryptosporidia oocysts are fully mature and immediately infective on passage in the feces.
- Following ingestion by another animal, sporozoites are released from the oocyst and attach to the microvilli of the small bowel epithelial cells, where they are transformed into trophozoites.
- These divide asexually by multiple fission (schizogony) to form schizonts containing eight daughter cells known as *type 1 merozoites.* On release from the schizont, each daughter cell attaches itself to another epithelial cell, where it repeats the schizogony cycle, producing another generation of type 1 merozoites.
- Eventually, schizonts containing *four type 2 merozoites* are seen.
- Incapable of continued asexual reproduction, these develop into male (microgamete) and female (macrogamete) sexual forms. Following fertilization, the resulting zygote develops into an *oocyst that is shed into the lumen of the bowel.* The majority possess a thick protective cell wall that ensures their intact passage in the feces and survival in the external environment.
- Approximately 20% fail to develop the thick protective wall. The cell membrane ruptures, releasing infective sporozoites directly into the intestinal lumen and initiating a new *"autoinfective" cycle* within the original host.
- In the normal host, the presence of innate or acquired immunity dampens both the cyclic production of type 1 merozoites and the formation of thin-walled oocysts, halting further parasite multiplication and terminating the acute infection. In the immunocompromised, both presumably continue, explaining why such individuals develop severe, persistent infections in the absence of external reinfection.

- **So , in summary :**

- Oocyst is the infective & diagnostic stage.
- Macrogamete (female) unite with microgamete (male) => oocyst => sporozoite => trophozoite => meront 1.
- Then Meront 1 gives either merozoite that becomes Trophozoite (bad immunity) or gives Meront 2 that becomes oocyst sexually (good immunity).
- Oocyst is double walled. It is resistant to: chloride, drying, progressive freezing, salt & water. Only oocyst in this stage can live in vivo.

- *Transmission :*

1. Fecal oral route: drinking water (even after treatment), swimming pools.
2. Unpasteurized apple cider.
3. Animal contact (domestic animals represent a reservoir)

- *Pathology :*
  - **Infective dose <10 organisms** (only 1 organism is needed to initiate infection).
  - Attach to epithelial cell of GIT.
  - Although the jejunum is most heavily involved, cryptosporidia have been found throughout the gastrointestinal tract, particularly in immunocompromised subjects.
  - Cryptosporidial cholecystitis is seen with some frequency in AIDS patients with enteritis.
  - By light microscopy, bowel changes appear minimal, consisting of mild to moderate villous atrophy, crypt enlargement and a mononuclear infiltrate of the lamina propria.
  - The pathophysiology of the diarrhea is unknown, but its nature and intensity suggest that a cholera-like entero-toxin may be involved.
  - May affect other tissues such as respiratory tract & conjunctiva.

- *Presentation :*
  - **I.P:** 2-10 days.
  - Can be *asymptomatic*.
  - **Symptomatic:** Watery diarrhea (some mucous but no blood), fever, myalgia, fatigue.
  - **In AIDS pts. :** Dehydration & weight loss. Infect lungs => Cough. Infect gall bladder => Cholecystitis.

- *Recovery :*
  - Immunocompetent : 1-2 weeks
  - Immunocompromised: months to years.
- *Complications* :
  1. Sclerosing cholangitis.
  2. Calculous cholecystitis.
  3. Pancreatitis.
  4. Pts. With AIDS => respiratory tract infection.

- *Diagnosis :*
  - Microscopy with acid fast stained stool smear (oocyst) e.g. modified Kinyoun acid-fast stain.
  - Direct florescent antibodies (DFA) is the best test (using a monoclonal antibody to oocyst wall).
  - ELISA for screening.

- *Treatment :*
- No effective therapy. Mainly Supportive with fluid & electrolyte
  - Nitazoxanide can be used for diarrhea.
  - If immunocompromised treat AIDS.

PATHOGENIC FREE LIVING AMEBAE

Naegleria fowleri:

- Causal agent of *primary amebic meningoencephalitis (PAM).*
- Transmitted from contaminated water swimming.
- Life cycle has **3 stages** : Trophozoite , temporary flagellar stage (ameboflagellate), cyst
- **Diagnosis:** by direct wet-mount, microscopy of CSF sample.
- **Treatment:** amphotericin B

Acanthamoeba:

- Causes granuloma like TB.
- Keratitis, blindness, lens contact.
- Disseminated granuloma.
- Granulation in brain.
- Treatment very difficult.

Trichomonas

- *Trichomonas vaginalis :*

  - Exclusively sexually transmitted (that's why no cyst form).
  - Most important STI (followed by Chlamydia, Gonorrhea & Syphilis).
  - In female the organism inhabits in vagina. In male it is found in urethra or prostate.

- *Morphology & life cycle :*
  - Has 4 flagella (Motile).
  - ***Only trophozoite***. Although it lacks a cyst form, the trophozoite can survive outside of the human host for 1 to 2 hours on moist surfaces. In urine, semen, and water, it is viable for up to 24 hours, making it one of the most resistant of protozoan trophozoites.
  - Transmitted mainly by *direct contact* during sexual intercourse but can also be transmitted by fomites.
- *Pathogenicity :*
  - Direct contact of T. vaginalis with the squamous epithelium of the genitourinary tract results in destruction of the involved epithelial cells and the development of a neutrophilic inflammatory reaction and petechial hemorrhages.
  - The precise pathogenesis of these changes is unknown. The organism is not invasive, and extracellular toxins have never been demonstrated.
  - ***Contact depends on cytotoxicity. Specterace (proteinase) causes cell lysis (damage cytoskeleton) by forming pores in the epithelium.***
  - High levels of maternal estrogen produce a transient decrease in the vaginal pH of the child, rendering it more susceptible to colonization. Within a few weeks, estrogen levels drop, the vagina assumes its premenarcheal state, and the parasite is eliminated.
- *Presentation :*
  - I.P: 4-28 days.
  - **In Females :**

  - **Vaginitis:** *foul smelling vaginitis* ***(usually fishy odor),*** *discharge is gray, but can be yellow or green & occasionally frothy or blood tinged, pruritis (itching) is common. (White creamy itchy discharge is seen in candidiasis).*
  - Vulvovaginitis.
  - Urethritis with Painful urination. Dyspareunia (painful sexual intercourse experienced by a woman) is also common.
  - Commonly, manifestations worsen during menses and pregnancy.
  - In symptomatic patients, physical examination reveals reddened vaginal and endocervical mucosa.

- In severe cases, petechial hemorrhages and extensive erosions are present. A red, granular, friable endocervix (strawberry cervix) is a characteristic but uncommon finding.
- Recent studies have demonstrated that trichomoniasis both increases the risk of preterm birth and enhances susceptibility to human immunodeficiency virus (HIV) infections

- ***In Males :***

- Infections are usually asymptomatic, possibly because of the efficiency with which the organisms are removed from the urogenital tract by voided urine.
- Include urethral discharge (range from scant to purulent), dysuria, urethral pruritis & some experience burning immediately after coitus.
- Trichomoniasis should be suspected in men presenting with nongonococcal urethritis, or a history of either prior trichomonal infection or recent exposure to trichomoniasis.

- *Complications :*

1. Low birth weight & preterm babies.
2. Respiratory or genital infection in newborns.
3. High risk of transmission of HIV (There is co-infection with AIDS 3/1000)
4. High risk of carcinoma of cervix.
5. Very recently high risk of prostate cancer.
6. Infertility.

- *Diagnosis :*
  - In women, a drop of vaginal discharge is the most appropriate specimen; in men, urethral exudate or urine sediment after prostate massage may be used.

1. **Wet film examination (Motile).**
2. **Culture** (in pouch culture system).
3. **Whiff test (amine odor test):** by adding several drops of 10% potassium hydroxide(KOH)
4. **Immunochromatographic test (ICT):** rapid Ag. Detection kit for Ag (best method).
5. **Direct immunofluorescence antibody** staining has a sensitivity of 70 to 90%.
6. **PCR** for researches.

- *Treatment :*
  - **Metronidazole** for both partners (cure rate may reach 95%) or other 5-nitroimidazoles.
  - Maintenance of low PH of vagina.
  - Use of condoms.

Dientamoeba Fragilis

(A flagellate without a flagella)

- Amoeboid appearance but ultrastructural & molecular evidence show clearly that it is related to trichomonas.
- Does not form a resistant cyst
- *Transmitted via enterobius eggs*.
- Cause itching around anus in children. D.D perianal itching in children is E.Vermicularis & T.Saginata & Diphilidium caninum, Tenia cruris (Dermatophyte infection).
    - Symptoms :
- Diarrhea, Abdominal pain, anal pruritis, Flatulence, Urticaria, and Fatigue.

- *Diagnosis :*
    - Best method for diagnosis is microscopy.
    - Trophozoite with eggs.
- *Treatment :*
    - Secnidazole is best choice.
    - Metronidazole is less effective.

Blastocystis hominis

- May be related to Irritable Bowel syndrome.
- Cotrimoxazole is the best choice of treatment.
- Metronidazole & Paromomycin are alternatives.

Malaria

- Malaria is a febrile illness caused by a parasitic infection of human erythrocytes transmitted by the bite of a mosquito.
- More than 200 million people worldwide have malaria, and more than 1 million die of it each year, making it the most common lethal infectious disease.
- It occurs primarily in tropical and subtropical areas, especially in Asia, Africa, and Central and South America

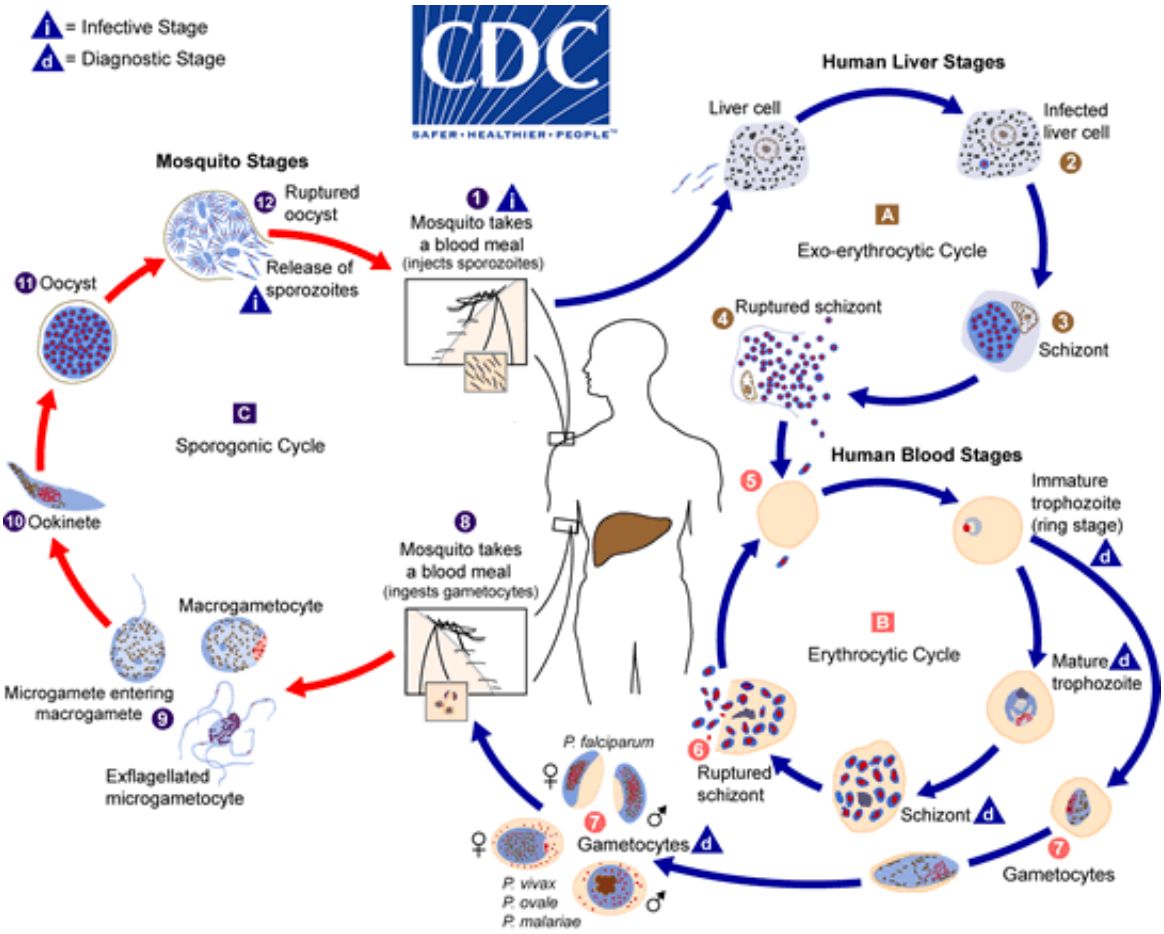
- *Species :*
    1. *Plasmodium falciparum.*
    2. *Plasmodium vivax* "tertian malaria, i.e., fever every 3 days".
    3. *Plasmodium ovale* "tertian malaria".
    4. *Plasmodium malariae* "quartan malaria, i.e., fever every 4 days".
    5. *P.Knowlsei:* same as P.Malariae, new & not well described.

- *Transmission :*
    1. Only Anopheles mosquitoes transmit human malaria.
    2. Blood transfusion.
    3. Transplacental (vertical / congenital).
    - All forms of malaria can be transmitted transplacentally or by blood transfusion or by needles shared among drug misusers when one is infected. Such cases do not develop a liver infection; thus, relapse does not occur.

- *Life cycle :*
    - The ***vector and definitive host for plasmodia is the female Anopheles mosquito*** (only the female takes a blood meal).
    - There are two phases in the life cycle: ***the sexual cycle***, which occurs primarily in mosquitoes, and the ***asexual cycle***, which occurs in humans, the intermediate hosts.
    - The sexual cycle is called *sporogony* because sporozoites are produced, and the asexual cycle is called *schizogony* because schizonts are made.
    - The life cycle in humans begins with the introduction of sporozoites into the blood from the saliva of the biting mosquito. The sporozoites are taken up by hepatocytes within 30 minutes. This "*exoerythrocytic" phase* consists of cell multiplication and differentiation into merozoites.
    - ***P. vivax and P. ovale produce a latent form (hypnozoite) in the liver; this form is the cause of relapses seen with vivax and ovale malaria.***
    - Merozoites are released from the liver cells and infect red blood cells.
    - During the erythrocytic phase, the organism differentiates into a r*ing-shaped trophozoite*. The ring form grows into an ameboid form and then differentiates into

a schizont filled with merozoites. After release, the merozoites infect other erythrocytes.

- ***This cycle in the red blood cell repeats at regular intervals typical for each species. The periodic release of merozoites causes the typical recurrent symptoms of chills, fever, and sweats seen in malaria patients.***
- The sexual cycle begins in the human red blood cells when some merozoites develop into male and others into female gametocytes.
- The gametocyte-containing red blood cells are ingested by the female Anopheles mosquito and, within her gut, produce a female macrogamete and eight sperm like male microgametes.
- After fertilization, the diploid zygote differentiates into a motile ookinete that burrows into the gut wall, where it grows into an oocyst within which many haploid sporozoites are produced. The sporozoites are released and migrate to the salivary glands, ready to complete the cycle when the mosquito takes her next blood meal.
- The time required for the completion of the cycle in mosquitoes varies from 1 to 3 weeks, depending on the species of insect and parasite as well as on the ambient temperature and humidity.



- A very important feature of P. falciparum is chloroquine resistance. Chloroquine-resistant strains now predominate in most areas of the world where malaria is endemic. Chloroquine resistance is mediated by a mutation in the gene encoding the chloroquine transporter in the cell membrane of the organism.

- Summary :
  - **In mosquitoes:** sexual and sporogony.
  - **Extraerythrocytic:** schizogony in liver, asexual.
  - **Erythrocytic:** schizogony in blood, asexual.
  - **Gametogony:** sexual in blood and mosquito gut.
- Extraerythrocytic "tissue" phase :
  - Blood is infected with sporozoites about 30 minutes after mosquito's bite.
  - The sporozoite enters liver cells where they multiply forming pre-erythrocytic schizogony. A process thought to be mediated by a ligand present in the sporozoites' outer protein coat (circumsporozoite protein).
  - P.vivax & P.ovale sporozoites form parasites in the liver called hypnozoites.
  - P.falciparum & P.malariae develop directly into schizonts in the liver, takes 6-16 days, then schizonts rupture releasing merozoites & producing clinical symptoms "invade RBCs".
- Relapsing malaria :
  - P.vivax & P.ovale hypnozoites remain dormant for months.
  - They develop the schizonts rupture releasing merozoites & producing clinical symptoms.
- Erythrocytic phase :
  - Trophozoites early stages in the ring forms.
  - Trophozoites divide forming a schizont.
  - Segmentation of schizonts form merozoites.
  - Schizonts rupture, releasing merozoites into blood Stream causing fever.
  - Merozoites invade other RBCs and schizogony is repeated.
  - Merozoites may develop to gametocytes, the sexual form of the parasite "when starting treatment or when patient is close to die".

- Schizogenic periodicity and fever patterns :
  - Schizogenic periodicity is the length of asexual erythrocytic phase.
  - 48 hours (in P.vivax & ovale) tertian malaria.
  - 72 hours (in P.malariae) quartan malaria.

- Gametocytogenesis :
  - Sexual dimorphism: microgametocyte & Macrogametocyte.
  - No pathology.
  - Infective stage for mosquito.

- Sporogony :
  - Occurs in mosquito intestine.
  - Fusion of micro and macrogametes.
  - Zygote => ookinete (24 hours).
  - Ookinete transverses gut epithelium (trans-invasion).
  - Sporozoites released.
  - Sporozoites invade salivary glands.
- Erythrocytic phase :
  - **Prepatent period:** interval between date of infection and detection of parasites in peripheral blood.
  - **Incubation period:** interval between infection and first appearance of clinical symptoms, 8-9 days or more.

- *Pathogenesis of malaria:*

This part contain a lot of EXTRA information

- Most of the pathologic findings of malaria result from the **destruction of red blood cells**. Red cells are destroyed both by *the release of the merozoites* and by the *action of the spleen* to first sequester the infected red cells and then to lyse them.
- The **enlarged spleen** characteristic of malaria is due to congestion of sinusoids with erythrocytes, coupled with hyperplasia of lymphocytes and macrophages.
- Malaria caused by **P. falciparum is more severe** than that caused by other plasmodia. It is characterized by infection of far more red cells than the other malarial species and by occlusion of the capillaries with aggregates of parasitized red cells.
- This leads to life-threatening hemorrhage and necrosis, particularly in the brain (cerebral malaria).
- Furthermore, extensive hemolysis and kidney damage occur, with resulting hemoglobinuria. The dark color of the patient's urine has given rise to the term "blackwater fever." The hemoglobinuria can lead to acute renal failure.
- The timing of the fever cycle is *72 hours for P. malariae* and 48 hours for the other plasmodia.
- Disease caused by *P. malariae* is called **quartan malaria** because it recurs every fourth day, whereas malaria caused by the *others* is called **tertian malaria** because it recurs every third day. Tertian malaria is subdivided into malignant malaria, caused by P. falciparum, and benign malaria, caused by P. vivax and P. ovale.
- *P. falciparum* causes a **high level of parasitemia** because it can **infect red cells of all ages** (including the erythropoietic stem cells in bone marrow). In contrast, P. vivax & P. ovale infect only reticulocytes and P. malariae infects only mature red cells; therefore, they produce much lower levels of parasites in the blood.
- In part, these differences may be related to the known differences in the *RBC receptor sites* available to the individual Plasmodium species.
- In the case of *P. vivax*, the site is closely related to the Duffy blood group antigens (Fay and Fib).
- **Duffy-negative** individuals, who constitute the majority of people of West African ancestry, are therefore **resistant to vivax malaria.**
- **RBC sialoglycoprotein**, particularly glycophorin A, has been implicated as the *P. falciparum* receptor site.

- Individuals with **sickle cell trait (heterozygotes)** are **protected against malaria** because their red cells have too little ATPase activity and cannot produce sufficient energy to support the growth of the parasite.
- People with homozygous sickle cell anemia are also protected but rarely live long enough to obtain much benefit.
- A similar protective effect may be exerted by **hemoglobins C, D, and E; thalassemias; and glucose-6-phosphate dehydrogenase (G6PD) or pyridoxal kinase deficiencies,** the protection in these conditions may be related to the increased susceptibility of such RBCs to oxidant stress.
- In thalassemia, the protection may also be related in part to the production of fetal hemoglobin, which retards maturation of P. falciparum, as well as an increased binding of antibodies to modified parasitic antigens (neoantigens) presenting on the surface of the erythrocytes.
- **[E]**Partial immunity based on humoral antibodies that block merozoites from invading the red cells occurs in infected individuals. A low level of parasitemia and low-grade symptoms result; this condition is known as premunition.
- **[E]**The B lymphocytes begin production of stage- and strain-specific antiplasmodial antibodies within the first 2 weeks of parasitemia. With the achievement of high levels of antibodies, the number of circulating parasites decreases.
- The infrequency with which malaria occurs in young infants has been attributed to the transplacental passage of such antibodies.
- It is uncertain whether they are directly lethal, act as opsonizing agents, or block merozoite invasion of RBCs.
- In contrast, a non-immune person, such as a first-time traveler to an area where falciparum malaria is endemic, is at risk of severe, life-threatening disease.
- Once invasion has occurred, malaria parasites may induce a number of changes in the erythrocytic membrane.
- These include alteration of its lipid concentration, modification of its osmotic properties, and incorporation of parasitic neoantigens, rendering the RBC susceptible to immunologic attack.

- *P. vivax* and *P. ovale* stimulate the production of caveolae-vesicle complexes, which are visualized as Schüffner's dots in stained smears.

- In *P. falciparum* infections, electron-dense elevated knobs or excrescences form on the RBC surface. These produce a strain specific, high-molecular-weight adhesive protein **(PfEMP1),** which mediates binding to receptors on the endothelium of capillaries and postcapillary venules of the brain, placenta, and other organs, where they can produce obstruction and microinfarcts.
- Moreover, this sticking to the walls of small blood vessels **sequesters** the parasite from passage through. The general circulation & spleen, thereby acting as a protective mechanism.
- Malarial parasites generate energy by the **anaerobic metabolism of glucose**. They appear to satisfy their protein requirements by the degradation of hemoglobin within their acidic food vacuoles, resulting in the formation of the malarial pigment (**hemozoin**).
- It has been estimated that the average plasmodium destroys between 25 and 75% of the hemoglobin of its host erythrocyte.
- Unlike their vertebrate hosts, malarial parasites synthesize folates de novo. As a result, antifolate anti-microbes such as pyrimethamine are effective antimalarial agents.

- The fever, anemia, circulatory changes, and immunopathologic phenomena characteristic of malaria are all the result of erythrocytic invasion by the plasmodia.

1. **Fever :**

- Fever, the hallmark of malaria, appears to be initiated by the process of *RBC rupture* that leads to the liberation of a new generation of merozoites (sporulation).
- It is possible that parasite-derived pyrogens are released at the time of sporulation; alternatively, the fever might result from the release of interleukin-1 **(IL-1)** and/or tumor necrosis factor **(TNF)** from macrophages involved in the ingestion of parasitic or erythrocytic debris.
- Early in malaria, RBCs appear to be infected with malarial parasites at several different stages of development, each inducing sporulation at a different time. The resulting fever is irregular and hectic.
- Because temperatures in excess of 40°C destroy mature parasites, a single population eventually emerges, sporulation is synchronized, and fever occurs in distinct paroxysms at 48-hour or, in the case of P. malariae, 72-hour intervals. Periodicity is seldom seen in patients who are rapidly diagnosed and treated.

2. **Anemia :**

- Parasitized erythrocytes are phagocytosed by a stimulated reticuloendothelial system or are destroyed at the time of sporulation.
- At times, the anemia is disproportionate to the degree of parasitism.
- **Depression of marrow function, sequestration of erythrocytes within the enlarging spleen, and accelerated clearance of nonparasitized** cells all appear to contribute to the anemia. The mechanisms responsible for the latter are unclear.
- Intravascular hemolysis, although uncommon, may occur, particularly in falciparum malaria.
- When hemolysis is massive, **hemoglobinuria** develops, resulting in the production of **dark urine.**
- This process in conjunction with malaria is known as **blackwater fever.**

3. **Circulatory Changes :**

- The high fever results in significant **vasodilatation.**
- In falciparum malaria, vasodilatation leads to a decrease in the effective circulating blood volume and hypotension, which may be aggravated by other changes in the small vessels and capillaries.
- The intense parasitemias P. falciparum is capable of producing and the adhesion of infected RBCs to the endothelium of visceral capillaries can impair the microcirculation and precipitate tissue hypoxia, lactic acidosis, and hypoglycemia.
- Although all deep tissues are involved, the brain is the most intensely affected.

4. **Cytokines :**

- Elevated levels of IL-1 and TNF are consistently found in patients with malaria. Probably released at the time of sporulation as a protective mechanism.

- However, TNF levels increase with parasite density and high concentrations appear harmful.
- TNF has been shown to cause upregulation of endothelial adhesion molecules; high concentrations might precipitate cerebral malaria by increasing the sequestration of P. falciparum–parasitized erythrocytes in the cerebral vascular endothelium.
- Alternatively, excessive TNF levels might precipitate cerebral malaria by directly inducing hypoglycemia and lactic acidosis.

5. <u>Other Pathogenic Phenomena (Thrombocytopenia & nephritis) :</u>

- Thrombocytopenia is common in malaria and appears to be related to both splenic pooling and a shortened platelet lifespan. Both direct parasitic invasion and immune mechanisms may be responsible.
- There may be an acute transient glomerulonephritis in falciparum malaria and progressive renal disease in chronic P. malariae malaria. These phenomena probably result from the host immune response, with deposition of immune complexes in the glomeruli.

- We will consider 2: immune-toxin and sequestration (Cytoadherence).
- TNFα: lead to the release of the mediators causing the symptoms of malaria.
    - **<u>Sequestration and Cytoadherence :</u>**

- **Rosetting:** adhesion of the RBCs to other RBCs.
- **Clumping:** adhesion between infected cells.
- Are mediated by **knobs**. Knobs made up by **PFEMP1.**

- **<u>Falciparum malignancy :</u>**

- Sequestration and Cytoadherence
- Each cycle produce 20 times more merozoites.
- Multiple infestation of all RBCs ages.
- Early hemolysis and endotoxin release.
- Resistant to chloroquine.
- **Note:** *P.vivax* & *P.ovale* love new RBCs (reticulocytes). *P.malariae* love old RBCs.

- **<u>Types of infections :</u>**
    1. **Relapse:** reactivation of hypnozoites form of a parasite in liver separate from previous infection with the same sp. (P.V, P.O), may occur up to 5 years.
    2. **Recrudescence:** exacerbation of persistent undetectable parasitemia, due to survival of erythrocytic form (P.F, P.M).
        - Plasmodium malariae infections lasting 40 years have been reported; this is thought to be a cryptic erythrocytic rather than an exoerythrocytic infection and is therefore termed a recrudescence to distinguish it from a relapse. P.F recrudescence may last for 1 year.
    3. **Recurrence or reinfection:** exoerythrocytic forms infect erythrocytes, separate from previous infection (all species).

- *Clinical presentation :*
    3. Acute uncomplicated malaria.
    4. Severe complicated malaria.
    5. Congenital.

- **Acute malaria :**

    - Malaria presents with **abrupt onset** of **fever and chills**, accompanied by headache, myalgias, and arthralgias, about 1-3 weeks after the mosquito bite.
    - The clinical manifestations vary with the species of plasmodia but typically include **chills, fever, splenomegaly, and anemia**.
    - The ***hallmark of disease is the malarial paroxysm***.
    - This manifestation begins with a **cold stage**, which persists for 20 to 60 minutes. During this time, the patient experiences continuous rigors and feels cold (begins as a synchronously dividing generation of parasites rupture their host red cells and escape into the blood).
    - With the consequent increase in body temperature, the rigors cease and vasodilatation commences, ushering in a **hot stage**. The temperature continues to rise for 3 to 8 hours, reaching a maximum of 40 to 41.7°C before it begins to fall. (The fever spike is accompanied by nausea, vomiting & abdominal pain). During this stage, the parasites invade new red cells.
    - The **wet stage** consists of a decrease in fever and profuse sweating (drenching sweating). It leaves the patient exhausted but otherwise well until the onset of the next paroxysm.
    - Typical paroxysms first appear in the second or third week of fever, when parasite sporulation becomes synchronized. In falciparum malaria, synchronization may never take place, and the fever may remain hectic and unpredictable.
    - The first attack is often severe and may persist for weeks in the untreated patient.
    - Eventually the paroxysms become less regular, less frequent, and less severe. Symptoms finally cease with the disappearance of the parasites from the blood.
    -

- **Summary :**

- Acute febrile illness may have periodic febrile paroxysms every 48-72 hours, with:
    - **Paroxysms** that last 8-12 hours start between midnight and midday.
    - **Cold stage**; rigors 1-2 hours.
    - **Hot stage**; 39-41˚c, 2-6 hours.
    - **Sweating stage**; 2-4 hours.
- **Early symptoms:** Headache , Malaise , Muscular pain , Fatigue , Nausea , Vomiting
- **At night:** Mild diarrhea , Mild jaundice , Respiratory symptoms
- **Signs:** Pallor, DIC (bleeding), Hepatosplenomegaly, Jaundice, Respiratory distress, mental status change.

- **Severe malaria :**

- Life threatening condition of P.falciparum malaria.
- **Clinical:** Cerebral malaria , Convulsions , Dyspnea , Bleeding disorders , Jaundice , Shock , Hyperpyrexia , Hyperparasitemia .
- **Lab:** Hyperparasitemia, Hypoglycemia, Metabolic acidosis, Hemoglobinuria, Acute renal failure (insufficiency), (ARF, AGN), Electrolyte acid/base imbalance.

1. Cerebral malaria:

- No focal lesions, no meningeal signs.
- Common in children.
- Unarousable coma that's not attributed to any cause but the presence of *P.falciparum.*
- Pathology of Cytoadherence.
- ***Pathogenomic feature: excess of malaria pigments in brain (hemazoin).***
- It is associated with **retinal whitening**, which may be a useful clinical sign in distinguishing Malaria from other causes of fever.
- **Complications:**

  1. Blindness 2.Deafness 3.hemiplegia 4.cerebellar ataxia. The commonest one is language deficit.

2. ALGID malaria:

- Characterized by shock (hypotension) & GI symptoms.
- Presentation: pale, cold with shock and severe diarrhea.
- Associated with Gram negative septicemia.

3. Black water fever:

- Syndrome of intravascular hemolysis lead to hemoglobinuria.
- Presentation: fever, pallor, jaundice, dark urine, hepatosplenomegaly & acute renal failure.

4. Pulmonary edema:

- Microvascular obstruction, ↑ vascular permeability.
- Presentation: dyspnea, cough, hypoxia.
- Represents 80% of the cases of severe malaria.

5. Multi-organ failure: Shock, DIC.

- Common features of P.vivax infection :
  - Typical prodrome of acute symptoms.
  - Milder than P.F (no severe malaria).
  - Splenic rupture, hypovolemic shock.
  - Carries high mortality rate.

- Common features of P.ovale :
  - Similar to P.vivax, but spontaneous recovery more common.
  - Milder.
  - Fewer relapses.

- Common features of P.malariae infection :
  - Similar to P.vivax, but prodrome may be severe and the rest of the disease is milder.
  - Can cause nephritic syndrome, prognosis is poor (proteinuria and loss of Abs leading to low immunity and increased susceptibility to bacterial infections).

- **Chronic complications of malaria :**
  - Tropical splenomegaly syndrome (Hyperreactive splenomegaly syndrome) (in endemic area).
  - Burkitt's lymphoma (D.D is EBV).
  - Nephropathy (membranous type) by P.malariae.

- Congenital malaria :
  - Transplacental infection.
  - All 4 species, most commonly in P.F in Sudan.
  - **1st trimester:** abortion.
  - **2nd trimester**: miscarriage.
  - **Presentation:** fever, irritability, feeding problems, anemia, hepatosplenomegaly & jaundice.

- *Diagnosis :*
- *Clinical Diagnosis :*
- Hyperendemic & holoendemic areas, fever or history of fever.

- *Lab diagnosis :*
- Specimen :
  - Blood can be collected by finger pricks. If other test is being used, we can use vein puncture. Smear should be prepared and stained within an hour.
- Microscopy :
  - ***The gold standard.***
  - **Thick film** considered gold standard for detection.
  - **Thin film** considered gold standard for identification.
  - Thick film: Large volume (10ml), Good screening test (detection), Parasitic density can be measured.
  - Thin film: Smaller volume, Good species identification, Low density infection can be missed.
  - A number of attempts have been made to improve on the standard thin and thick smear. One such procedure involves acridine orange staining of centrifuged parasites in quantitative buffy coat (QBC) tubes.

- Malaria parasite erythrocyte stages :
  - Ringform, Schizonts, Trophozoites: in RBCs.
  - Gametocytes: inside & outside RBCs.
  - *P.falciparum*: **more than 1 ring stage** inside the RBCs (more malignant). Rarely merozoites are found in peripheral blood because of knobs protein. Mature **gametocyte** looks like **"banana".** If more than 5% of red blood cells are parasitized, the diagnosis is usually P. falciparum malaria. Infected RBCs have black dots (Maurer's dots).

  - *P.Vivax*: 1 or rarely 2 ring stages. **Deformed RBCs**. **Gametocyte is round.** Infected RBCs have red dots (Schuffner's dots). Note that red dots in P.O infected RBCs are called James dots.

  - *P.Malariae*: 1 ring stage. **Trophozoite is typically band shaped.** Gametocyte is round with dark pigment. Infected RBCs have Zeeman dots (rarely seen).

- Parasitemia & clinical correlates :
  - % / Parasite/ml / Clinical correlates.
  - 2-5 % / 100,000 – 250,000 / Hyperparasitemia / severe malaria.
  - 10 % / 500,000 / Exchange transfusion.

- Fluorescent microscopy :
  - Modification of light microscopy. Fluorescent dyes detect RNA & DNA. Expensive. Kawamoto technique can be used.

- Malarial antigen detection :
  - **Immunochromatographic (ICT) or rapid diagnostic test "RDTs". Used with blood.**
  - The most widely used test, *ParaSight F*, detects a protein **(HRP2)** excreted by P. falciparum within minutes as well as from infected RBCs (but not present in mature Gametes). The test can be performed under field conditions and has a sensitivity more than 95%.
  - Histidine Rich Protein 2 **(HPR2)** persists for 14 days after treatment or even 28 days. So it is not a good test for monitoring treatment.
  - The principle of the test is use of *Monoclonal Abs*. against HRP-2. It is more sensitive than OptiMal but it cannot detect mixed infection & do not cross react with other species.

  - A second rapid test, *OptiMAL*, detects parasite **lactate dehydrogenase**, and, unlike ParaSight F, can distinguish between P. falciparum and P. vivax.

  - The principle of the test is use of monoclonal & polyclonal Abs. for detection of parasite LDH.
  - PLDH: P.F & pan specific bands, closely reflects parasite viability, found in asexual & sexual stages, potential for monitoring. P.V, P.O, P.M specific mabs developed.
  - It is less sensitive than ParaSight F but it can differentiate between Falciparum & non-Falciparum malaria. In the past it couldn't differentiate between non-Falciparum malaria but now differentiation is possible.
  - A third antigen that can be detected is *aldolase*: Pan-specific, found in asexual & sexual stages.

- Malarial serology :
  - **Antibody detection**. Abs may persist for months .Positive test indicates past infection.
  - **IgM specific immunoglobulin used in hyper malaria Splenomegaly syndrome.**
  - Immunofluorescence test (IF). Radioimmunoassay (RIA).
  -
- Polymerase chain reaction (PCR) :
  - Molecular technique to identify parasite's genetic material.
  - For screening blood donation.
  - Can differentiate between species.
  - Can detect up to 5 parasites / ul.
  - Detect mutations (drug resistance).

- *Treatment :*
  - The indications for treatment rest on two factors. The first is the infecting species of Plasmodium, and the second is the immune status of the afflicted patient.
  - Falciparum malaria is potentially lethal in nonimmune individuals such as new immigrants or travelers to a malarious area and immunosuppressed indigenous individuals such as pregnant women. These individuals must be treated emergently.
  - **The complete treatment of malaria requires the destruction of three parasitic forms: the erythrocytic schizont, the hepatic schizont, and the erythrocytic gametocyte**.
  - The first terminates the clinical attack, the second prevents relapse, and the third renders the patient noninfectious to Anopheles and thus breaks the cycle of transmission.
  - Unfortunately, no single drug accomplishes all three goals.
  - Generally, supportive treatment is important e.g. Reduction of fever, Anticonvulsants, Antiemetics, rehydration, blood transfusion in severe anemia ....ECT.

- Uncomplicated malaria :
  - In 2004 the national drug policy for malaria was changed from mono-therapy to ACT (artemisinin based combination therapy), (tissue-cidal)
    .
  - **Artemether + lumefantrine (Coartem),** Best treatment.
  - **Artesunate + fansidar (sulfadoxine – pyrimethamine), used in Sudan (the worst).**
  - Others : (Artesunate + amodiquine) Or (Artesunate +mefloquine) Or (Artesunate + piperaquine) .
  - Treatment for Malaria in Sudan is what should be written in Exam.

- Failure :
  - Treatment failure with 14 days of receiving drug ACT.
  - Second line drugs :
  - **Artesunate + tetracycline or doxycycline or clindamycin, for 7 days.**
  - **Quinine + tetracycline or doxycycline or clindamycin, for 7 days.**

  - **Note: quinine** can cause severe hypoglycemia (given with dextrose) & Hypotension, nephrotoxicity (Black water fever). Its other side effect is cinchonism (Ringing noise in the ear & sometimes deafness, blurred vision & sometimes blindness, GI symptoms like nausea, vomiting & diarrhea).

- Pregnant :

  - **Quinine + clindamycin (no Artesunate)** => 1st trimester.
  - **ACT Or (Artesunate + clindamycin) or (quinine + clindamycin)** => 2nd & 3rd trimesters => for 7 days.

- Notes about treatment :
  - ACT [**Artesunate + fansidar (as + sp)**] is used for P.vivax, in **combination with primaquine** for radical cure.
  - Two antimalarial medicines have an effect specifically on gametocytes (gametocidal): Primaquine & Artemisinin.
  - Primaquine may induce severe hemolysis in those with G6PD deficiency, so testing for this enzyme should be done before the drug is given. The only anti-malarial that can be given to a person with G6PD deficiency is mefloquine.
  - Chloroquine is the drug of choice for acute malaria caused by sensitive strains. Chloroquine kills the merozoites, thereby reducing the parasitemia, but does not affect the hypnozoites of P. vivax and P. ovale in the liver. These are killed by primaquine, which must be used to prevent relapses.

- Radical cure :
  - When P.vivax & P.ovale malaria parasites are eliminated from the blood, the remaining hypnozoites must be removed from the liver by administration of a 14-day-course of primaquine.
- Lactating women :
  - ACT except primaquine and tetracycline.

- Severe malaria :
  - **Intravenous Artesunate or IM can be used.**
  - Only in hospitals, not outpatient clinics.
  - 2nd line: **Quinine or Artemether** by IM route.
  - Given parentrally for 24 hours and completed by giving course of ACT.

- Prophylaxis :
  - Against hypnozoites: **Primaquine** or Malarone (Atovaquone + proguanil).
  - Against RBCs stage: **Mefloquine** (pregnant & children) or Doxycycline.

[Extra]

- Side effects :
- **Mefloquine :** Neuropsychiatric side effects (anxiety , paranoia , hallucination , depression , confusion , loss of balance) , pneumonitis & eosinophilia pneumonia , cardiac arrhythmia .
- **Primaquine:** hemolytic anemia in pts. With G6PD deficiency, methemoglobinemia (self-limiting), visual disturbances & intense itching. Contraindicated in pregnancy because the G6PD status of the fetus would be unknown.
- **Artesunate:** Lower reticulocyte count, safety in pregnancy is unclear (there is evidence of embryo toxicity in animal models).
- **Chloroquine:** deposition in the retina (irreversible) and cornea (reversible).

- Vaccine :
  - No vaccine.
  - RTS or masquirix, and experimental vaccine for malaria (but not used).
- Why?
  - As immunity to malaria is stage specific, the relative advantages and disadvantages of vaccines prepared against each of the plasmodial stages found in the human host (sporozoite, merozoite, and gametocyte) need to be considered.
  - An effective sporozoite vaccine, by blocking the invasion of hepatocytes by mosquito-introduced sporozoites, would prevent the establishment of the infection within the host and, if widely administered, would interrupt parasite transmission within a community.
  - However, to be effective, a sporozoite vaccine would have to prevent the invasion of all injected sporozoites.
  - Theoretically, if even a single parasite reached and penetrated a liver cell, it would multiply intracellularly and later enter the bloodstream to invade erythrocytes.
  - The patient could develop clinical disease and serve as a reservoir for subsequent transmission to others.
  -
  - A vaccine directed at the erythrocytic or merozoite stage, although preventing neither hepatic nor bloodstream infection, would limit the severity of the parasitemia and thus moderate or abort clinical manifestations of disease.
  - Gametogenesis, and thus parasite transmission, would probably proceed unimpaired.
  -
  - Antibodies formed in response to a gametocyte vaccine might block the union of male and female gametes within the mosquito gut, interrupting parasite transmission.
  - It would, however, neither prevent nor moderate malaria in the immunized patient.
  - The limitations of each vaccine type has led some investigators to advocate the combination of all three in a single polyvalent preparation. Unfortunately, the results of field tests of a number of candidate vaccines have been disappointing.

Trypanosomiasis

Human African Trypanosomiasis (HAT)
(African sleeping sickness)

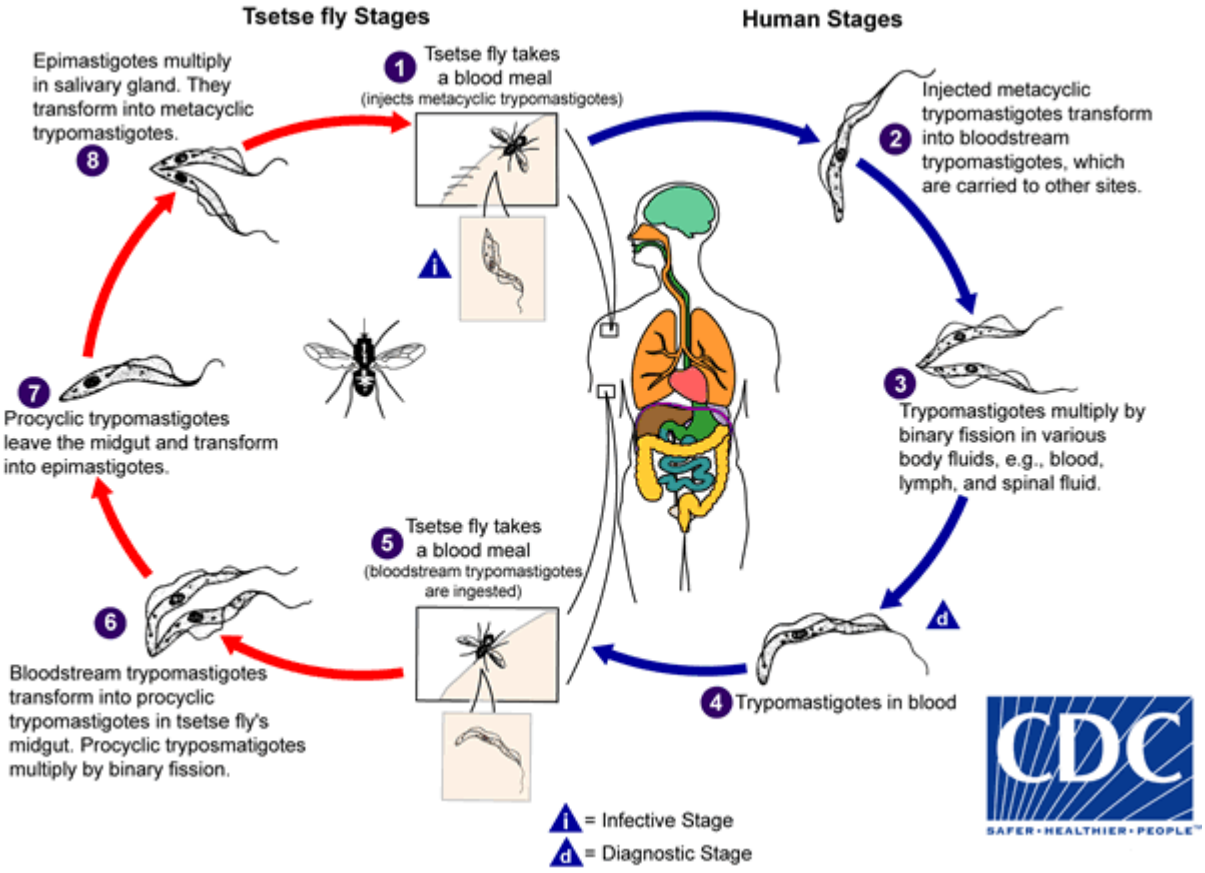
- *Epidemiology* :
  - Fatal and neglected disease.
  - 50,000 in Africa die because of this. 70 million are at risk.
  - Human African Trypanosomiasis (HAT) affects 36 countries at sub-Saharan Africa.
- *Causative agents :*
  - Caused by the protozoan Trypanosoma Brucei.
  - Has 3 subspecies:
  1. ***Trypanosoma brucei gambiense.***
  2. ***Trypanosoma brucei rhodesiense***.
  3. Trypanosoma brucei brucei in animals only (not important clinically).
  - Extracellular parasite transmitted by **Tsetse fly (Glossina).**

- *Geographical distribution :*
- Over 200 active foci of HAT between 5 degrees north and 15 degrees south ("tsetse belt").
- Trypanosoma brucei gambiense is found in western and central Africa. Over 95% of the cases of human infection in Sudan.
- Trypanosoma brucei rhodesiense is found in eastern and southern Africa.
- **Sudan is endemic of Trypanosoma.**

	T.b gambiense	***T.b rhodesiense***
Virulence	Less	More
Reservoir	Human	Animal
Zoonotic	Less	More
Vector	G. Palpalis	G.Mortisans
Distribution	Western Africa	Eastern Africa
Presentation	Chronic	Acute
Prevalence	90%	10%

- *Transmission :*
- **Glossina palpalis** (important in Sudan) & Glossina mortisans. **Bites during daytime.** Both the male and female of the fly can transmit the disease. *It can pierce the clothes.*
- Vertical transmission (transplacental).

- *Life cycle :*
  - The 3-week life cycle in the tsetse fly begins with **ingestion of trypomastigotes** in a blood meal from the reservoir host.
  - They multiply in the insect gut and then migrate to the salivary glands, where they transform into epimastigotes, multiply further, and then form metacyclic trypomastigotes, which are transmitted by the tsetse fly bite.
  - The organisms in the saliva are injected into the skin, where they enter the bloodstream, differentiate into blood-form trypomastigotes (extracellular), and multiply, thereby completing the cycle.



  - Note that these species are rarely found as amastigotes in tissue, in contrast to T. cruzi and Leishmania species, in which amastigotes are commonly found.

  - Mature trypomastigote: **in humans.**
  - Metacyclic trypomastigote, Epimastigote, Procyclic trypomastigote: **In TseTse fly.**

- *Pathophysiology :*
  - These trypanosomes exhibit remarkable **antigenic variation** of their surface glycoproteins, with hundreds of antigenic types found.

- One antigenic type will coat the surface of the parasites for approximately 10 days, followed by other types in sequence in the new progeny.
- This variation is **due to** sequential movement of the glycoprotein genes to a preferential location on the chromosome, where only that specific gene is transcribed into mRNA (Gene rearrangement).
- Antibodies are formed because it is extracellular (Humoral response).
- These antigenic variations allow the organism to continually evade the host immune response. I.e. This disease is never be self-limited (you will never clear trypanosoma by immune response).
- The trypomastigotes spread from the skin through the blood to the lymph nodes and the brain.
- The typical somnolence (sleeping sickness) progresses to coma as a result of a **demyelinating encephalitis** (by Hypersensitivity reaction type 1 & 2).
- In the acute form, a **cyclical fever spike** (approximately every 2 weeks) occurs that is related to antigenic variation.
- As antibody-mediated agglutination and lysis of the trypomastigotes occur, the fever subsides. However, a few antigenic variants survive, multiply, and cause a new fever spike.
- This cycle repeats itself over a long period. The lytic antibody is directed against the surface glycoprotein.

- It may also affect: hematologic system, lymphatic system, Heart, GIT and central nervous systems.

- **Immune-invasion by antigenic variation of parasite surface glycoproteins: Variant Surface Glycoprotein (VSG).**

    - **<u>VSG specific IR :</u>**

- **IgM** response against VSG.
- IgM response often > IgG *(Trypanosomiasis is the only disease that causes IgM more than IgG,* because these VSGs are T cell independent Ags that stimulate ADCC, thereby stimulating B cells directly to produce IgM but no class switching occurs and also because once IgM is formed and the parasite is cleared from the blood a new antigenic variant emerges that stimulates production of new IgM).
- Trypanosoma disappear within hours
- VSG specific IgG appears not relevant (like brucella).
- The level of the parasite will be fluctuating, high parasitemia, low parasitemia, high parasitemia... etc. (like brucella).

- *Clinical presentation :*
    - Asymptomatic phase: incubation period at least 5 days.
        - **First stage (haemolymphatic phase).**
        - **Second stage (neurological phase).**

- First stage: (Haemolymphatic phase) :
    - The parasite in the lymph and blood.
    - **Painless skin chancre** (first presentation can be like this) that appears 5-10 days after the bite, resolving spontaneously.
    - Intermittent fever, Malaise, myalgia, headache, Arthralgia.
    - **Winterbottom sign:** Posterior cervical lymphadenopathy, *Characteristic of Trypanosoma brucei gambiense.*
    - Urticarial, erythematous or **macular rash**.

- Second stage :
    - Fatal.
    - Eventually, the disease will manage to cross the blood-brain barrier.
    - **Persistent headache.**
    - **Daytime somnolence followed by night time insomnia (disturbance in sleeping cycle).**
    - Behavioral changes, mood swings, Aggression, Depression and psychiatric symptoms.
    - Loss of appetite, wasting syndrome.
    - Sleeping all the time eventually.
    - Coma and death.

    - **So in summary:** The encephalitis is characterized initially by headache, insomnia, and mood changes, followed by muscle tremors, slurred speech and apathy that progress to somnolence and coma. Untreated disease is usually fatal as a result of pneumonia.

    - *Signs :*

- Fever.
- Chancre (first sign).
- Skin lesions (which are called **trypanids**).
- Lymphadenopathy: the classic Winterbottom sign is clearly visible.
- Kerandel's sign (patient when sleeping will not respond to pain).
- Hepatosplenomegaly.

- *Lab diagnosis :*
  - Acute stage is diagnosed by **direct microscopy** from the *blood, lymph node or the aspirate of the chancre.*
  - Blood for first stage and for T.b rhodiensae
  - Lymph node aspirate from Winterbottom area for T.b gambiense.
  - Acute stage can be detected by antigen detection in just T.b gambiense and this by **Cord Agglutination Test for trypanosoma (CATT).** Like ICT in malaria.

  - CNS stage (2nd stage) can be detected by **direct microscopy** by *lumbar puncture* (using double centrifugation method).

  - The other method for detection of CNS stage is the detection of **intrathecal IgM in the CSF**.

  - Rarely ELISA and PCR can be used (in both acute stage & CNS stage).

- *Chemotherapy :*
- **Western African Trypanosomiasis :** ***(T.b gambiense)***

	Stage 1	**Stage 2**
First Line	Pentamidine	Melarsoprol
Second Line	Melarsoprol or Eflornithine.	Eflornithine

- **Eastern African trypanosomiasis :** ***(T.b rhodiensae)***

	Stage 1	**Stage 2**
First Line	Suramin (Doesn't cross the BBB)	Melarsoprol (suramin to clear the parasitemia should be used first).
Second Line	Melarsoprol	Nifurtimox combined with Melarsoprol.

- *Prevention :*
  - No vaccine against African Trypanosomiasis.
  - You have to fight the fly.

American trypanosomiasis (Chagas Disease)

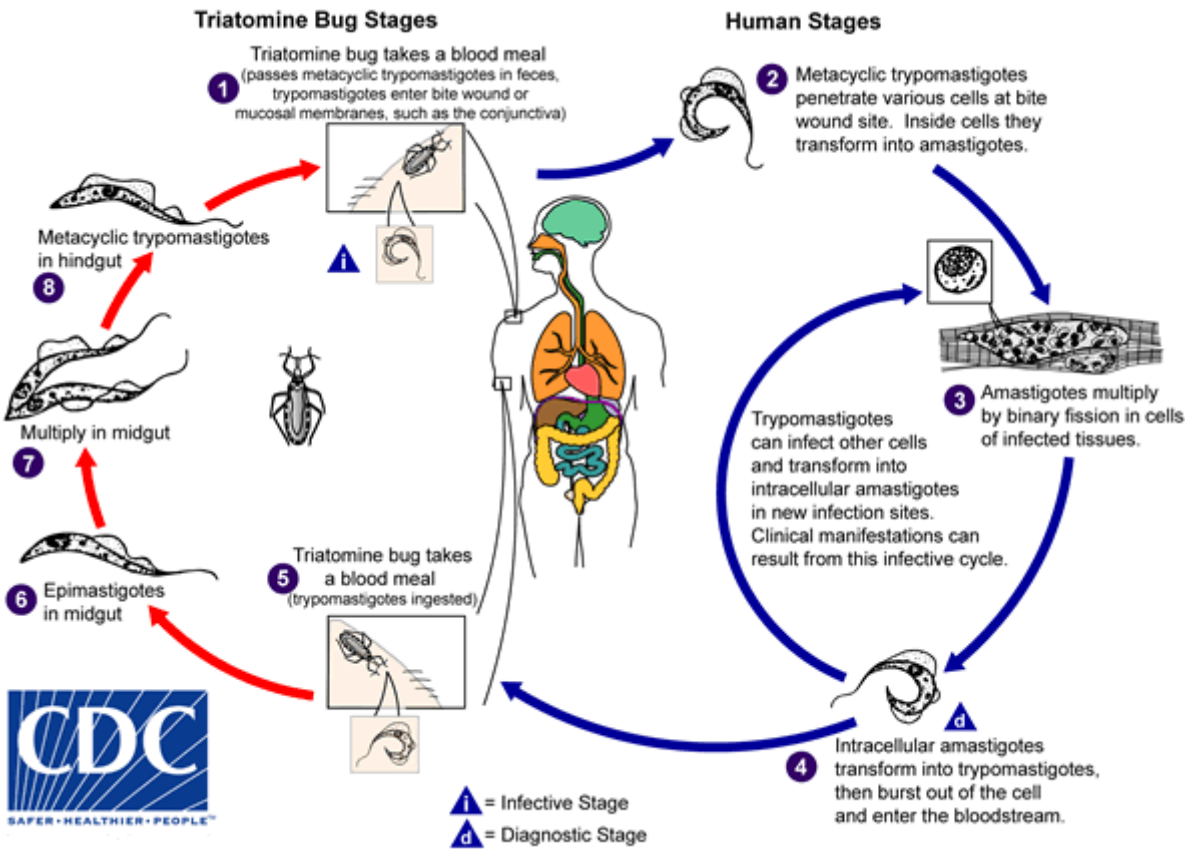
- *Epidemiology :*
  - 1960s.
  - 16-18 million people affected as of 2008.
  - ~100 million at risk.
  - Kills around 20,000 annually.
  - Discovered by chagas and for that it's called Chagas disease.
  - The vector is the kissing bug which usually bites at night.
- *Transmission :*
  1. **By vector:** Blood sucking insect of the subfamily Triatominae **(reduviid bug)** :
  - Emerges and bites at night.
  - Bites, feeds, and then defecates.
  - The disease is seen primarily in rural areas because the reduviid bug lives in the walls of rural huts and feeds at night.
  - It bites preferentially around the mouth or eyes, hence the name "kissing bug".

  2. Blood transfusion, Organ transplants, or breast milk.

  3. Congenital transmission :
  - 13% of stillborn deaths in parts of Brazil.
  - 15% of them die.
  - 15% of intrauterine deaths are due to Chagas disease.

  4. Food contamination.

- *Causative agent :*
  - Caused by ***Trypanosoma Cruzi***:
  - Sylvatic cycles of transmission: raccoons and monkeys.
  - Domiciliary (dogs and cats).
- *Life cycle :*
  - Trypomastigote enter your body through faeces of the buck, metacyclic trypomastigote will enter you, and stay both inside and outside the cell, inside the cells, trypomastigote will be converted onto amastigote (looks like leishmania), when amastigote rupture will lead to trypomastigote, and continue the cycle.



- The difference is that the trypomastigote will not enter the salivary gland, but it's in the gut of the vector**. This mean that the vector is not injecting.**

- *<u>Pathophysiology :</u>*
  - The amastigotes can kill cells and cause inflammation, consisting **mainly of mononuclear cells.**
  - **Cardiac muscle** is the most frequently and severely affected tissue (Affect the heart => chronic inflammation leading to **myocarditis and dilated cardiomyopathy**).
  - In addition, neuronal damage leads to cardiac arrhythmias and loss of tone in the colon **(megacolon)** and esophagus **(megaesophagus).** (The GIT symptoms result from denervation of hollow viscera, reaches the mucosa as well as the muscles).
  - During the **acute phase**, there are *both trypomastigotes in the blood and amastigotes intracellularly in the tissues.*
  - In the **chronic phase**, the organism persists in the *amastigote form* => chronic inflammation => Intracellular parasitism of muscles.
  - Death from chronic Chagas disease is usually due to cardiac arrhythmias and failure.

- *Clinical manifestations :*
- Signs and symptoms :
    - Asymptomatic.
    - Incubation period: 7-14 days (1-2 weeks).

- Symptoms of acute stage :
    - Nonspecific symptoms i.e. fever, diarrhea, vomiting.
    - Swelling and inflammation.
    - **Chagoma** (redness and inflammation at the bite site).
    - **Romana sign:** (unilateral painless palpebral edema) (unilateral periorbital edema), there is usually conjunctivitis but it is hard to be identified. Accompanied by enlarged preauricular lymph nodes.
    - No chancre in Chagas disease.

- Signs of Acute stage :
    - Chagoma (erythema).
    - Romana sign.
    - Facial edema.
    - Generalized lymphadenopathy (like visceral leishmaniasis).
    - Schizotrypanides.
    - Hepatosplenomegaly.

- Another Presentation :
    - Indetermine phase.
    - Does not cause any symptoms but the pt. is seropositive (like syphilis).
    - In this phase there is no treatment for adults, children are treated.

- Symptoms of chronic stage :
    - Fatal and irreversible.
    - About 30% develop medical problems.
        - **Cardiac damage** (dilated cardiomyopathy) causing atrial and ventricular rhythm disturbances, and congestive heart failure.
        - **Mega syndrome** :
    - **Mega oesophagus** => Dysphagia => malnutrition => weight loss => fatal.
    - **Megacolon (gastric dilatation)** => constipation and gas production.
    - **Megaureter** => obstructive uropathy => can't produce urine.
        - **Digestive system damage.**
        - **Neurological disorders :**
    - In late stage of the disease.
    - Because of infection of the parasite to the CNS as well as cardiac myopathy.

- Signs of chronic stage :
  - Cachexia.
  - Hypertrophy of the salivary gland => no eating.
  - Pneumonia: because of mega oesophagus, the food will enter into the larynx => trachea => Aspiration pneumonia.
  - Can lead to death because of :
    - Heart failure & Shock.
    - Aspiration pneumonia.

- *Lab diagnosis :*
- Acute Chagas disease :
  - Direct microscopy of the blood (mainly).
  - PCR to ID strains (for confirmation).
  - Neither Xenodiagnosis nor Hemoculture are useful.

- Chronic Chagas disease :
  - Parasite inside the heart, esophagus, colon.
  - Biopsy is difficult.

1. **Serological diagnosis :**

- IIF is the earliest to become positive, ELISA, Indirect hemoagglutination, The Chagas Radioimmune Precipitation Assay (Chagas RIPA).

2. **PCR.**
3. **Xenodiagnosis**, which consists of allowing an uninfected, laboratory-raised reduviid bug to feed on the patient and, after several weeks, examining the intestinal contents of the bug for the organism.
4. **Biopsy**: if the patient died.
5. **Others**: can use imaging by CT and MRI for dilated esophagus as well as the colon and heart.

- *Treatment :*

1. **Acute Chagas disease :**
   - First line: **Benznidazole** (for Indetermine phase).
   - Second line: **Nifurtimox**.
2. **Indeterminate-phase Chagas disease :**
   - Children should receive either Benznidazole or Nifurtimox (not useful for adults).
3. **Chronic symptomatic chagas disease :**
   - General medical treatment.
   - Surgery.
   - No cure.
   - Colostomy, gastrotomy tube, cardiac transplantation, nephrotomy tube, anti-peristaltic, Diuretics etc...

Leishmaniasis

- Parasitic disease, transmitted by Sand fly (the vector).
- Found in 88 countries.
- Leishmania species are obligate intracellular parasites of mammals, like Toxoplasma.
- 3 main forms of Leishmaniasis :
  1. **Cutaneous (involving skin).**
  2. **Mucocutaneous (involving mucous membranes of mouth & nose).**
  3. **Visceral (liver, spleen & bone marrow).**

Cutaneous Leishmaniasis

- About 1.5 million cases each year.
- Its distribution is divided into old world & new world (America).
- Spectrum of the disease:
  1. Localized L. (LCL).
  2. Diffuse L. (DCL).
  3. Mucosal L. (destructive mucosal inflammation in mouth & nose).
- Different spp. Of Leishmania cause different types of disease.
- Found in exposed areas of the body (face, forearm, feet "rare").

- *Transmission :*
  - Old world: **Phlebotomus sand fly** (orientries).
  - Female hematophagous.
  - New world: Lutzomyia sand fly.
  - Humans become involved when they enter forested areas to harvest chicle for chewing gum and are bitten by infected sandflies.

- *Causative agent :*
  1. ***L. aethiopica*** (causes LCL & DCL, zoophilic reservoir is animals, in Sudan: Camels & rodents).
  2. ***L. major*** (major causative agent). Causes all 3 forms of the disease, most severe & most virulent spp.
  3. ***L. tropica:*** Causes LCL, DCL & MCL but mainly LCL, anthropophilic, benign & no animal reservoir.

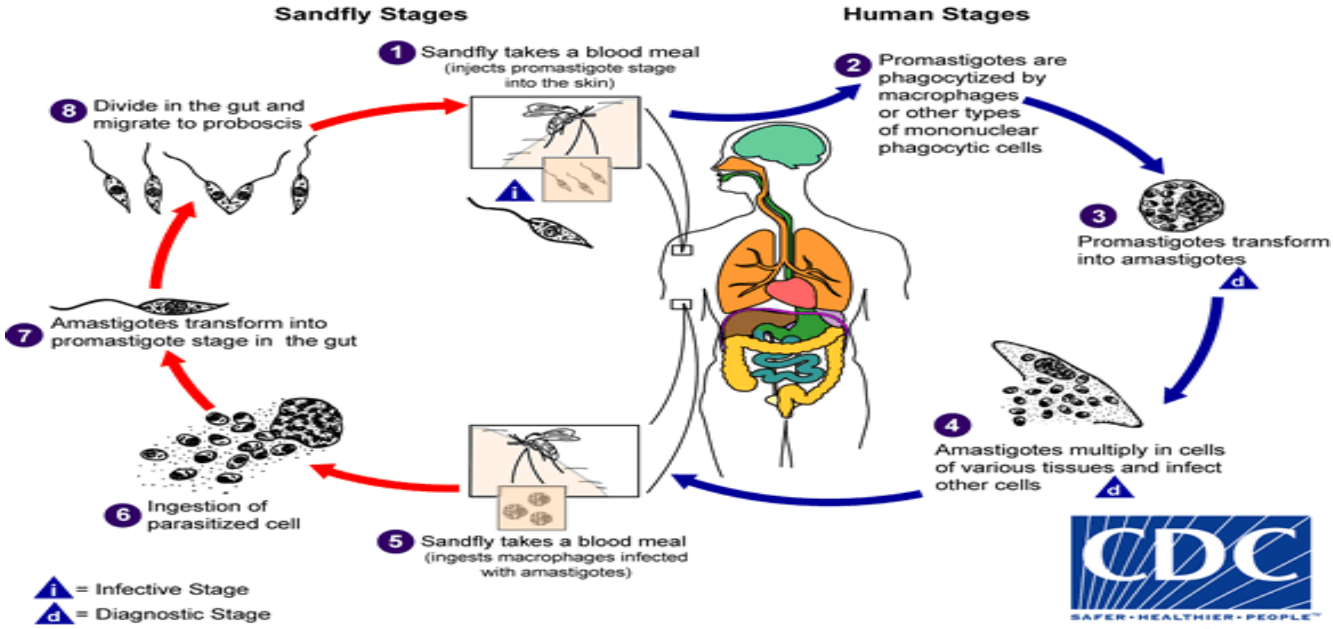
- *Life cycle :*

1. **Promastigote :**

- Insect stage. Motile (flagella). In the midgut of the insect.

2. **Amastigote :**

- Mammalian stage. None-motile. Intracellular (inside macrophage), the parasite can't live outside the cell.
- The parasite causes infection, macrophages move toward the parasite (non-motile) & it causes rupture of macrophages.



-

- When the sandfly sucks blood from an infected host, it ingests macrophages-containing amastigotes.
- After dissolution of the macrophages, the freed amastigotes differentiate into promastigotes in the gut. They multiply and then migrate to the pharynx, where they can be transmitted during the next bite. The cycle in the sandfly takes approximately 10 days.
- Shortly after an infected sandfly bites a human, the promastigotes are engulfed by macrophages.
- Amastigotes can remain in the cytoplasm of macrophages because they can prevent fusion of the vacuole with lysosomes.
- Continued multiplication leads to the rupture of the phagocyte and release of the daughter cells. Some may be taken up by a feeding sandfly; most invade neighboring mononuclear cells.
- The infected cells die and release progeny amastigotes that infect other macrophages and reticuloendothelial cells. The cycle is completed when the fly ingests macrophages containing the amastigotes.

- **So in summary:** *Sand Fly => enter the body => (promastigote) => enter macrophage => (amastigote) => taken by Sand fly.*
- Only female flies are vectors because only they take blood meals (a requirement for egg maturation).

- *Initial infection :*
  - Inoculation of promastigote.
  - Receptor mediated phagocytosis into macrophages.
  - Inflammation **(ulceration).**
  - Pathogenesis appear to be related to **T-cell cytotoxicity**.
  - The lesions are confined to the skin in cutaneous leishmaniasis and to the mucous membranes, cartilage, and skin in mucocutaneous leishmaniasis. A granulomatous response occurs, and a necrotic ulcer forms at the bite site. The lesions tend to become superinfected with bacteria.
- **Forms of Cutaneous Leishmaniasis :**
  1. Local Cutaneous Leishmaniasis (LCL).
  2. Disseminated Cutaneous Leishmaniasis (DCL).
  3. Mucocutaneous Leishmaniasis (MCL).

- **LCL (Local Cutaneous Leishmaniasis) (oriental sore or chiclero ulcer) :**
  - Incubation period 2 weeks-month.
  - Lesions usually appear on the **extremities or face** (the ear in cases of chiclero ulcer).
  - Lesion starts as **erythema**, develops into a **papule** then a **nodule** that progressively **ulcerates** over a period of 2 weeks to 6 months, then heals by fibrosis causing scar.
  - Skin sores (oriental / Bagdad – sores) of cutaneous L. can heal by their own (2-15 month).
  - Sores can leave significant scars (healing by fibrosis), it can be disfiguring if they occur on the face.
  - Occasionally the lesions fail to heal, particularly on the ears, leading to progressive destruction of the pinna (chiclero ulcer by L.major).
  - If the infection is by L. tropica it can spread to contiguous mucous membrane (Upper lip to nose).
  - There is usually a **single lesion that heals spontaneously** in patients with a competent immune system. However, in certain individuals, if cell-mediated immunity does not develop, the lesions can spread to involve large areas of skin and contain enormous numbers of organisms.

- **Leishmaniasis Recidivans :**

  - Due to the chronicity of the ulcer and because the central part of the lesion undergoes necrosis, the parasite lives in the edges of the lesion, this leads to Reactivation of dormant parasites or new infection By a different spp.
  - New ulcers & papules form over the edge of the old scar.

- If the immunity is low, parasites are reactivated in the normal skin around the old lesion.

- **DCL (Diffuse Cutaneous Leishmaniasis) :**
  - Non-ulcerative nodules (As in M.Leprae) disseminated from the initial site of infection & cover the pt.'s entire body.
  - In immune-compromised & malnourished, DCL is difficult to be treated & the disease is not self-limited.
  - Differential Diagnosis of a face full of nodules: DCL, Lepromatous Leprosy, PKDL.
- **Mucocutaneous Leishmaniasis (MCL) (espundia) :**
  - More severe than cutaneous L. & can cause death.
  - Species :
    1. L. braziliensis (the most common).
    2. L. Mexicana.
       - The only spp. You should consider.
    3. L. venzwellensis.
  - All are zoonotic, first because LCL & then it develops to MCL.
  - Affect cartilage, muscle, fibrous tissues (except bone & teeth).
  - Mucocutaneous leishmaniasis begins with **a papule at the bite site**, but then **metastatic lesions** form, usually at the **mucocutaneous junction of the nose and mouth**. It occasionally affects the perineum.
  - Disfiguring granulomatous, ulcerating lesions destroy nasal cartilage but not adjacent bone. These lesions heal slowly, if at all.
  - Death can occur from secondary infection.
  - Sometimes, decades pass and the primary lesion totally resolves before the metastases manifest themselves. Destruction of the nasal septum produces the characteristic tapir nose. Erosion of the hard palate and larynx may render the patient aphonic.
  - In blacks, the lesions are often large, hypertrophic, polypoid masses that deform the lips and cheeks.
  - Fever, anemia, weight loss, and secondary bacterial infections are common.
    - There is 2 types of MCL :

1. **<u>Mild MCL :</u>**

   - Benign with nasal infection & stiffness, Ulceration of the nasal mucosa & perforation of the septum.

2. **<u>Severe MCL :</u>**

   - A hole in the soft palate (brain), pharynx (dysphagia => malnutrition), or larynx (pneumonia & respiratory compromise).
   - Never heal spontaneously.
   - Death from secondary bacterial infection.

- *Immunity* :

  - Disease resolution is achieved by the cell mediated response.
  - The primary activation of T-cell subsets is important for the development of :

1. **T-helper 1 => LCL => activation of cell-mediated immunity => killing the intracellular parasite => more localized infection. Useful.**

   - In the localized cutaneous forms of leishmaniasis, this immune response results in the development of a **positive delayed skin (leishmanin) reaction**, lymphocytic infiltration, reduction in the number of parasites, and, eventually spontaneous disappearance of the primary skin lesion.
   - In infections with L. braziliensis, this sequence may be followed weeks to months later by mucocutaneous metastases.
   - These secondary lesions are highly destructive, presumably as a result of the host's hypersensitivity to parasitic antigens.
   - Some strains of L. tropica and L. mexicana fail to elicit an effective intracellular immune response in certain hosts.
   - Such patients appear to have a selective suppressor T lymphocyte–mediated anergy to leishmanial antigens.
   - Consequently, there is no infiltration of lymphocytes or decrease in the number of parasites.
   - The skin test remains negative, and the skin lesions disseminate and become chronic (diffuse cutaneous leishmaniasis).

2. **T-helper 2 => DCL activation of Ab. Production through B-cell => more antibodies without killing the intracellular parasite. Not useful.**

- **Patients with any of the following findings should be referred :**
  1. Big lesions (greater than 1 inch in size).
  2. Many lesions (3 or more, DCL).
  3. Sores in the face (MCL).
  4. Sores in hands & feet (affect life style).
  5. Sores over the joint (can cause stiffness & loss of function after healing by fibrosis).

- *Lab diagnosis :*

1. **Microscopic examination (gold standard-best method of detection):**
   - The sample is aspirate or biopsy.
   - By Giemsa stain: see amastigote inside macrophages.
2. **Culture (for identification) :**
   - NNN (Nicolle-Novy-MacNeal's) media: See promastigote.
3. **PCR** :
   - Indications: With low parasite load (mucosal L.) and for therapy monitoring.

4. **Montenegro skin test (Leishmanin test) :**

   - Inject PPD (purified protein derivative of the parasite) => if there is swelling means the pt. has the disease in the past or now.
   - Not effective!!! Because it can't differentiate between acute & chronic.
   - It is negative in DCL & Visceral Leishmaniasis. It is positive LCL & MCL.
   - Like Tuberculin test (Mantoux test).

5. **Serological diagnosis is rarely used in cutaneous L. diagnosis.**

- *Treatment :*
- **Cutaneous & Mucocutaneous L. :**
- Cutaneous L. is treated to accelerate cure & to reduce scaring, otherwise **it can heal spontaneously.**

- **Antimony (Pentostam & Sodium stibogluconate) is the drug of choice**, given I.V. or Intra-lesion to act locally. But it is very painful.

- Second line: **Amphotericin B** (antifungal). **Paromomycin (**anti parasitic). **IFN ɣ** (immune mediator to increase T-cell immunity). **Fluconazole** (antifungal).

- *Vaccines :*
  1. **Leishmanisation** :
  - Currently not recommended by WHO, Inoculation of the virulent L. parasites.
  2. **Killed vaccine**:
  - Killed parasites.
  - Had been developed in South & Central America, Sudan & Iran.
  - Not useful.

Visceral Leishmaniasis (Kala-azar)

- Causative agent: Leishmania Donovani complex.
- Sub species :

1. ***L.d. donovani (main).***
2. ***L.d. infantum (main).***
3. L.d. chagas.
4. L.d. archibaldi.

- *Epidemiology :*
  - 500,000 new cases/ year, >50, 00 deaths.
  - Very common in Sudan.
  - Animal reservoir: Dogs, Jackels & foxes.

- *Transmission :*
  - By female phlebotomine sand flies.

- *Digenic life cycle:*
  - Promastigote in the sand flies & amastigotes in the human.
  - Life cycle similar to that of C.L the difference in V.L is the tissue tropism :
  - L.d likes blood therefore expected to be found in the RES (liver, spleen, and Bone marrow), lymph nodes & the blood.

- *Pathogenesis* :

  - Inoculation of promastigotes into skin, internalized by dendritic cells & macrophages in the dermis & transform into amastigotes.
  - Here, they activate complement by the classic (L. donovani) or alternative pathway and are opsonized with C3, which mediates attachment to the CR1 and CR3 complement receptors of macrophages.
  - Following phagocytosis, the promastigotes lose their flagella and multiply as the rounded amastigote form within the phagolysosome.
  - In stained smears, the parasites take on a distinctive appearance and have been termed **Leishman–Donovan bodies.**
  - Intracellular survival is mediated by a surface lipophosphoglycan and an abundance of membrane-bound acid phosphatase, which inhibit the macrophage's oxidative burst and/or inactivate lysosomal enzymes.
  - In visceral leishmaniasis, the organs of the reticuloendothelial system (liver, spleen, and bone marrow) are the most severely affected.

- Reduced bone marrow activity, coupled with cellular destruction in the spleen, results in anemia, leukopenia, and thrombocytopenia. This leads to secondary infections and a tendency to bleed.
- The striking enlargement of the spleen is due to a combination of proliferating macrophages and sequestered blood cells.
- The marked increase in IgG is neither specific nor protective.

- **So in summary :**

  - Macrophages disseminate through the lymphatic & vascular system (dendritic cells stay in the skin) in :
  - Bone marrow => failure. Lymph node => generalized lymphadenopathy. Liver => hepatomegaly. Spleen => hypersplenomegaly.
  - Immunity is cell mediated (mainly Th-1 cells).

- *Risk factors :*
  - Malnutrition, Immunosuppressive diseases (e.g. HIV, leukemia, immunosuppressive drugs), Young age, Decrease production of Interferon gamma (low immunity), Polymorphism (mutation in the gene that leads to more than one allele) in the TNF (low immunity).

- *Clinical features :*
- In Sudan >30% asymptomatic.
- Symptoms usually occur **after months** due to :
  1. Division cycle of amastigote is slow (similar to M.TB).
  2. Time taken to reach the RES where proliferation occurs.

  - **Fever** (any type but mainly low grade fever). A double-quotidian pattern (two fever spikes in a single day) is a characteristic but uncommon finding.
  - **Weight loss (*due to high metabolic rate despite V.Good appetite*),** Nausea, vomiting, low grade watery diarrhea.
  - **Generalized lymphadenopathy, Hepatosplenomegaly, Hyper pigmentation in Light-skinned pts.** (Black fever in India, Kala-azar means Black sickness). This greyish pigmentation usually occurs on face & hands.
  - **Anemia** due to: Bone marrow suppression & infiltration (due to amastigotes proliferation). Chronic diseases (due to IL-1, IL-6, TNF) & Hypersplenism (destruct RBCs, platelets)
  - **Leukopenia**: complicated by secondary bacterial infection (agranulocytosis with secondary bacterial infections contributes to lethality).
  - **Thrombocytopenia**: epistaxis & bleeding presentation (especially GI bleeding).
  - Elevated liver enzymes & presentation of **Jaundice**.
  - **Hypergammaglobulinemia:** B-cell respond to different amastigotes in different macrophages by proliferation & polyclonal Abs. production that are not useful

because of leishmania is an intracellular organism that requires the CMI. The importance of this is that the B-cells get exhausted & when the body is infected by an extracellular organism it can't defend itself against it by Ab. Production.

- **Post Kalazar Dermal Leishmanoid (PKDL) :**
  - Complication of Visceral Leishmaniasis.
  - Occurs Between 6 months – 2 years after recovery.
- **Pathophysiology :**

- Recrudescence (reactivation of un-detectable parasites in the dendritic cells that have not been destructed by the treatment, it works more on macrophages of the RES).
- Macular, maculopapular & nodular skin lesions that start periorally & then extend to the whole body.
- The main loci are in Sudan where PKDL follows healed in 50%.

- The disease is a spectrum :

1. Good immunity: low parasite number => Cutaneous Leishmaniasis.
2. Low immunity: high parasite number => Visceral.L / chronic cut.L (worst).
3. Better immunity than that of VL: PKDL.
4. V.good immunity: v.low parasite number => Asymptomatic.

- **D.D of Kala-azar :**
  1. Resistant Malaria.
  2. Typhoid fever.
  3. Brucellosis.

- *Lab diagnosis :*
- **Specimen:**
  - Aspirate & biopsy of LN/ BM (huge spleen/liver & low platelets causes severe bleeding that can lead to death so not taken from there).
- **Microscopy :**
  - Visualization of amastigotes in macrophages (Leishman Donovan bodies) – "gold standard."
- **Culture :**
  - On NNN media => promastigote

- **Serology :**

1. **Ag. Detection :**
   - Latex agglutination test. Two urinary Ags **(CHO Ag).** The urine must be boiled to avoid false positive (to destroy the Abs).
   - Disadvantages: the pt. must be symptomatic. Advantages: easy, specific & sensitive.

2. **Ab. Detection :**

   - **Anti – rk39 by ICT** (Immune-chromatographic test) Takes 10 mins. Useful in the field.
   - **DAT (Direct Agglutination Test). IFAT** (immune fluorescent Ab test). **ELISA**.
   - Abs to Leishmania represent previous infection/ chronic disease.
   - *Positive Ab. Test + clinical symptoms= disease. Positive Ab. Test + no symptoms = previous infection.*

- **Others :**
  - DNA detection methods (PCR).
  - CBC (Pancytopenia).
  - **Formal gel test:** Polyclonal hypergammaglobulinemia. Disadvantages: non-specific (+ve also in Brucella).
  - A skin test using a crude homogenate of promastigotes (leishmanin) as the antigen is available. The skin test is negative during active disease but positive in patients who have recovered.

- *Treatment :*
- **First line therapy :**
  - Sodium stibogluconate, pentavalent antimonies (Pentostam).
  - Amphotericin B.
  - Miltefosine (anticancer also).
  - Paromomycin
  - Toll-like receptor agonist (Imiquimod): improve T-cell immunity.
- **Combination therapy :**
  - AmBisome + Miltefosine.
  - AmBisome + Paromomycin.
  - Miltefosine + Paromomycin.
  - Note that AmBisome is a liposomal Amphotericin B.

- *Vaccine :*
  - Killed vaccine not recommended.
  - Immune chemotherapeutic vaccines (drug + vaccine):
    - In Sudan, Autocleaved L.major + BCG + Pentostam.
  - **Used for Treatment of PKDL & for prevention of Visceral Leishmaniasis.**

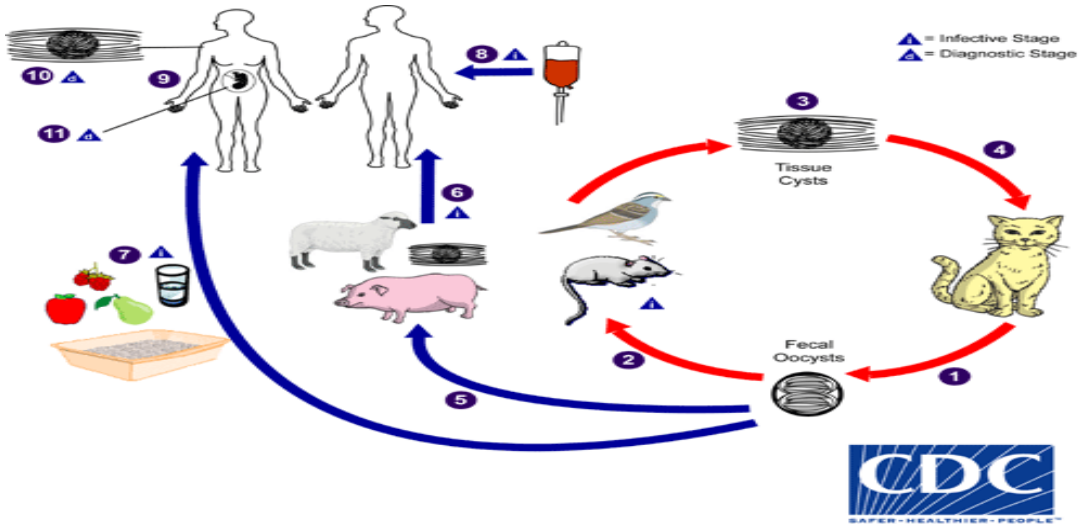
Toxoplasmosis

- Toxoplasma Gondii was first discovered in 1908 in desert rodent, the gondii.
- Most common chronic infection.
- The parasite is Obligate intracellular (like Leishmania).
- 3-4 % of AIDS patients develop CNS toxoplasmosis.
- Congenital toxoplasmosis is a serious disease.

- *Epidemiology :*
  - **Definitive host** is cats. Sexual cycle → oocyst.
  - **Intermediate hosts** are humans, mice, pigs and sheep. Asexual cycle → tissue cyst.

- *Transmission :*
  1. **Oral** :
     - Ingestion of undercooked pork or lamb meat (ingestion of tissue cyst)
     - Exposure to oocyst: Ingestion of contaminated vegetables or direct contact with cat feces.
  2. **Transplacental (**the infective stage is Tachyzoite).
  3. **Blood product transfusion** (Tachyzoite).
  4. **Organ Transplantation** (Tachyzoite & Bradyzoite)

- *Life cycle :*
  - The protozoa reproduce asexually in the intermediate host: Ingested oocyst goes to the digestive system, Engulfed by macrophages, Tachyzoites develop and travel to various parts of the body via blood stream (heart, spleen, liver, brain). Tachyzoites encyst to Bradyzoites that multiply slowly (mainly in brain & eye).
  - **All 3 states are infective.**



- The cycle within the cat begins with the ingestion of cysts in raw meat, e.g., mice. Bradyzoites are released from the cysts in the small intestine, infect the mucosal cells, and differentiate into male and female gametocytes, whose gametes fuse to form oocysts that are excreted in cat feces.
- The cycle is completed when soil contaminated with cat feces is accidentally ingested.
- Human infection usually occurs from eating undercooked meat, e.g., lamb and pork, from animals that grazed in soil contaminated with infected cat feces.

- *Pathogenesis :*
  - Infective stage → tachyzoites (invasive form, crescent shaped) → disseminate throughout the body → Infection (any nucleated cell → multiplication →cell destruction →necrotic foci →inflammation) → tissue cyst → lifelong chronic infection (Tachyzoites proliferate, producing necrotic foci surrounded by a cellular reaction (inflammation)).
  - **In immunodeficient, the acute infection progresses, resulting in dissemination: pneumonitis, myocarditis, and necrotizing encephalitis.**
  - Tissue cysts produce recrudescent disease in immunocompromised or congenitally infected.
  -
- *Clinical presentation of acquired infection in :*
- **Immunocompetent :**
  - Most initial infections are asymptomatic. When contained, the organisms persist as cysts within tissues. There is no inflammation and the individual remains well unless immunosuppression allows activation of organisms in the cysts.
  - Mononucleosis like syndrome (10-20%) : Cervical lymphadenopathy , Sore throat , Fever , Malaise , Night sweating , Myalgia's , Abdominal pain (mesenteric lymphadenopathy) .
  - Rare: pneumonia, myocarditis, polymyositis.
  - Note: D.D of Mononucleosis like syndrome: Toxoplasmosis, HIV, CMV & HHV-6.
- **Immunocompromised (non AIDS patients) :**
  - **Pneumonitis, Myocarditis, Encephalitis**, Meningoencephalitis, Mass lesion, Chorioretinitis.

- **In AIDS patients :**

1. **Cerebral :**
   - Manifested primarily as **toxoplasmic encephalitis**, include: Altered mental status, focal neurologic deficit, headache, fever and seizures. CT scan shows ring enhancing lesion.
2. **Extracerebral :**
   - **Ocular**: Chorioretinitis; confluent, thick, opaque. Anterior uveitis.
   - **Pulmonary**: Sepsis like syndrome.
   - **Cardiac**: Cardiac tamponade. Biventricular failure.

- **<u>Congenital Toxoplasmosis :</u>**
  - Congenital infection of the fetus occurs only when the mother is infected during pregnancy (Transmitted mainly with acute infection in 3rd trimester).
  - If she is infected before the pregnancy, the organism will be in the cyst form and there will be no tachyzoites to pass through the placenta.
  - The mother who is reinfected during pregnancy but who has immunity from a previous infection will not transmit the organism to her child.
  - Roughly one-third of mothers infected during pregnancy give birth to infected infants, but only 10% of these infants are symptomatic.
- Outcome :
  1. Abortion.
  2. Still birth.
  3. Congenital disease :

  - Classical triad of **chorioretinitis, intracerebral (cortical) calcifications, and hydrocephalus**.
  - Microcephaly, Mental retardation.
  - Hepatosplenomegaly, Jaundice.
  - Rash (macular or blueberry muffin lesion)
  - Fever.
- **Note :**

  - Probably the most common delayed manifestation of congenital toxoplasmosis is chorioretinitis.
  - This condition, which is thought to result from the reactivation of latent tissue cysts, typically presents during the second or third decade of life as recurrent bouts of eye pain and loss of visual acuity. The lesions are usually bilateral but focal.
  - Fetal involvement occurs in 17% of first-trimester, 30% of second trimester and 65% of third-trimester infections. Conversely, the earlier a fetal infection is acquired, the more severe it is likely to be.
  - Infection during the **first trimester** generally results in **stillbirth or major CNS anomalies**. **Second and third trimester** infections induce ***less severe*** neurologic damage, though they are far more common.
  - Clinical manifestations of these infections may be delayed until long after birth, even beyond childhood. Neurologic problems or learning difficulties may be caused by the long-delayed effects of late prenatal toxoplasmosis.

- *<u>Lab diagnosis :</u>*

1. Isolation from :

  - Blood, amniotic fluid (diagnostic of congenital infection), CSF. Then inoculate in human cell lines or mouse.
  - Isolation is rarely done.

2. **Serology :**

   - Unreliable in Immunodeficient pts.
   - IgM usually indicate acute infection (best for congenital infection).
   - Rising IgG antibodies (best for adult infection): Peaks within 2 weeks after infection & Remains detectable for life.
   - **Sabin – Feldman dye test (gold standard). [**The principle of the test is that when viable parasites are incubated with serum from an infected pt. , If the pt. serum contains antibodies , they cause coating of the parasite , thus preventing staining by alkaline methylene blue . The test is considered +ve if more than 50% of the parasites are stained**]**
   - **IFA. ELISA**
   - IgG avidity test (best for pregnancy infection): Low results indicate acute infection. High results indicate past infection.

3. **PCR** for detection of the organism in blood or any other body fluids.

- **<u>Notes about serology in acute infection :</u>**

  - Normally IgM & IgG rise simultaneously.
  - Elevated IgM is diagnostic for recent infection.
  - Negative IgG or IgM titer excludes the diagnosis (both should be positive if acutely infected).
  - If IgG screening is positive then do the IgM test, positive IgM test confirms acute Toxoplasmosis?
  - Low IgG avidity test in pregnant women indicates acute infection.

- **<u>Note :</u>**
  - Bilateral chorioretinitis + cortical (intracerebral) calcification + hydrocephalus = **Toxoplasmosis** => detected mainly by **serology**.
  - Bilateral chorioretinitis + periventricular calcification + hydrocephalus = **CID** => detected mainly by **PP65 antigenemia assay**.
  - Microcephaly + Microphthalmia + Heart problems = **CRS** => detected mainly by **serology & interference with CPE of Echovirus**.
  - Microcephaly + Microphthalmia + Hypoplastic limbs = **Congenital Varicella**.

- *Treatment :*
    - No treatment in asymptomatic pts. Because it is self-limiting except in children to prevent the ocular abnormalities (retinal inflammation).

    - First line: **Pyrimethamine + Sulfadiazine + Folic acid** (the therapy cause folic acid deficiency).

    - Second line: **Pyrimethamine + Folic acid + Clindamycin or Clarithromycin**.

    - In pregnant patients: ***Spiramycin (septrin + folic acid) => better***. Or **Pyrimethamine + sulfadiazine + folic acid.**

- Note :

    - Although the pyrimethamine–sulfonamide combination is very effective against tachyzoites, it is inactive against the cyst forms.
    - Atovaquone, a recently introduced hydroxy-naphthoquinone, possesses activity against both tachyzoites and cysts.
    - Its use, therefore, may result in radical cure of toxoplasma encephalitis, eliminating the need for chronic suppression.

- *Prophylaxis :*
    - **Indications :**

1. T. Gondii seropositive AIDS patients with CD4+ T cell count of < 100 regardless of clinical status.
2. T. Gondii seropositive AIDS patients with CD4+ T cell count of < 200 if an opportunistic infection or malignancy develops.

- In these patients give ***Trimethoprim /Sulfamethoxazole [Co-trimoxazole / septrin]*** or **Dapsone + Pyrimethamine + Folic acid**.

PART TWO

HELMINTHOLOGY

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Cestodes

- **Platyhelminthes** (platy means flat; helminth means worm) are divided into two classes: **Cestoda** (tapeworms) and **Trematoda** (flukes).
- Tapeworms consist of two main parts: a rounded head called a **scolex** and a flat body of multiple segments called **proglottids**.
- The scolex has specialized means of attaching to the intestinal wall, namely, suckers, hooks, or sucking grooves.
- The worm grows by adding new proglottids from its germinal center next to the scolex (the neck).
- Each proglottid possesses a complete male & female reproductive system, hence cestodes are **hermaphrodite.**
- In each segment there is a number of testes, a bilobed ovary & a convoluted uterus with a central stem & lateral branches. The *number of these lateral branches is of a diagnostic importance.*
- The oldest proglottids at the distal end are gravid and produce many eggs, which are excreted in the feces and transmitted to various intermediate hosts such as cattle, pigs, and fish.
- Humans usually acquire the infection **when undercooked flesh containing the larvae is ingested**. However, in two important human diseases, ***cysticercosis and hydatid disease, it is the eggs that are ingested and the resulting larvae cause the disease.***
- The eggs contain the embryo, which is called oncosphere, it possesses six hooks so it is hexa canth embryo.
- There is no mouth or digestive system. Nutrients are directly absorbed through. The surface of the worm (no need for GIT => physiological adaptation).
- Pathogenicity is either by passive obstruction or migration to unusual sites or by competition with the host for nutrients.
- There are five medically important cestodes:
    - ***Taenia solium & Taenia saginata, Diphyllobothrium latum, Echinococcus granulosus & Hymenolepis nana.***

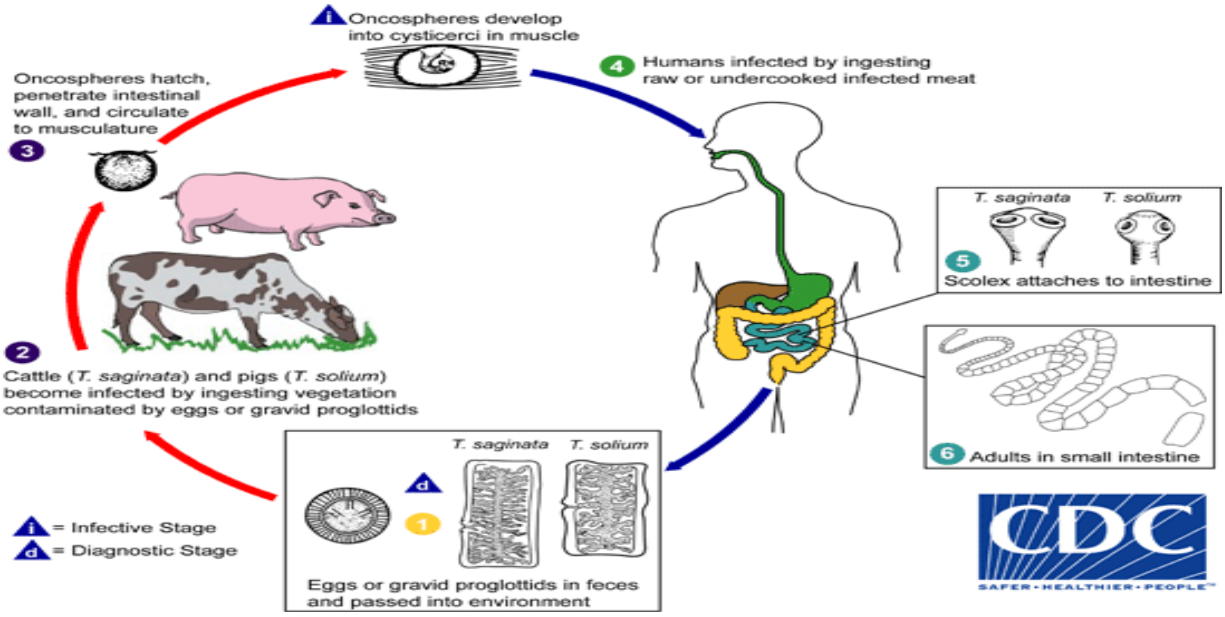
- Two cestodes of lesser importance are: Echinococcus multilocularis and Dipylidium caninum.
- **Praziquantel** is effective against all flat worms.
- **Niclosamide** is also effective.

Taenia

- *Taenia solium (The pork tapeworm) :*
  - The adult form of T. solium causes **taeniasis**. T. solium larvae cause **cysticercosis**.

- Important Properties :
  - T. solium can be identified by its scolex, which has four suckers and circle of hooks, and by its gravid proglottids, which have 5 to 10 primary uterine branches. The eggs appear the same microscopically as those of T. saginata and Echinococcus species.

- Life cycle :
  - In taeniasis, the adult tapeworm is located in the human intestine. This occurs when humans are infected by **eating raw or undercooked pork containing the larvae**, called **cysticerci**. (A cysticercus consists of a pea-sized fluid-filled bladder with an invaginated scolex).
  - In the small intestine, the larvae attach to the gut wall and take about 3 months to grow into adult worms measuring up to 5 m. The number of proglottids is 800-1000.



  - The gravid terminal proglottids containing many eggs detach daily, are passed in the feces, and are accidentally eaten by pigs. Note that pigs are infected by the worm eggs; therefore, it is the larvae (cysticerci) that are found in the pig.
  - A six-hooked embryo (oncosphere) emerges from each egg in the pig's intestine. The embryos burrow into a blood vessel and are carried to skeletal muscle. They develop into cysticerci in the muscle, where they remain until eaten by a human.

- **Humans are the definitive hosts, and pigs are the intermediate hosts**.
- In cysticercosis, a more dangerous sequence occurs when a person ingests the worm eggs in food or water that has been contaminated with human feces.
- Note that in cysticercosis, humans are infected by eggs excreted in human feces, not by ingesting undercooked pork. Also pigs do not have the adult worm in their intestine, so they are not the source of the eggs that cause human cysticercosis.
- The eggs hatch in the small intestine, and the oncospheres burrow through the wall into a blood vessel. They can disseminate too many organs, especially the eyes and brain, where they encyst to form cysticerci. Each cysticercus contains a larva.

- Pathogenesis & Epidemiology :
  - The adult tapeworm attached to the intestinal wall causes little damage.
  - The cysticerci, on the other hand, can become very large, especially in the brain, where they manifest as a **space-occupying lesion.**
  - Living cysticerci do not cause inflammation, but when they die they can release substances that provoke an inflammatory response. Eventually, the cysticerci calcify.
  - The epidemiology of taeniasis and cysticercosis is related to the access of pigs to human feces and to consumption of raw or undercooked pork. The disease occurs worldwide but is endemic in areas of Asia, South America, and Eastern Europe.

- Clinical Findings :
  - Most patients with adult tapeworms are asymptomatic, but **anorexia** and **diarrhea** can occur. Some may notice proglottids in the stools.
  - *Cysticercosis* in the brain causes **headache, vomiting, and seizures**. Cysticercosis in the eyes can appear as **uveitis** or **retinitis**, or the larvae can be visualized floating in the vitreous.
  - **Subcutaneous nodules** containing cysticerci commonly occur (they appear as spindle shaped calcified material in the X-ray). Diagnosed by Histopathology.

- Laboratory Diagnosis :
  - **Identification** of *T. solium* consists of finding gravid proglottids with 5 to 10 primary uterine branches in the stools. In contrast, *T. saginata* proglottids have 15 to 20 primary uterine branches. Eggs are found in the stools less often than are proglottids.
  - Diagnosis of **cysticercosis** depends on demonstrating the **presence of the cyst in tissue**, usually by surgical removal or CT scan or MRI. Histopathology for subcutaneous nodules. Radiology for presence of calcified material.
  - Serologic tests, e.g., ELISA, that detect antibodies to T. solium antigens are available, but they may be negative in neurocysticercosis.

- Treatment :
  - The treatment of choice for the intestinal worms is **Praziquantel**.
  - The treatment for cysticercosis is either **Praziquantel** or **albendazole**, but ***surgical excision may be necessary.***

- Prevention :
  - Prevention of taeniasis involves cooking pork adequately and disposing waste properly so that pigs cannot ingest human feces.
  - Prevention of cysticercosis consists of treatment of patients to prevent autoinfection plus observation of proper hygiene, including handwashing, to prevent contamination of food with the eggs.

- ***Taenia saginata (The beef tapeworm) :***

  - T. saginata causes **taeniasis.**
  - T. saginata larvae do not cause cysticercosis.

- Important Properties
  - T. saginata has a scolex with four suckers but, in contrast to T. solium, no hooklets. Its gravid proglottids have 15 to 25 primary uterine branches, in contrast to T. solium proglottids, which have 5 to 10.
  - The eggs are morphologically indistinguishable from those of T. solium (rounded with a thick shell which is radically striated & contains the hexacant embryo) except that T. solium eggs have 4-6 hooklets.

- Life cycle :
  - Humans are infected by eating raw or undercooked beef containing larvae (cysticerci).
  - In the small intestine, the larvae attach to the gut wall and take about 3 months to grow into adult worms measuring up to 10 m. The number of proglottids may reach 1000-2000.
  - The gravid proglottids detach, are passed in the feces, and are eaten by cattle.
  - The embryos (oncospheres) emerge from the eggs in the cow's intestine and burrow into a blood vessel, where they are carried to skeletal muscle. In the muscle, they develop into cysticerci (cysticercus bovis).
  - This is a fluid-filled bladder which contains an inverted or invaginated scolex, and it is visible to the naked eye. It gives the meat a measly appearance (meat with white spots).
  - The cycle is completed when the cysticerci are ingested. Humans are the definitive hosts and cattle the intermediate hosts.
  - Unlike T. solium, T. saginata does not cause cysticercosis in humans.

- Pathogenesis & Epidemiology :
  - Little damage results from the presence of the adult worm in the small intestine.
  - The epidemiology of taeniasis caused by T.Saginata is related to the access of cattle to human feces and to the consumption of raw or undercooked beef.
  - The disease occurs worldwide but is endemic in Africa, South America, and Eastern Europe.

- Clinical Findings :
  - In spite of its large size, the worm is well tolerated by the host and it is usually a single adult worm (multiple worms are rare).
  - Most patients with adult tapeworms are asymptomatic.
  - Symptomatic infection includes :
    1. Abdominal pain described as hunger pain (the pt. feels with pain when he is hungry).
    2. Malaise.
    3. Rarely can it cause intestinal obstruction.
    4. When the Gravid proglottids pass through. The anus they may cause itching & great embracement.

- Laboratory Diagnosis :
  - Identification of T. saginata consists of finding gravid proglottids with 15 to 20 uterine branches in the stools.
  - The uterus can also be stained by ingestion of dies like India ink thro. The genital pore & can be easily visualized.
  - Eggs are found in the stools less often than are the proglottids.

- Treatment :
  - The treatment of choice is **Praziquantel**.
  - Niclosamide is also useful.
  - **Purgatives** may be given to facilitate expulsion of the worms & identification *(Niclosamide kills the worm & the worm is expelled digested, so by Niclosamide we can't identify it, because if the head & neck of the worm are not expelled the worm will develop again in 3 months).*

- Prevention :
  - Prevention involves cooking beef adequately and disposing waste properly so that cattle cannot consume human feces.
  -

Diphyllobothrium latum

- Diphyllobothrium latum, the fish tapeworm, causes **diphyllobothriasis**.

- Important Properties :
  - In contrast to the other cestodes, which have suckers, the scolex of D. latum has two elongated sucking grooves by which the worm attaches to the intestinal wall (bothria). The scolex has no hooks, unlike T. solium and Echinococcus.
  - The proglottids are wider than they are long, and the gravid uterus is in the form of a rosette. Unlike other tapeworm eggs, which are round, D. latum eggs are oval and have a lidlike opening (operculum) at one end.
  - D. latum is the longest of the tapeworms, measuring up to 13 m.

- Life cycle :
  - Humans are infected by ingesting raw or undercooked fish containing larvae (called plerocercoid or sparganum larvae).
  - In the small intestine, the larvae attach to the gut wall and develop into adult worms.
  - Gravid proglottids release fertilized eggs through a genital pore, and the eggs are then passed in the stools. The immature eggs must be deposited in fresh water for the life cycle to continue.
  - The embryos emerge from the eggs (ciliated embryo => Coracidium) and are eaten by **tiny copepod crustacea (first intermediate hosts).** There, the embryos differentiate and form procercoid larvae in the body cavity.
  - When the copepod is eaten by freshwater fish, e.g., pike, trout, and perch, the larvae differentiate into **plerocercoids in the muscle of the fish (second intermediate host).**
  - The cycle is completed when **raw or undercooked fish is eaten by humans (definitive hosts**).

- Pathogenesis & Epidemiology :
  - Infection by D. latum causes little damage in the small intestine.
  - In some individuals, ***megaloblastic anemia occurs as a result of vitamin B12 deficiency caused by preferential uptake of the vitamin by the worm.***
  - The epidemiology of D. latum infection is related to the **ingestion of raw or inadequately cooked fish and to contamination of bodies of fresh water with human feces.**
  - The disease is found worldwide but is endemic in areas where eating raw fish is the custom, such as Scandinavia, northern Russia, Japan, Canada, and certain north-central states of the United States.

- Clinical Findings :
  - Most patients are asymptomatic, but abdominal discomfort and diarrhea can occur.

- Laboratory Diagnosis :
  - Diagnosis depends on finding the typical eggs, i.e., oval, yellow-brown eggs with an operculum at one end, in the stools.
  - There is no serologic test.

- Treatment :
  - The treatment of choice is **Praziquantel (or) Niclosamide + vitamin B12 supplement.**

- Prevention :
  - Prevention involves adequate cooking of fish and proper disposal of human feces.

Hymenolepis nana

- H. nana (dwarf tapeworm) is very common, it is one of the most frequently found tapeworms in Sudan.
- It is only 3 to 5 cm long, the scolex possesses 4 suckers & one row of hooks. It is different from other tapeworms because its eggs are directly infectious for humans, i.e., ingested eggs can develop into adult worms without an intermediate host.
- Within the duodenum, the eggs hatch and differentiate into cysticercoid larvae (in intestinal villi) and then into adult worms.
- Gravid proglottids detach, disintegrate, and release fertilized eggs. The eggs either pass in the stool or can reinfect the small intestine (autoinfection).
- In contrast to infection by other tapeworms, where only one adult worm is present, many H. nana worms (sometimes hundreds) are found.
- Infection causes little damage, and most patients are asymptomatic. Heavy infection may cause diarrhoea, abdominal pain, headache, dizziness & nonspecific symptoms. Eosinophilia is common.
- The organism is found worldwide, commonly in the tropics. In the United States, it is most prevalent in the southeastern states, usually in children.
- Diagnosis is based on finding eggs in stools. The characteristic feature of H. nana eggs is the 8 to 10 polar filaments lying between the membrane of the six-hooked larva and the outer shell.
- The treatment is praziquantel or Niclosamide.
- Prevention consists of good personal hygiene and avoidance of fecal contamination of food and water.

  - **Note: intestinal autoinfection is seen in: H.nana, Strongyloides, and Cryptosporidium & Enterobius.**

Echinococcus granulosus

- Echinococcus granulosus (dog tapeworm) causes **echinococcosis**.
- The **larva** of E. granulosus causes unilocular **hydatid cyst disease.**
- Multilocular hydatid disease is caused by E. multilocularis, which is a minor pathogen.

- Important Properties :
  - E. granulosus is composed of a **scolex and only three proglottids** (the first is immature, the second is mature & the third is the gravid segment), making it one of the smallest tapeworms (3-6 mm in length).
  - The scolex has a circle of hooks and four suckers similar to T. solium.
  - **Dogs** are the most important **definitive hosts**. The intermediate hosts are usually sheep. **Humans are almost always dead-end intermediate hosts.** So it is a zoonotic disease.

- Life cycle :
  - In the typical life cycle, worms in the dog's intestine liberate thousands of eggs, which are ingested by sheep (or humans).
  - The oncosphere embryos emerge in the small intestine and migrate primarily to the liver but also to the lungs, bones, and brain.
  - The embryos develop into large fluid-filled hydatid cysts. If we examined the cyst we will identify **3 layers: 1. an outer fibrous layer formed by the host, 2. Laminated layer formed by the parasite (non-nucleated layer) and 3. Inner nucleated germinal layer** which generates many protoscoleces within "**broad capsules**."
  - The life cycle is completed when the entrails (e.g., liver containing hydatid cysts) of slaughtered sheep are eaten by dogs.

- Pathogenesis & Epidemiology :
  - E. granulosus usually forms one large fluid-filled cyst (unilocular) that contains thousands of individual scoleces as well as many daughter cysts within the large cyst. Free broad capsules & free protoscoleces lying at the bottom of the large cyst are called "**hydatid sand**" => diagnostically important.
  - The cyst acts as a space-occupying lesion, putting pressure on adjacent tissue. The outer layer of the cyst is thick, fibrous tissue produced by the host. The cyst fluid contains parasite antigens, which can sensitize the host. Later, if the cyst ruptures spontaneously or during trauma or surgical removal, life-threatening anaphylaxis can occur.
  - **Rupture of a cyst can also spread protoscoleces widely.**
  - The disease is found primarily in shepherds living in the Mediterranean region, the Middle East, and Australia. In the United States, the western states report the largest number of cases.

- Clinical Findings :
  - The cyst size may reach up to 20 cm^2 and the fate of the Hydatid cyst is unpredictable. Some grow until rupture, some of them stop growing & regress in size while other cysts are sterile from the beginning with no protoscoleces.
  - 70% of Hydatid cysts develop in the **liver**, 20% develops in the **lungs**, 10% develop in other sites e.g. **brain**.
  - The clinical presentation depends on: the mechanical effect of the cyst, allergic reaction to cyst components & complications due to rupture of the cyst.

1. **Mechanical effect of the cyst :**
   - Cyst may press on adjacent organs: **Liver** => painful enlargement (common presentation). Bile ducts or on major blood vessels. **Lungs** => Cysts in the lungs can erode into a bronchus causing cough, breathlessness, hemoptysis and it may cause lung collapse if it compresses a main bronchus. **Brain** => cerebral cysts can cause headache and focal neurologic signs (SOL).
2. **Allergic reaction to cyst components :**
   - Hydatid fluid may escape to the circulation and it can cause ***fatal anaphylactic shock***, if Hydatid fluid is in small amount it only cause's urticaria.
3. **Complications due to rupture of the cyst :**
   - *Anaphylaxis*, *dissemination* of the cyst to other organs (occurs by seeding of viable germinal epithelium) & *secondary bacterial infection*.

- **D.D of a Hydatid cyst in the liver :**
  1. Pyogenic liver abscess.
  2. Amebic liver abscess (ALA).
  3. Necrotic hepatoma.

- **D.D of unilateral proptosis :**
  1. Orbital Tumor (most common cause).
  2. Sinus Aspergillosis.
  3. Hydatid cyst.

- Laboratory Diagnosis :
  - Diagnosis is based on **microscopic** examination demonstrating the presence of **broad capsules containing multiple protoscoleces** or **Histopathology** (detection of the three layers). Aspiration for diagnostic purposes should not be done when the cyst is inside the body.
  - **Serologic tests**, e.g., the indirect hemagglutination test, ELISA, CIEP, and CFT (may give positive results in pts. with lung cancer).
  - **Cansoni skin test (Asten test):** inject 0.1 ml sterile Hydatid fluid intradermally, immediate reaction in 20 minutes means positive result. Unreliable test because it may remain positive long after the cyst has been removed.
  - **Antigen detection is the best way to diagnose Hydatid cyst, an important antigen is (arc 5), and it is detected by ELISA.**

- Treatment :
  - Treatment involves **Albendazole** with or without surgical removal of the cyst. It causes cyst regression & prevents recurrence.
  - Extreme care must be exercised to prevent release of the protoscoleces during surgery.
  - A **protoscolicidal agent**, e.g., hypertonic saline, should be injected into the cyst to kill the organisms and prevent accidental dissemination. other agents include : Cetrimide , H_2O_2 , Ethanol , Silver nitrate , Formaline (may cause biliary damage => not recommended) .

- Prevention :
  - Prevention of human disease involves not feeding the entrails of slaughtered sheep to dogs.

Cestodes of minor importance

- ***Echinococcus multilocularis :***

  - Many of the features of this organism are the same as those of E. granulosus, but the definitive hosts are mainly foxes and the intermediate hosts are various rodents.
  - Humans are infected by accidental ingestion of food contaminated with fox feces.
  - The disease occurs primarily in hunters and trappers and is endemic in northern Europe, Siberia, and the western provinces of Canada. In the United States, it occurs in North and South Dakota, Minnesota, and Alaska.
  - Within the human liver, the larvae form multiloculated cysts with few protoscoleces.
  - No outer fibrous capsule forms, so the cysts continue to proliferate, producing a honeycomb effect of hundreds of small vesicles.
  - The clinical picture usually involves jaundice and weight loss.
  - The prognosis is poor. Albendazole treatment may be successful in some cases. Surgical removal may be feasible.

- ***Dipylidium caninum :***
  - D. caninum is the most common tapeworm of dogs and cats.
  - It occasionally infects humans, usually young children, while playing with their pets.
  - Human infection occurs when dog or cat fleas carrying cysticerci are ingested. The cysticerci develop into adult tapeworms in the small intestine.
  - Most human infections are asymptomatic, but diarrhea and pruritus ani can occur.
  - The diagnosis in animals and humans is made by observing the typical "barrel-shaped" proglottids in the stool or diapers.
  - Niclosamide is the drug of choice.
- **D.D of perianal pruritis:** *T. saginata, Diphylidium caninum, Enterobius vermicularis, Dientamoeba Fragilis, Taenia cruris (dermatophyte infection). (2 Di, 2 T & E).*

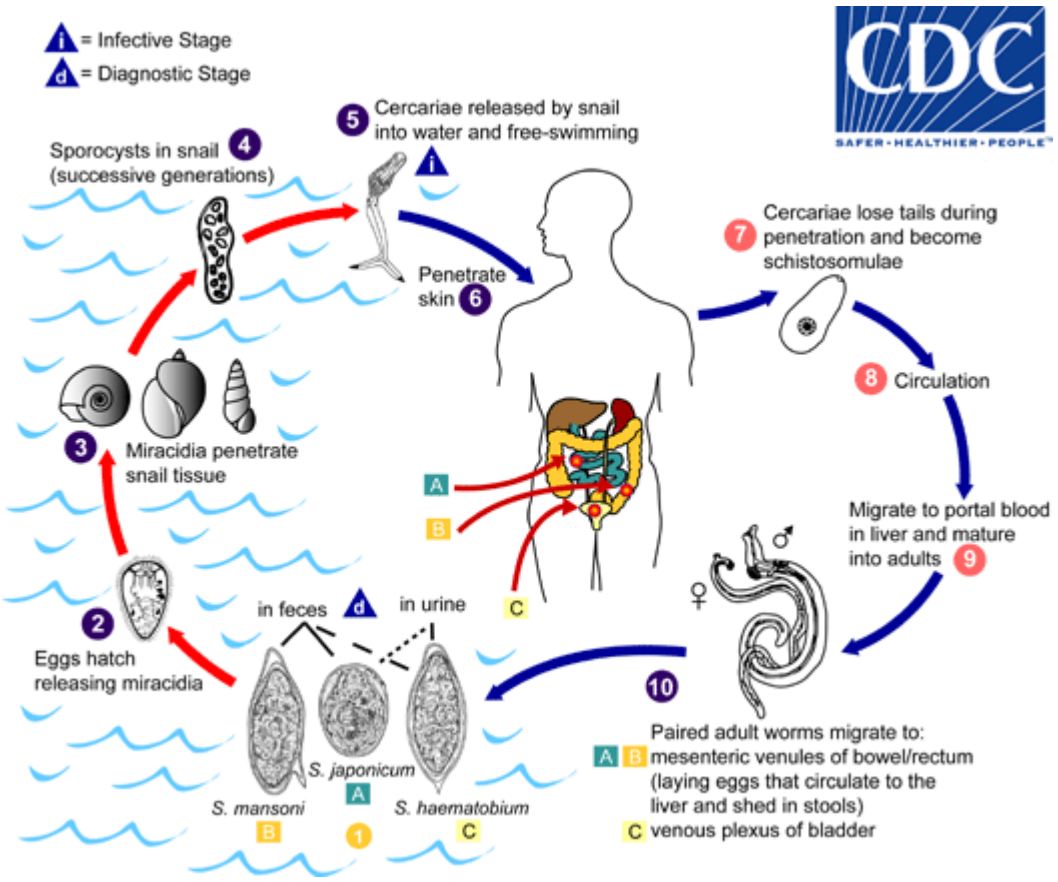
Trematodes (flukes)

- Trematoda (flukes) and Cestoda (tapeworms) are the two large classes of parasites in the phylum Platyhelminthes.
- Characteristics of Trematodes :
  1. They are flat dorso-ventrally and so are called flat helminths.
  2. They are bilaterally symmetrical.
  3. They have a digestive system, composed of a mouth, esophagus & two blind ended cecum.
  4. They are true hermaphrodites except for Schistosoma species.
  5. They have suckers which are muscular organs used for attachment.
  6. They produce eggs & they are mostly parasitic.
- The most important trematodes are **Schistosoma species** (blood flukes), **liver flukes**, **intestinal flukes** and **Paragonimus westermani** (lung fluke).
- Schistosoma's have by far the greatest impact in terms of the number of people infected, morbidity, and mortality.
- The life cycle of the medically important trematodes involves a sexual cycle in humans (**definitive host**) and asexual reproduction in freshwater snails (**intermediate hosts**).
- Transmission to humans takes place either via *penetration of the skin* by the free-swimming cercariae of the schistosomes or via *ingestion of cysts* in undercooked (raw) fish or crabs in Clonorchis and Paragonimus infection, respectively.

- They are divided into :
  1. **Blood flukes**: Schistosoma.
  2. **Intestinal flukes:** Fasciolopsis buski, Heterophyes heterophyes & Metagonimus species.
  3. **Liver flukes:** Fasciola hepatica, Fasciola gigantica & Clonorchis sinensis.
  4. **Lung flukes:** Paragonimus species.

Blood flukes
Schistosomiasis (Bilharziasis)

- Schistosoma causes **schistosomiasis**. *Schistosoma mansoni* and *Schistosoma japonicum* as does Schistosoma mekongi affect the **gastrointestinal tract**, whereas *Schistosoma hematobium* affects the **urinary tract**.
- In Sudan, the prevalence of schistosomiasis is more than 40% => El Jazeera, 25% in the White Nile.
- From egg to adult worm.



- **<u>Pathogenesis & Epidemiology :</u>**
  - Most of the pathologic findings are caused by the **presence of eggs** in the liver, spleen, or wall of the gut or bladder.
  - Eggs in the liver induce **granulomas (Bilharziomas**), which lead to fibrosis, hepatomegaly, and **<u>portal hypertension</u>**.

- The granulomas are formed in response to antigens secreted by the eggs. Hepatocytes are usually undamaged, and liver function tests remain normal. Portal hypertension leads to **splenomegaly.**
- *Sch. mansoni* eggs damage the wall of the distal colon (**inferior mesenteric venules**), whereas *Sch. japonicum* eggs damage the walls of both the small and large intestines (superior and inferior mesenteric venules).
- The damage is due both to digestion of tissue by proteolytic enzymes produced by the egg and to the host inflammatory response that forms granulomas in the venules. The eggs of S. haematobium in the wall of the bladder induce granulomas and fibrosis, which can lead **to carcinoma of the bladder**.
- Schistosomes have evolved a remarkable process for evading the host defenses.
- There is evidence that their surface becomes coated with host antigens, thereby limiting the ability of the immune system to recognize them as foreign.
- The epidemiology of schistosomiasis depends on the presence of the specific freshwater snails that serve as intermediate hosts.
- S. mansoni is found in Africa and Latin America (including Puerto Rico), whereas S. haematobium is found in Africa and the Middle East. S. japonicum is found only in Asia and is the only one for which domestic animals, e.g., water buffalo and pigs, act as important reservoirs.
- More than 150 million people in the tropical areas of Africa, Asia, and Latin America are affected.

- **Characteristics of Sh.mansoni :**

- It is found in Africa, Asia, central & South America.
- In Sudan, It is found mainly in irrigation projects because it needs a continuous supply of water.
- The worms is leaf-like & it can live up to 5 years, but in some cases 37 years old worms occur.
- Snails are of the genus **Biomphalaria pferifferri**.

- **Characteristics of Sh.jabonicum :**
  - Found in Japan , China & Philippine , it causes more severe infection than Sh.mansoni :

1. It causes more morbidity because it produces more eggs than Sh.mansoni (3000 / day compared to 300 / day).
2. Eggs are smaller & so they can reach body organs easier => more eggs are carried to the CNS.
3. Complications appear earlier.
4. The disease is zoonotic, it can affect all domestic animals around people, so sources of infection are multiple.
5. The snail of Sh.jabonicum is amphibian I.e. it can live in water & earth unlike the others.

- Snails are of the genus **Oncomelania**.

- **Characteristics of Sh.haematobium :**
  - Eggs are excreted in urine.
  - Usually affects young age group, not found in those above 15-20 years old & the worm do not live long.
  - Eggs are yellow & contain the miracidium.
  - Snails are of the genus Bulinus truncates.
  - **It is usually benign, but if it is taken by the inferior vena cava & affect the lung it may cause Cor-pulmonale.**
  - Sh.haematobium is associated with **Carcinoma of the bladder** & **formation of urinary calculi**.

- **Clinical Findings :**
  - Most patients are asymptomatic, but chronic infections may become symptomatic.
  - The acute stage (**Katayama fever**) , which begins *shortly after cercarial penetration*, consists of **itching** and **dermatitis** followed 2 to 3 weeks later by fever, chills, diarrhea, lymphadenopathy , and hepatosplenomegaly. **High Eosinophilia** is seen in response to the migrating larvae.
  - This stage usually resolves spontaneously.

  - The chronic stage can cause significant morbidity and mortality.
  - In patients with *Sch. mansoni* or *S. japonicum* infection, **gastrointestinal hemorrhage**, **hepatomegaly**, and **massive splenomegaly** can develop*. Colonic polyposis with bloody diarrhea is associated mostly with Sh. mansoni*. The most common cause of death is **exsanguination from ruptured esophageal varices**.

  - This is called **(liver Schistosomiasis)** which is manifested by:
    - Acute intestinal phase (dysentery) & Hepatosplenic phase (Hepatomegaly, Hypersplenism & pancytopenia).
  - Liver schistosomiasis is the second most common cause of esophageal varices.

  - **[Extra:]** Sch. japonicum can affect the CNS causing: cerebral granulomatous disease by ectopic eggs in the brain. And granulomatous lesions around ectopic eggs in the spinal cord (from both Sh. mansoni & Sh. japonicum) that may result in transverse myelitis with flaccid paralysis.

  - Patients infected with S. haematobium have **terminal hematuria** as their chief early complaint. **Superimposed bacterial urinary tract infections** occur frequently (burning micturition).
  - This is called **(urinary Schistosomiasis)** which may be complicated by fibrosis of the bladder & ureter leading to **obstructive Uropathy** and also **Carcinoma of the bladder**.
  - Pathologically the bladder is small with **sandy patches** that represents deposits of eggs in the mucous membrane.

- **Laboratory Diagnosis :**
  - Clinically by history of endemicity, age, occupation & history of contact with water.
  - In the lab Diagnosis depends on finding the **characteristic ova in the feces or urine**.

  - The **large lateral spine** of *Sch. mansoni* and the rudimentary spine of S. japonicum are typical, as is the **large terminal spine** of *Sch. haematobium*.

  - **Qualitative tests assess** => presence or absence of eggs (e.g. rectal snip). **Quantitative tests** => number of eggs (for assessment of morbidity & for follow up) by Kato technique, Bell's technique & Teesatle amin's method.
  - **Ultrasound** is used to assess the degree of fibrosis in the liver. Endoscopy can be used for detection of esophageal varices.
  - Serologic tests are not useful. Moderate eosinophilia occurs.

  - Note: In 1% of cases, eggs of Sh.haematobium can be found in the stool beside the urine & can be found by examining rectal snip. Also in 1% of Sh.mansoni cases eggs can be found in urine.

- **Treatment :**
  - **Praziquantel** is the treatment of choice for all three species.
  - Hepatic schistosomiasis can also be treated by **Hyacanthone** or **Oxamniquine**.
  - Urinary schistosomiasis can also be treated by **Metrifonate**.
  - Esophageal varices are treated by **Sclerotherapy** & **shunt operations**.
  - Judge the pt. response to treatment by examining stool & urine for eggs by performing the hatching test (add the eggs in fresh water to hatch).

- **Prevention :**
  - Prevention involves proper disposal of human waste and eradication of the snail host when possible. Swimming in areas of endemic infection should be avoided.

- **Other species of Schistosoma :**
- Sh.mekongi & Sh.intercalatum causes intestinal Bilharziasis.
- Sh.spurious causes "Swimmer's itch," which consists of pruritic papules, is a frequent problem in many lakes in the world. The papules are an immunologic reaction to the presence in the skin of the cercariae of nonhuman schistosomes.
- The pruritic papules appear within minutes to hours after exposure indicating that this is an immediate (IgE-mediated) hypersensitivity. Treated by Anti-histamines & Calamine lotions.
- These nonhuman schistosomes are incapable of replicating in humans and do not cause disseminated disease.

Intestinal flukes

- *Fasciolopsis buski :*

  - Fasciolopsis buski is an intestinal parasite of humans and pigs that is endemic to Asia and India. Pigs are the definitive host.
  - It is the largest fluke that infects man (known as Giant intestinal fluke).
  - Humans are infected by eating aquatic vegetation that carries the cysts.
  - After excysting in the small intestine, the parasites attach to the mucosa and differentiate into adults. Eggs are passed in the feces; on reaching fresh water, they differentiate into miracidia.
  - The ciliated miracidia penetrate snails and, after several stages (sporocyst => radiae) develop into cercariae that encyst on aquatic vegetation.
  - The cycle is completed when plants carrying the cysts are eaten. (Metacercaria of F.buski & F.hepatica are found in aquatic plants while metacercaria of other flukes are found in raw fish).
  - Pathologic findings are due to damage of the intestinal mucosa by the adult fluke.
  - Most infections are asymptomatic, but **ulceration, abscess formation, and hemorrhage** can occur with heavy infection.
  - Diagnosis is based on **finding typical eggs in the feces** (Large, oval & has small operculum (lid)). Adult worm is not usually seen in stool, it is seen only after the use of purgatives or anti-helminthic drugs.
  - **Praziquantel** is the treatment of choice.
  - Prevention consists of proper disposal of human sewage.

- *Heterophyes heterophyes :*

  - Mainly a fluke of animals. Found China & Japan, in Africa it is found only in Egypt.
  - Eggs are very small. Infection is acquired by eating raw fish containing metacercaria.
  - Treated by Praziquantel.

- *Metagonimus species :*

  - Found in Japan. Reservoir of infection are cats & dogs.
  - Eggs are very small. Infection is acquired by eating raw fish containing metacercaria.
  - Treated by Praziquantel.

Liver flukes

- ***Fasciola hepatica :***
- Fasciola hepatica, the sheep liver fluke, causes disease primarily in sheep and other domestic animals in Latin America, Africa, Europe, and China.
- Humans are infected by eating watercress (or other aquatic plants) contaminated by larvae (metacercariae) that excyst in the duodenum, penetrate the gut wall, and reach the liver, where they mature into adults (about 4 months after ingestion).
- Hermaphroditic adults in the bile ducts produce eggs, which are excreted in the feces.
- The eggs hatch in fresh water, and miracidia enter the snails. Miracidia develop into cercariae, which then encyst on aquatic vegetation.
- Sheep and humans eat the plants, thus completing the life cycle. The flukes can live for many years in the host.
- Symptoms are due primarily to the presence of the adult worm in the biliary tract.
- In early infection, fever, right-upper-quadrant pain and hepatomegaly can occur, but most infections are asymptomatic.
- Months or years later, obstructive jaundice can occur (Thickening of Bile ducts & liver enlargement). The Gallbladder can also be infected.
- Halzoun is a painful pharyngitis caused by the presence of adult flukes on the posterior pharyngeal wall.
- The adult flukes are acquired by eating raw sheep liver.
- Diagnosis is made by identification of eggs in the feces => resembles those of F.buski (it poses an anterior conical projection). Eggs are found in feces only in chronic infection. Eggs can also be found in duodenum aspirate & in bile. There is no serologic test.
- The drug of choice is triclabendazole. Adult flukes in the pharynx and larynx can be removed surgically.
- Prevention involves not eating wild aquatic vegetables or raw sheep liver.

- **Marara syndrome (Halzoun) :**
- After taking raw liver containing F.hepatica worms, the worms sometimes stick to the upper respiratory passage causing upper respiratory tract obstruction.

- ***Fasciola gigantica :***
- Cattle fluke (liver). Larger than F.hepatica. Can sometimes cause human infection.

- ***Clonorchis:***
- Clonorchis sinensis causes clonorchiasis (Asian liver fluke infection).

- Important Properties :
  - Humans are infected by eating raw or undercooked fish containing the encysted larvae (metacercariae).
  - After excystation in the duodenum, immature flukes enter the biliary ducts and differentiate into adults.
  - The hermaphroditic adults produce eggs, which are excreted in the feces. Upon reaching fresh water, the eggs are ingested by snails, which are the first intermediate hosts.
  - The eggs hatch within the gut and differentiate first into larvae (rediae) and then into many free-swimming cercariae.
  - Cercariae encyst under the scales of certain freshwater fish (second intermediate hosts), which are then eaten by humans.

- Pathogenesis & Epidemiology :
  - In some infections, the inflammatory response can cause hyperplasia and fibrosis of the biliary tract, but often there are no lesions.
  - Clonorchiasis is endemic in China, Japan, Korea, and Indochina, where it affects about 20 million people.

- Clinical Findings :
  - Most infections are asymptomatic.
  - In patients with a heavy worm burden, upper abdominal pain, anorexia, hepatomegaly, and eosinophilia can occur.
  - Complications include: **Cholangitis , Cholangiocarcinoma , stones in the biliary tree & obstructive jaundice**
- Laboratory Diagnosis :
  - Diagnosis is made by finding the typical small, brownish, operculated eggs in the stool. Serologic tests are not useful.
- Treatment :
  - Praziquantel is an effective drug.
- Prevention :
  - Prevention centers on adequate cooking of fish and proper disposal of human waste.

Lung fluke (Paragonimus)

- Paragonimus westermani, the lung fluke, causes paragonimiasis.

- Important Properties :
  - Humans are infected by eating raw or undercooked crab meat (or crayfish) containing the encysted larvae (metacercariae).
  - After excystation in the small intestine, immature flukes penetrate the intestinal wall and migrate through the diaphragm into the lung parenchyma. They differentiate into hermaphroditic adults and produce eggs that enter the bronchioles and are coughed up or swallowed.
  - Eggs in either sputum or feces that reach fresh water hatch into miracidia, which enter snails (first intermediate hosts). There, they differentiate first into larvae (rediae) and then into many free-swimming cercariae. The cercariae infect and encyst in freshwater crabs (second intermediate hosts).
  - The cycle is completed when undercooked infected crabs are eaten by humans.

- Pathogenesis & Epidemiology :
  - Within the lung, the worms exist in a fibrous capsule that communicates with a bronchiole. Secondary bacterial infection frequently occurs, resulting in bloody sputum.
  - Paragonimiasis is endemic in Asia and India.

- Clinical Findings :
  - The main symptom is a **chronic cough with bloody sputum**, also there is fever & night sweating (The disease can resemble Tuberculosis).
  - Dyspnea, pleuritic chest pain, and recurrent attacks of bacterial pneumonia occur.
  - Flukes are found in cavities surrounded by inflammatory reactions. After treatment or death, healing occurs with scar formation, so in chest X-ray a cavity is seen (similar to Tb).
- Laboratory Diagnosis :
  - Diagnosis is made by finding the typical operculated eggs in sputum or feces. Serologic tests are not useful.
- Treatment :
  - Praziquantel is the treatment of choice.
- Prevention :
  - Cooking crabs properly is the best method of prevention.

Nematodes

- Nematodes (also known as Nemathelminthes) are **round worms** with a cylindrical body and a complete digestive tract, including a mouth and an anus. The body is covered with a noncellular, highly resistant coating called a cuticle.
- Nematodes have **separate sexes**; the female is usually larger than the male. The male typically has a coiled tail.
- The medically important nematodes can be divided into **two categories** according to their primary location in the body, namely, intestinal and tissue nematodes.
- The **1. Intestinal nematodes** (soil-transmitted worms) include *Enterobius (pinworm), Trichuris (whipworm), Ascaris (giant roundworm), Necator and Ancylostoma (the two hookworms), Strongyloides (small roundworm), and Trichinella.*
- **Enterobius, Trichuris,** and **Ascaris** are transmitted by ingestion of eggs; the others are transmitted as larvae (penetration).
- There are **two larval forms**: the first- and second-stage (**rhabditiform**) larvae are noninfectious, feeding forms; the third-stage (**filariform**) larvae are the **infectious**, nonfeeding forms.
- As adults, these nematodes live within the human body, except for Strongyloides, which can also exist in the soil.
- The **larvae of Ascaris lumbricoides, Strongyloides stercoralis & Hook worms undergo migration thro. The right side of the heart & lung (Heart lung migration).**

    - Lab diagnosis is based on :

- **Detection of Eggs in stool**: for *Ascaris, T.Trichuria & hook worms.*
- **Detection of Eggs in perianal region**: for *E.Vermicularis*.
- **Detection of Larvae in stool:** for *Strongyloides stercoralis*.
- **Detection of Larvae in muscle:** *Trichinella*.

- The important (**2.) Tissue nematodes** *Wuchereria, Onchocerca, and Loa* are called the "**filarial worms**," because they produce motile embryos called microfilariae in blood and tissue fluids.
- These organisms are transmitted from person to person by **blood sucking mosquitoes or flies.**
- A fourth species is the guinea worm, *Dracunculus*, whose larvae inhabit tiny crustaceans (copepods) and are ingested in drinking water.

[Extra]

- The nematodes described above cause disease as a result of the **presence of adult worms within the body.**
- In addition, several secies cannot mature to adults in human tissue, but their larvae can cause disease.

- The most serious of these diseases is visceral larva migrans, caused primarily by the larvae of the dog ascarid, Toxocara canis.
- Cutaneous larva migrans, caused mainly by the larvae of the dog and cat hookworm, Ancylostoma caninum, is less serious.
- A third disease, anisakiasis, is caused by the ingestion of Anisakis larvae in raw seafood.

- In infections caused by certain nematodes that migrate through tissue, e.g., Strongyloides, Trichinella, Ascaris, and the two hookworms Ancylostoma and Necator, a striking increase in the number of eosinophils **(eosinophilia)** occurs.
- Eosinophils do not ingest the organisms; rather, they attach to the surface of the parasite via IgE and secrete cytotoxic enzymes contained within their eosinophilic granules.
- Host defenses against helminths are stimulated by interleukins synthesized by the Th-2 subset of helper T cells; e.g., the production of IgE is increased by interleukin-4, and the number of eosinophils is increased by interleukin-5.
- Cysteine proteases produced by the worms to facilitate their migration through tissue are the stimuli for IL-5 production.

Intestinal Nematodes

Ascaris lumbricoides

- Ascaris lumbricoides (earth worm) causes **ascariasis**.

- Important Properties :

- Humans are infected by **ingesting worm eggs in food or water contaminated with human feces.**
- Children particularly affected heavily because they play in soil and contaminate their hands.
- Eggs of Ascaris can survive in soil for years because the egg is surrounded by a highly resistant tough albuminous corrugated membrane, which resists dryness but is sensitive to exposure to sunlight.
- The eggs hatch in the small intestine, and the larvae migrate through the gut wall into the bloodstream and then to the lungs. They enter the alveoli because they can't pass through. The small pulmonary capillaries .They pass up the bronchi and trachea by cilia and are swallowed.
- Within the small intestine, they become adults. They live in the lumen, do not attach to the wall, and derive their sustenance from ingested food.
- The adults are the largest intestinal nematodes, often growing to 25 cm or more (female is about 20-25 cm while male is about 15-30 cm). A. lumbricoides is known as the "giant roundworm." The oral cavity of both sexes is triangular in shape and is surrounded by 3 lips. The posterior end of the male is bended & it possesses 2 chitinous spicules.
- Thousands of eggs are laid daily (200,000 / day), are passed in the feces, and differentiate into embryonated eggs in warm, moist soil. First eggs are not infective & contain non segmented embryo.
- Ingestion of the embryonated eggs completes the cycle.
    -

- Pathogenesis & Clinical Findings :
    - The major damage occurs during **larval migration** rather than from the presence of the adult worm in the intestine.
    - **Ascaris Larvae are large & antigenic.** Therefore during pulmonary migration they cause a lot of damage to the alveoli & allergic reactions.
    - When a large number of Larvae are migrating at the same time they cause a severe type of pneumonia called ***verminous pneumonia***, which manifested clinically as fever, cough, dyspnea, wheezes, changing X-ray shadows and **eosinophilia**.
    - Eosinophilia may be seen in the sputum. Disintegrated eosinophils may produce crystals called **Charcot's crystals** (in the sputum) which are also found in bronchial asthma.
    - This condition is also called **Loffler's syndrome** (*chest symptoms & eosinophilia*), which also occurs in hook worms & Strongyloides infection. Loffler's syndrome resolves spontaneously after few days.

- **D.D of Loeffler's syndrome**: Tropical pulmonary eosinophilia (W.Bancrofti), allergic bronchopulmonary aspergillosis, Katayama Fever and some drugs (Mefloquine & Disodium cromoglycate).

- The effect of adult worms depends on the worm load. Severe disease is associated with high worm load.

- The main effects of the worms are **mechanical** effect and **toxic & metabolic** effects.

1. **Mechanical effect** :
   - The worm may obstruct the small intestine especially in children because of the small size of their intestines. So it can cause intestinal obstruction in form of **volvulus & intussusception**.
   - The worm may obstruct the appendix causing **acute appendicitis**.
   - It may obstruct the biliary tree causing **obstructive jaundice**, or it may cause **intrahepatic abscess** if the worm dies in the liver.
   - It can obstruct the main pancreatic duct causing **acute pancreatitis**.
   - If a large number is passing through. The larynx, they can cause **asphyxia**.

2. **Toxic & metabolic effects :**

   - Not well understood, but it is estimated that 15-50 worms lead to loss of 4 grams of proteins / day.
   - So heavy infection may cause **malnutrition** & **growth retardation in children**.

- Clinical presentation :
  - Pts. may present with *recurrent abdominal colics, nausea & vomiting.* Pts. may Vomit worms or they may be coughed (*the only worm that can be vomited or coughed*), may be passed in the stool if there is diarrhoea of any cause.
  - Pts. may present **with one of the complications**: Acute appendicitis, asphyxia, malnutrition in children ... etc. . . .

- Epidemiology :
  - Ascaris infection is very common, especially in the tropics; hundreds of millions of people are infected. In the United States, most cases occur in the southern states.

- Laboratory Diagnosis :
  - Diagnosis is usually made **microscopically by detecting eggs in the stools.** The egg is **oval** with an irregular surface, **yellow brown in color**. Sometimes the eggs can be unfertilized if males are few, they are narrow, long and with dark brown pigment.
  - Occasionally, the patient sees **adult worms in the stools**, identified by size, shape & by the posterior end.
  - Eosinophilia is usually mild.

- Treatment :
  - Pulmonary complications respond well to steroids.
  - **Mebendazole (Vermox)** is effective.
  - Piperazine salt, levamisole & Albendazole are also effective.
  - * **Mebendazole** & **Albendazole** are contraindicated in *pregnant women*.

- Prevention :
  - Proper disposal of feces can prevent ascariasis.

Ankylostoma duodenale & Necator americanus

- *Ancylostoma duodenale* (Old World hookworm) and *Necator americanus* (New World hookworm) cause hookworm infection.
- Called Hookworms because the head is sharply blended, forming a definitive hook.
- The adult worms are similar but Necator is slightly smaller. The worms are reddish brown in color because they ingest blood and you can see a thread.

- Important Properties :
  - Humans are infected when **filariform larvae in moist soil penetrate the skin**, usually of the feet or legs. They are carried by the blood to the lungs, migrate into the alveoli and up the bronchi and trachea, and then are swallowed (like Ascaris).
  - They develop into adults in the small intestine, attaching to the wall with either cutting plates (Necator) or teeth (Ancylostoma). They feed on blood from the capillaries of the intestinal villi.
  - Because they suck blood & proteins, they suck at regular intervals and from time to time they change the place of attachment.
  - Thousands of eggs per day are passed in the feces. Eggs develop first into noninfectious, feeding (rhabditiform) larvae and then into third-stage, infectious, nonfeeding (filariform) larvae, which penetrate the skin to complete the cycle.
  - Ancylostoma lays more eggs than Necator (2:1).

- Pathogenesis & Clinical Findings :
  - The major damage is due to the **loss of blood** at the site of attachment in the small intestine & loss of proteins.
  - Ancylostoma **(more)** causes loss of about 0.5 ml / worm / day while Necator causes loss of about 0.03 ml / worm / day.
  - Blood is consumed by the worm and oozes from the site in response to an anticoagulant made by the worm. Weakness and pallor accompany the **microcytic anemia** caused by blood loss.

- Development of **Iron deficiency anemia** depends on: the worm load, worm type, Iron stores & presence of associated conditions like pregnancy & menstruation.
- During larval migration thro. The lungs, **Loeffler's syndrome** arises with cough wheezes, X-ray shadows & Eosinophilia. This is less severe than Ascaris because the larva of the Hookworm is smaller than the larva of Ascaris, thus causing less damage.
- "**Ground itch**," a pruritic papule or vesicle, can occur at the site of entry of the larvae into the skin.

- Epidemiology :
  - Hookworm is found worldwide, especially in tropical areas. In the United States, Necator is endemic in the rural southern states.
  - Walking barefooted on soil predisposes to infection. An important public health measure was requiring children to wear shoes to school.

- Laboratory Diagnosis :
  - Diagnosis is made **microscopically by observing the eggs in the stools.** Egg is rounded or oval & it is transparent, the ova which appear segmented or lobulated are surrounded by a black membrane or shell. If they are kept more than 12 hours in the dark they hatch and release the larvae.
  - The ***Larvae has a long oral cavity but no esophageal bulb.***
  - Occult blood in the stools is frequent. Eosinophilia is typical.
  - Iron deficiency anemia must be diagnosed & other causes of anemia must be excluded.
  -
- Treatment :
  - **Mebendazole** (Vermox) is effective.
  - **Iron supplement** is necessary.

- Prevention :
  - Disposing of sewage properly and wearing shoes are effective means of prevention.

Strongyloides stercoralis

- Strongyloides stercoralis causes **strongyloidiasis.**
- It is the only intestinal Nematode that can exist in a free living state.

- Important Properties :
  - *S. stercoralis* has two distinct life cycles, one within the human body and the other free-living in the soil.
  - The life cycle in the human body begins with the **penetration of the skin**, usually of the feet, by infectious (filariform) larvae and their migration to the lungs. They enter the alveoli, pass up the bronchi and trachea, and then are swallowed.
  - In the small intestine, the larvae molt into adults that enter the mucosa and produce eggs.
  - The eggs usually hatch within the mucosa, forming rhabditiform larvae that are passed in the feces.
  - Some larvae molt to form filarial larvae, which penetrate the intestinal wall directly without leaving the host and migrate to the lungs (**autoinfection**).
  - In immunocompetent patients, this is an infrequent, clinically unimportant event, but in **immunocompromised patients**, e.g., those who have AIDS or are taking high-dose corticosteroids, or patients who are severely malnourished, *autoinfection can lead to massive reinfection, with larvae passing to many organs and with severe, sometimes fatal consequences.*
  - If larvae are passed in the feces and enter warm, moist soil, they molt through successive stages to form adult male and female worms. After mating, the entire life cycle of egg, larva, and adult can occur in the soil.
  - After several free-living cycles, filarial larvae are formed. When they contact skin, they penetrate and again initiate the parasitic cycle within humans.
  -
- Pathogenesis & Clinical Findings :
  - Most patients are **asymptomatic**, especially those with a low worm burden.
  - Adult female worms in the wall of the small intestine can cause inflammation, causing **upper abdominal pain** similar to ulcer pain and **diarrhoea alternating with constipation**.
  - **Heavy infection in children**: may cause *malabsorption*, because the worms are in the small intestine.
  - In **autoinfection**, the penetrating larvae may cause sufficient damage to the intestinal mucosa that sepsis caused by enteric bacteria can occur.
  - Larvae in the lungs can produce a pneumonitis similar to that caused by Ascaris & Hookworms (Loeffler's syndrome).
  - **Pruritus (ground itch)** can occur at the site of larval penetration of the skin, as with hookworm.

- Epidemiology :
  - Strongyloidiasis occurs primarily in the tropics, especially in Southeast Asia. Its geographic pattern is similar to that of hookworm because the same type of soil is required. In the United States, Strongyloides is endemic in the southeastern states.

- Laboratory Diagnosis :
  - Diagnosis depends on **finding larvae**, rather than eggs, **in the stool**.
  - As with many nematode infections in which larvae migrate through tissue, **eosinophilia** can be striking in early infection but moderate in chronic infection.
  - Larvae can also be found by examination of the duodenal content either directly by duodenal aspirate or indirectly by **String test (enterotest capsule).**
  - ***Larvae of Strongyloides should be differentiated from larvae of the Hookworms. In Strongyloides the oral cavity is short and there is an esophageal bulb, while in the Hookworms the oral cavity is long and there is no esophageal bulb.***
  - **Serologic** tests are useful when the larvae are not visualized e.g. ELISA, DAT.
  - An enzyme immunoassay that detects antibody to larval antigens is available through the CDC in Atlanta.

- Treatment : **
  - **Ivermectin** is the drug of choice. **Thiabendazole** is an alternative drug.

- Prevention :
  - Prevention involves disposing of sewage properly and wearing shoes.

Enterobius vermicularis

- Enterobius vermicularis causes **pinworm infection (enterobiasis).**

- Important Properties :
  - The life cycle is confined to humans. The infection is acquired by **ingesting the worm eggs.** The eggs hatch in the small intestine, where the larvae differentiate into adults and migrate to the colon. The adult male and female worms live in the colon, where mating occurs.
  - At night, the female migrates thro. The anus and releases thousands of fertilized eggs on the **perianal skin** and into the environment (this causes severe itching).
  - Within 6 hours, the eggs develop into embryonated eggs and become infectious.
  - **Reinfection** can occur if they are carried to the mouth by fingers after scratching the itching skin.
  - The eggs may remain viable & infective for many weeks in clothes, utensils & in the dust.
  - Rarely, **retro-infection** may occur I.e. when the egg hatches in the perianal region and the larva finds its way back to the intestine thro. The anus.

- Pathogenesis & Clinical Findings :
  - **Perianal pruritus** is the most prominent symptom.
  - Pruritus is thought to be an *allergic reaction* to the presence of either the adult female or the eggs.
  - Scratching predisposes to ***secondary bacterial infection, UTI in males or vulvovaginitis in females.***
  - Worms in the appendix may obstruct it causing **acute appendicitis**.

- Epidemiology :
  - Enterobius is found worldwide and is the most common helminth in the United States.
  - Children younger than 12 years of age are the most commonly affected group.

- Laboratory Diagnosis :
  - The eggs are recovered from perianal skin by using the **Scotch tape technique** (silotape technique) and can be observed **microscopically**.
  - The ovum is very characteristic, it is asymmetrical or oval in shape, flat in one side & convex in the other side (**D-shaped**), and it is transparent & contains the larvae.
  - Unlike those of other intestinal nematodes, these eggs are not found in the stools. The small, whitish adult female worms can be found in the stools or near the anus of diapered children. Males are rarely seen.

- The head of the worm is surrounded by 2 cervical alae and this helps to distinguish the worm in cross section in the appendix.
- No serologic tests are available.

- Treatment :
  - **Mebendazole** is effective. They kill the adult worms in the colon but not the eggs, so retreatment in 2 weeks is suggested (repeat treatment). Reinfection is very common.

- Prevention :
  - There are no means of prevention. Instruct the pt. to wash his hands & clothes to prevent spread of the disease to other members in the family.

Trichuris trichiura

- *Trichuris trichiura* causes **whipworm infection** (**trichuriasis**).

- Important Properties :
  - The worm is about 3-5 cm. The anterior part is thin & is occupied by the esophagus in both male & female. It is partially buried in the mucosa of the large intestine. The posterior part is thick and is occupied by the uterus in females, while in males it is curved thro. 360* and can be used for identification.
  - Humans are infected by **ingesting worm eggs in food or water contaminated with human feces**. The eggs hatch in the small intestine, where the larvae differentiate into immature adults.
  - These forms migrate to the colon, where they mature, mate, and produce thousands of fertilized eggs daily, which are passed in the feces. Eggs deposited in warm, moist soil form embryos. When the embryonated eggs are ingested, the cycle is completed.
  - "Whip like" appearance of the adult worm is very characteristic.

- Pathogenesis & Clinical Findings :
  - Although adult Trichuris worms burrow their hair like anterior ends into the intestinal mucosa, they do not cause significant anemia, unlike the hookworms. They feed on tissue juices not on blood.
  - Trichuris may cause **diarrhea**, but most infections are asymptomatic.
  - Trichuris may also cause **rectal prolapse** in children with heavy infection. Prolapse results from increased peristalsis that occurs in an effort to expel the worms, moreover high numbers of embedded worms in the rectum cause edema. The whitish worms may be seen on the prolapsed mucosa.

- It may also cause **chronic diarrhoea (dysentery**), **ulceration in the bowel**, wasting & rarely anemia.
- The pts. Are predisposed to develop **Amebiasis** & **Bacillary dysentery** because the damage caused by the worm enhances entry of these organisms. (Complications)

- Epidemiology :
  - Whipworm infection occurs worldwide, especially in the tropics; more than 500 million people are affected.
  - In the United States, it occurs mainly in the southern states.

- Laboratory Diagnosis :
  - Diagnosis is based on finding the typical **eggs**, i.e., **barrel-shaped** (lemon-shaped) with a plug at each end, yellow brown in color, in the **stool**.
  - If rectal prolapse occurs, worms can be seen attached to the rectal mucosa.
  - **Proctoscopy**: red, ulcerated mucosa in the rectum, with worms attached to it.
  - Eosinophilia is mild or absent.

- Treatment :
  - **Mebendazole** is the drug of choice.
    Albendazole is an alternative.

- Prevention :
- Proper disposal of feces prevents transmission.

Trichinella spiralis

- Trichinella spiralis causes trichinosis.
- It is an intestinal Nematode , but differs in that :

1. Man is not the normal host.
2. Females are viviparous.
3. The worm stays in the intestines only for a very short time and then migrates to muscles where they become encysted => considered as tissue Nematodes.

- Important Properties :
- Any mammal can be infected, but pigs are the most important reservoirs of human disease in the United States (except in Alaska, where bears constitute the reservoir).
- Humans are infected by eating raw or undercooked meat containing larvae encysted in the muscle.
- The larvae excyst and mature into adults within the mucosa of the small intestine.

- Eggs hatch within the adult females, and larvae are released and distributed via the bloodstream to many organs; however, they develop only in striated muscle cells.
- Within these "nurse cells," they encyst within a fibrous capsule and can remain viable for several years but eventually calcify.
- The parasite is maintained in nature by cycles within reservoir hosts, primarily swine and rats.
- Humans are end-stage hosts, because the infected flesh is not consumed by other animals.

- Pathogenesis & Clinical Findings :
- A few days after eating undercooked meat, usually pork, and the patient experiences diarrhea followed 1 to 2 weeks later by fever, muscle pain, periorbital edema, and eosinophilia.
- Subconjunctival hemorrhages are an important diagnostic criterion. D.D of subconjunctival Hemorrhage: Infective Endocarditis, Whooping cough (B.pertussis) & Leptospirosis.
- Signs of cardiac and central nervous system disease are frequent, because the larvae migrate to these tissues as well.
- Death, which is rare, is usually due to congestive heart failure or respiratory paralysis.

- Epidemiology :
- Trichinosis occurs worldwide, especially in Eastern Europe and West Africa. In the United States, it is related to eating home-prepared sausage, usually on farms where the pigs are fed uncooked garbage. Bear and seal meat also are sources.
- In many countries, the disease occurs primarily in hunters who eat undercooked wild game.

- Laboratory Diagnosis :
- Muscle biopsy reveals larvae within striated muscle.
- Serologic tests, especially the bentonite flocculation test, become positive 3 weeks after infection.

- Treatment :
- There is no treatment for trichinosis, but for patients with severe symptoms, steroids plus mebendazole can be tried.
- Thiabendazole is effective against the adult intestinal worms early in infection.

- Prevention :
- The disease can be prevented by properly cooking pork and by feeding pigs only cooked garbage.

Tissue Nematodes

- They cause a group of diseases collectively known as **Filariasis**.
- They are viviparous I.e. give birth to larvae. The larval stage is called Microfilaria.
- Intermediate host is usually **insects.**
- Species that cause Filariasis :
    1. *Wuchereria bancrofti.*
    2. *Brugia malayi.*
    3. *Onchocerca volvulus.*
    4. *Loa loa.*

- They are characterized by periodicity :

1. Nocturnal periodicity :

- The appearance of Microfilaria in blood mainly at night, reaching maximum number between 10 pm & 2 am. In the day they rest in the capillaries. E.g. W.Bancrofti & B.Malayi. Transmitted mainly by night feeding insects.

2. Diurnal periodicity :

- Microfilaria are found in blood only during the day, they are absent during night. E.g. Loa loa. Transmitted mainly by day feeding insects.

- **Onchocerca Microfilaria are not found in blood (in subcutaneous tissue).**

- The vector :
    1. *W.Bancrofti* is transmitted by mosquitoes, mainly **Anopheles, Aedes & Culex**.
    2. *B.Malayi* is transmitted mainly by mosquitoes **Anopheles & Mansonia.**
    3. *Onchocerca volvulus* is transmitted by a fly called **Simulium**.
    4. *Loa loa* is transmitted by a fly called **Chrysops**.

- - They are treated by **Diethylcarbamazine (DEC),** except Onchocerca volvulus
- - Diagnosis can be made by demonstrating the shape of microfilariae microscopically.
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Wuchereria bancrofti

- Wuchereria bancrofti causes **filariasis**. Brugia malayi causes filariasis in Malaysia.
- **Elephantiasis** is a striking feature of this disease.
- **Tropical pulmonary eosinophilia** is an immediate hypersensitivity reaction to W. bancrofti in the lung.

- Important Properties :
  - They are equipped with sheath. The head is rounded, tail is tapering, they have **nuclei in all the body but not reaching the tip of the tail**.
  - Humans are infected when the female mosquito (especially Anopheles and Culex species) deposits infective larvae on the skin while biting.
  - The larvae penetrate the skin, enter a **lymph node** and after 1 year, mature to adults that produce microfilariae. These circulate in the blood, chiefly at night, and are ingested by biting mosquitoes.
  - Within the mosquito, the microfilariae produce infective larvae (in muscles of the thorax) that are transferred with the next bite.
  - There is no multiplication in the insect I.e. one microfilaria gives rise to one infective stage.
  - Humans are the **only definitive hosts.**

- Pathogenesis & Clinical Findings :
  - Adult worms in the lymph nodes cause inflammation that eventually obstructs the lymphatic vessels, causing **edema**. Massive edema of the legs is called **elephantiasis**. Note that microfilariae do not cause symptoms.

  - Early infections are **asymptomatic**. *Later*, **fever, lymphangitis, and cellulitis** develop.
  - Gradually, the obstruction leads to edema and fibrosis of the **legs and genitalia**, especially the scrotum. ***Choluria*** may develop (a condition due to rupture of the lymphatics in the kidney leading to presence of lymph in the urine).
  - All these manifestations are due to the presence of the adult worm.
  - Elephantiasis occurs mainly in patients who have been repeatedly infected over a long period. Tourists, who typically are infected only once, do not get elephantiasis.
  - Wolbachia species are rickettsia-like bacteria found intracellularly within filarial nematodes such as Wuchereria and Oncocerca.
  - Wolbachia release endotoxin-like molecules that are thought to play a role in the pathogenesis of Wuchereria and Oncocerca infections.
  - Evidence for this includes the use of doxycycline, which kills the Wolbachia resulting in a reduction of the inflammatory response to the nematode infection.

- **Tropical pulmonary eosinophilia** is characterized by **coughing and wheezing**, especially **at night**. These symptoms are caused by microfilariae in the lung that elicit an immediate hypersensitivity reaction characterized by a high immunoglobulin E (IgE) concentration and eosinophilia.

- Epidemiology :
  - This disease occurs in the tropical areas of Africa, Asia, and Latin America. The species of mosquito that acts as the vector varies from area to area. Altogether, 200 to 300 million people are infected.

- Laboratory Diagnosis :
  - Clinical features & **high eosinophilia**.
  - Thick blood smears taken from the patient at night reveal the microfilariae (**have a sheath and the nuclei don't extend to the tip of the tail**).
  - Serologic tests are not useful.

- Treatment :
  - **Diethylcarbamazine (DEC)** is effective only against microfilariae; no drug therapy for adult worms is available.
  - It is preferable to begin with a small dose to minimize the side effects of the drug. The main side effect is allergic reaction to the rapid death of the Microfilaria.

- Prevention :
- Prevention involves mosquito control with insecticides and the use of protective clothing, mosquito netting, and repellents.

Brugia malayi

- Causes **lymphatic Filariasis**.
- Transmitted by Anopheles & Mansonia.
- Periodicity is nocturnal in countries where Anopheles transmit the disease.
- Periodicity is both nocturnal & diurnal where Mansonia transmit the disease.
- Clinical presentation is similar to W.Bancrofti except that **in B.Malayi infection there is no scrotal involvement.**
- Diagnosis is based on seeing Microfilaria similar to W.Bancrofti but **has a nucleus at the tip of the tail (only one nucleus).**
- Treated by **DEC** (same as W.bancrofti).

Onchocerca

- Onchocerca volvulus causes **onchocerciasis (River blindness).**

- Important Properties :
  - Humans are infected when the female **blackfly**, **Simulium** (Simulium domnosum mainly), deposits infective larvae while biting.
  - The larvae enter the wound and migrate into the **subcutaneous tissue**, where they differentiate into adults, usually within dermal nodules. The female produces microfilariae that are ingested when another blackfly bites. The microfilariae develop into infective larvae in the fly to complete the cycle.
  - Humans are the only definitive hosts.

- Pathogenesis & Clinical Findings :
  - All clinical manifestations are due to the reaction caused by the **dead Microfilaria** and not by the adult worms except Onchocercoma.
  - Inflammation occurs in subcutaneous tissue, and **pruritic papules** and **painless nodules** (**Onchocercoma**) form in response to the adult worm proteins. These nodules are mainly found over bony prominences like the Pelvis or the face.
  - **Microfilariae** migrate through subcutaneous tissue, ultimately concentrating in the *eyes*. There they cause lesions that can lead to **blindness**.
  - Loss of subcutaneous elastic fibers leads to **wrinkled skin**, which is called "**hanging groin**" when it occurs in the inguinal region.
  - Thickening, scaling, and dryness of the skin accompanied by severe itching are the manifestations of a **dermatitis** often called "**lizard skin**" or **Onchodermatitis**.
  - The role of Wolbachia in the pathogenesis of onchocerciasis has been discussed earlier in "Wuchereria."
- In sudan :
  - Abu Hamad dermatitis.
  - In South Sudan => dermatitis & blindness occur.
- In Yemen :
  - Sowdah (black disease): a severe allergic response affecting one limb with darkening of the skin.

- **Note :**
  - **Ocular lesions** affect either the anterior chamber or the posterior chamber.
  - **Anterior chamber lesions** => Sclerosing keratitis & Iritis are the main causes of blindness (allergic reaction to dead Microfilaria).
  - **Posterior chamber lesions** => Chorioretinitis +/- atrophy leads to blindness.

- Epidemiology :
  - Millions of people are affected in Africa and Central America.
  - The disease is a major cause of blindness. It is called river blindness, because the blackflies develop in rivers and people who live along those rivers are affected.
  - Infection rates are often greater than 80% in areas of endemic infection.
  -
- Laboratory Diagnosis :
  - Biopsy of the affected skin reveals microfilariae. Microfilaria are **unsheathed and the nuclei do not reach the tip of the tail.**
  - Examination of the blood for microfilariae is not useful because they do not circulate in the blood (unlike W.bancrofti & Loa loa). **Eosinophilia is common**.

  - **Mazzotti test**: give a small dose of DEC that kills the Microfilaria causing serious allergic reaction in heavy infection. Not justified unless in mild infection i.e. when the skin snip is negative.

    - Serologic tests are not helpful.

- Treatment :
  - **Ivermectin** is effective *against microfilariae* but not adults. DEC is also useful.
  - Skin nodules can be **removed surgically**, but new nodules can develop; therefore, a surgical cure is unlikely in areas of endemic infection.

- Prevention :
  - Prevention involves control of the blackfly with insecticides. Ivermectin prevents the disease.

Loa loa

- Loa loa (eye worm) causes **loiasis**.

- Important Properties :
  - Humans are infected by the bite of the deer fly (mango fly), **Chrysops**, which deposits infective larvae on the skin.
  - The larvae enter the bite wound, wander in the body, and develop into adults.
  - The females release microfilariae that enter the blood, particularly during the day.
  - The microfilariae are taken up by the fly during a blood meal and differentiate into infective larvae, which continue the cycle when the fly bites the next person.

- Pathogenesis & Clinical Findings :
  - There is no inflammatory response to the microfilariae or adults, but a hypersensitivity reaction causes **transient, localized, non-erythematous, subcutaneous edema (Calabar swellings)**. Characterized by *reappearance at a site after disappearance from another site.*
  - The most dramatic finding is an adult worm **crawling across the conjunctiva** of the eye, a harmless but disconcerting event.

- Epidemiology :
  - The disease is found only in tropical central and West Africa, the habitat of the vector Chrysops.

- Laboratory Diagnosis :
  - Diagnosis is made by visualization of the microfilariae in a blood smear. Microfilaria are characterized by **presence of sheath, moreover the nuclei extend to the tip of the tail.**
  - There are no useful serologic tests.

- Treatment :
  - **Diethylcarbamazine (DEC)** eliminates the microfilariae and may kill the adults. Worms in the eyes may require surgical excision.
  - **Ivermectin is contraindicated because it causes post-therapeutic encephalopathy**.

- Prevention :
  - Control of the fly by insecticides can prevent the disease.

Dracunculus medinensis

- Dracunculus medinensis (guinea fire worm or Medina worm) causes **dracunculiasis**.

- Important Properties :
  - Humans are infected when tiny crustaceans (copepods) containing infective larvae are **swallowed in drinking water**.
  - The larvae are released in the small intestine and migrate into the body, where they develop into adults. They mature in the connective tissue of the retroperitoneal space.
  - Meter-long adult females reach gravidity in about one year, cause the skin to ulcerate and then release motile rhabditiform larvae into fresh water.
  - Copepods eat the larvae, which molt to form infective larvae. The cycle is completed when these are ingested in the water.

- Pathogenesis & Clinical Findings :
  - The adult female produces a substance that causes **inflammation, blistering, and ulceration of the skin**, usually of the lower extremities. The inflamed papule burns and itches, and the ulcer can become **secondarily infected** (secondary infections & cellulitis are common, particularly if the worm is ruptured during the process of extraction).
  - Few days before the formation of the blisters, the patient may have fever & generalized urticaria.
  - Manifestations are thought to represent allergic reaction to prematurely liberated larvae.
  - Diagnosis is usually made clinically by finding the worm in the skin ulcer.

- Epidemiology :
  - The disease occurs over large areas of tropical Africa, the Middle East, and India. Tens of millions of people are infected.

- Laboratory Diagnosis :
  - Clinical presentation is characteristic, well known in endemic areas.
  - If a worm is seen protruding from an ulcer, placing a small amount of water on the worm results in discharge of larvae that can be examined microscopically. The anterior end is round while the posterior end is tapering and it is always coiled.
  - Dead & calcified worms can be seen in X-ray in chronic areas.
  - Eosinophilia.

- Treatment :

1. **Traditional treatment :**

- The time-honored treatment consists of gradually extracting the worm by winding it up on a stick over a period of days. The worm should not be broken inside the tissue because: the fluid released can cause severe allergy and the worm will retract inside the tissues with severe inflammation & destruction of tissues.

2. **Anti-helminths**: **Thiabendazole** or **Metronidazole** makes the worm easier to extract and relief the symptoms.
3. **Antibiotics:** to prevent secondary bacterial infection.
4. **Anti-tetanus vaccine** should be given. The ulcer should be cleaned & dressed clearly to prevent bacterial infection.

- Prevention :

- Prevention consists of **filtering** or boiling drinking water.

Animal Nematodes

Toxocara

- Toxocara canis is the major cause of visceral larva migrans.
- T. cati and several other related nematodes also cause this disease.

- Important Properties :
  - The definitive host for T. canis is the dog.
  - The adult T. canis female in the dog intestine produces eggs that are passed in the feces into the soil. Humans ingest soil containing the eggs, which hatch into larvae in the small intestine.
  - The larvae migrate too many organs, especially the liver, brain, and eyes. The larvae eventually are encapsulated and die.
  - The life cycle is not completed in humans; humans are therefore accidental, dead-end hosts.
- Pathogenesis & Clinical Findings :
  - Pathology is related to the granulomas that form around the dead larvae as a result of a delayed hypersensitivity response to larval proteins.
  - The most serious clinical finding is blindness associated with retinal involvement. Fever, hepatomegaly, and eosinophilia are common. Nephritis, cardiac dysfunction & sometimes neurological manifestations occur.
- Epidemiology :
  - Young children are primarily affected, because they are likely to ingest soil containing the eggs.
  - T. canis is a common parasite of dogs in the United States.
- Laboratory Diagnosis :
  - Serologic tests are commonly used, but the definitive diagnosis depends on visualizing the larvae in tissue.
  - The presence of hypergammaglobulinemia and eosinophilia supports the diagnosis.

- Treatment :
  - The treatment of choice is either albendazole or mebendazole, combined with steroids, but there is no proven effective treatment. DiEthylCarbamazine (DEC) for 21 days is also an option.
  - Many patients recover without treatment.

- Prevention :
- Dogs should be dewormed, and children should be prevented from eating soil.

Ancylostoma

- Cutaneous larva migrans is caused by the filariform larvae of Ancylostoma caninum (dog hookworm) and Ancylostoma braziliense (cat hookworm), as well as other nematodes e.g. Strongyloides of animals.
- The organism cannot complete its life cycle in humans.
- The larvae penetrate the skin and migrate through subcutaneous tissue for several months causing a severe localised allergic reaction and as they migrate they form tortuous tunnels. The progression of the anterior end of the larvae every few days can be easily observed. Thus lesions are called ("creeping eruption") and they are extremely pruritic.
- The disease occurs primarily in the southern United States, in children and construction workers who are exposed to infected soil.
- The diagnosis is made clinically; the laboratory is of little value.
- Oral or topical thiabendazole is usually effective.

Minor animal Nematodes

Angiostrongylus

- The larvae of the rat lung nematode Angiostrongylus cantonensis cause eosinophilic meningitis, i.e., a meningitis characterized by many eosinophils in the spinal fluid and in the blood. Usually at least 10% of the white cells are eosinophils.
- The larvae are typically ingested in undercooked seafood, such as crabs, prawns, and snails. Infection by this organism most often occurs in Asian countries.
- The diagnosis is made primarily on clinical grounds, but occasionally, the laboratory will find a larva in the spinal fluid.
- There is no treatment. Most patients recover spontaneously without major sequelae.
- Eosinophilic meningitis is also caused by the larvae of two additional nematodes.
- Gnathostoma spinogram, an intestinal nematode of cats and dogs, is acquired by eating undercooked fish and Baylisascaris procyonis, a raccoon roundworm, is acquired by accidentally ingesting raccoon feces.
- These organisms cause more severe disease than Angiostrongylus, and fatalities occur.
- Albendazole may be effective against Gnathostoma, but there is no treatment for Baylisascaris.

Anisakis

- Anisakiasis is caused by the larvae of the nematode, Anisakis simplex.
- The larvae are ingested in raw seafood and can penetrate the submucosa of the stomach or intestine.
- The adult worms live in the intestines of marine mammals such as whales, dolphins, and seals.
- The eggs produced by the adults are eaten by crustaceans, which are then eaten by marine fish such as salmon, mackerel, and herring.
- Gastroenteritis, abdominal pain, eosinophilia, and occult blood in the stool typically occur.
- Acute infection can resemble appendicitis, and chronic infection can resemble gastrointestinal cancer.
- Most cases in the United States have been traced to eating sushi and sashimi (especially salmon and red snapper) in Japanese restaurants.
- The diagnosis is typically made endoscopically or on laparotomy.
- Microbiologic and serologic tests are not helpful in the diagnosis.
- There are no effective drugs. Surgical removal may be necessary. Prevention consists of cooking seafood adequately or freezing it for 24 hours before eating.
- Another member of the Anisakid family of nematodes is Pseudoterranova decepiens, whose larvae cause a noninvasive form of anisakiasis.
- The larvae are acquired by eating undercooked fish and cause vomiting and abdominal pain.
- The diagnosis is made by finding the larvae in the intestinal tract or in the vomitus.
- There is no drug treatment. The larvae can be removed during endoscopy

Protozoology
Helminthology

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