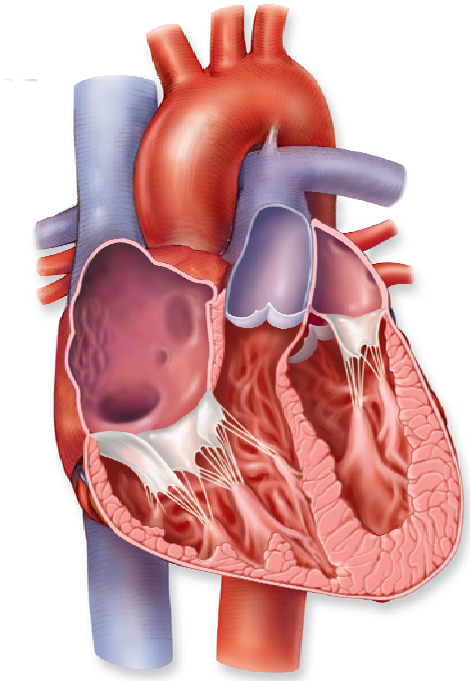
Infectious Diseases Affecting the Cardiovascular and Lymphatic Systems

Chapter 23



Bacterial Diseases

- Sepsis
- Endocarditis
- Rheumatic Fever
- Anthrax
- Cat Scratch Disease

Sepsis

- Blood normally a sterile tissue
- Blood may contain bacteria // bacteriemia
- Sepsis = systemic inflammatory response syndrome (SIRS)
- Sepsis occurs due to focus infection which releases mediators of inflammation into the blood stream
- Septiemia = bacteria in blood rapidly multiplying

Sepsis & Septicemia

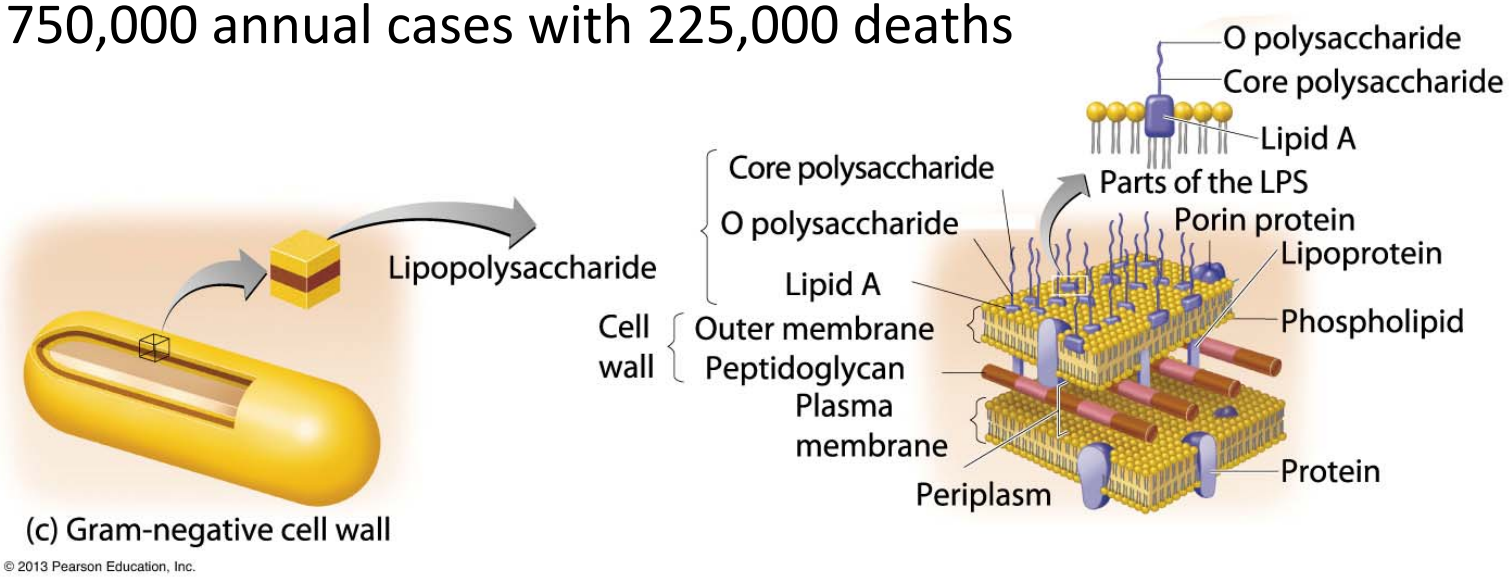
- SIRS exhibits profile including fever, chills, rapid heart rate, increase respiratory rate, neutrophilia, hemolysis with increase iron in blood, appearance of lymphagitis, increase in circulating cytokines

- Severe sepsis = drop in blood pressure and at least on organ failure

- Septic shock = final stage // no longer control blood pressure with addition of fluids

Sepsis Etiology

- Gram-negative sepsis
  - Gram negative bacteria most likely cause
  - Bacteria shed lipopolysacharide endotoxins (endotoxin shock)
  - Progression rapid and generally impossible to treat // Lipid A induce macrophage to release cytokines // Fever, shock, and DIC
  - 750,000 annual cases with 225,000 deaths



Sepsis Etiology

- Gram-positive sepsis
  - Now gram positive bacteria becoming more common cause
  - Staphylococcus and Streptococcus both produce exotoxins // cause toxic shock syndrome
  - Actual bacterial components unknown with certainty
  - Enterococcus in colon now responsible for many nosocomial infections
    - resistance to penicillin // now some also resistant to vancomycin – last of known antibiotic group still sensitive to enterococcus

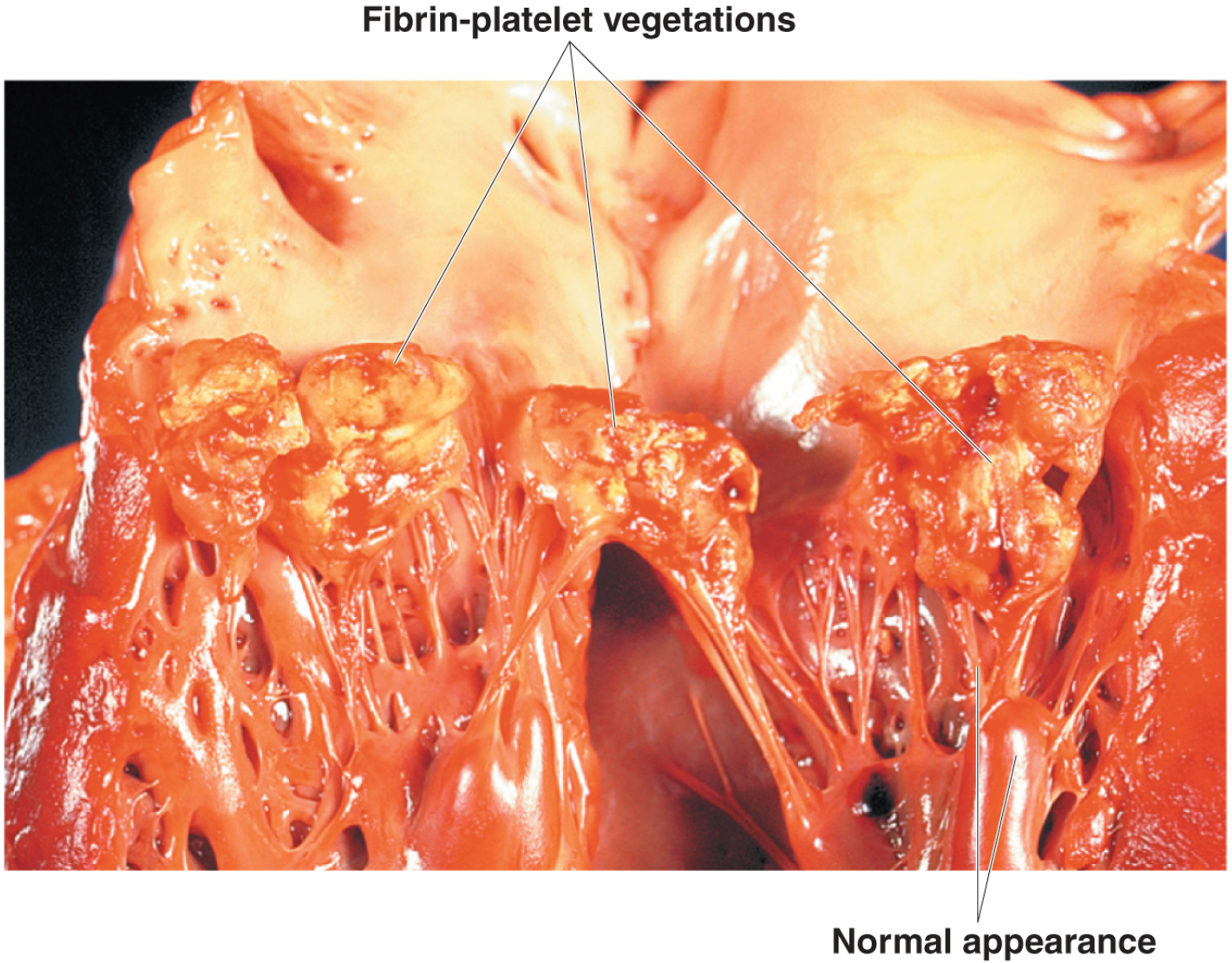
Endocarditis

- Endocardium – simple squamous epithelial cells which line interior of heart chambers, cordae tendinae, and heart valves
- Endocarditis = inflammation of the endocarium
- Sub-acute bacterial endocarditis // develops slowly with fever, general weakness, and heart murmur
- Alpha hemolytic streptococcus common in oral cavity mostly likely cause // tooth extraction allow bacteria into blood but even body piercing may allow bacteria into blood
- People with abnormal heart valves due to preexisting lesions from rheumatic fever or syphilis give bacteria opportunity to attach to these lesions

Endocarditis

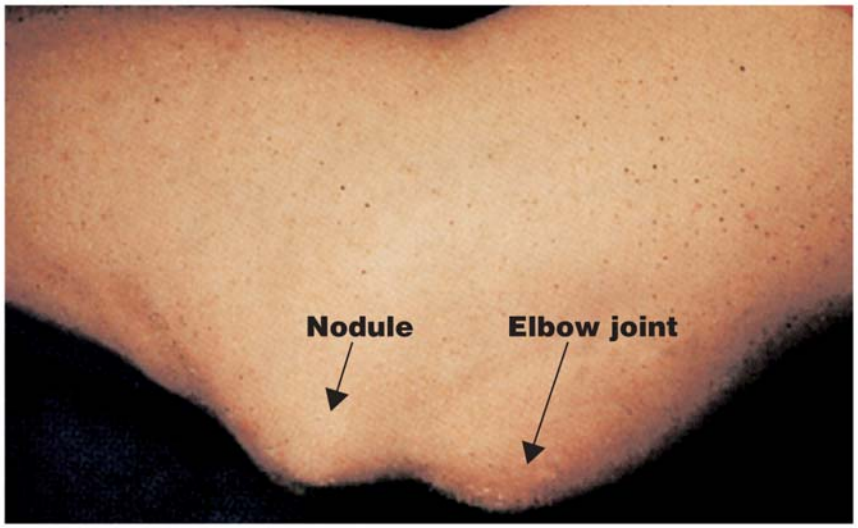
- Over weeks or months form fibrin-platelet vegetations // clots may break off and block blood vessels or lodge in kidney
- Untreated fatal within few months
- Acute bacterial endocarditis // more likely caused by Staphylococcus // rapid destruction of heart valves // fatal within a few days
- Streptococcus may also cause pericarditis

Endocarditis



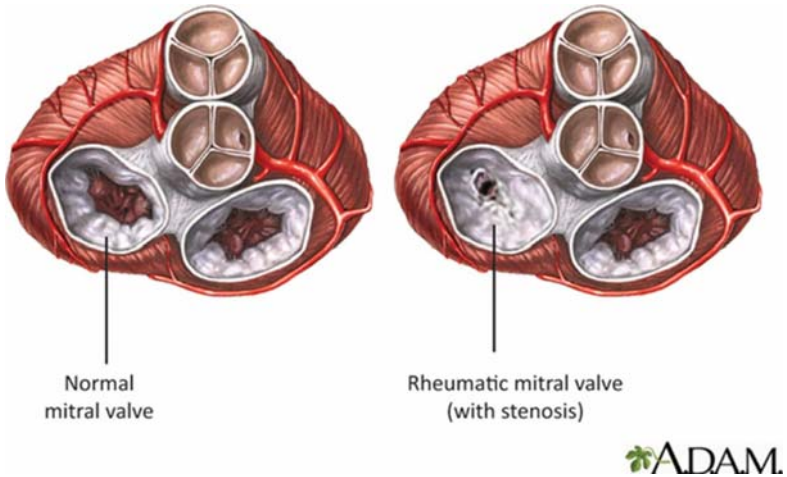
Rheumatic Fever

- Considered an autoimmune complication
- Associated with Streptococcus pyogenes throat infection // primarily seen in children age 4 to 18
- First expressed as short period of arthritis and fever // associated with formation of nodules at joints



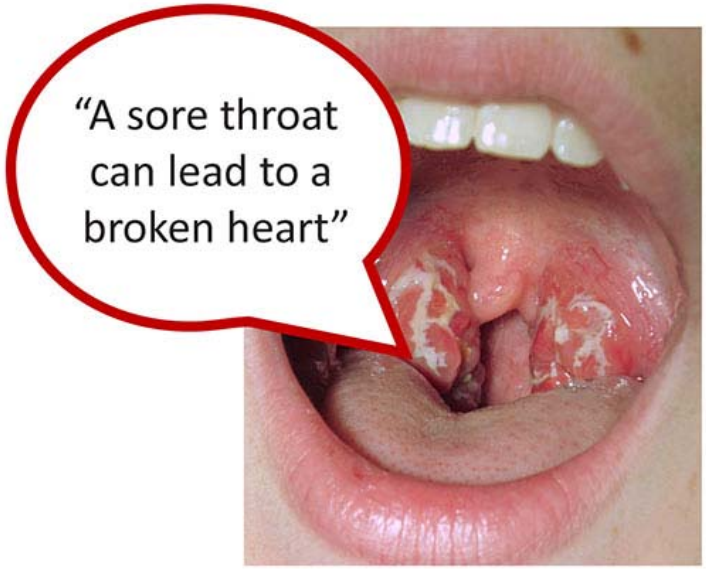
Rheumatic Fever

- About half of people then develop inflammation of heart that damage the bicuspid valve // misdirected immune reaction of Streptococcal M protein

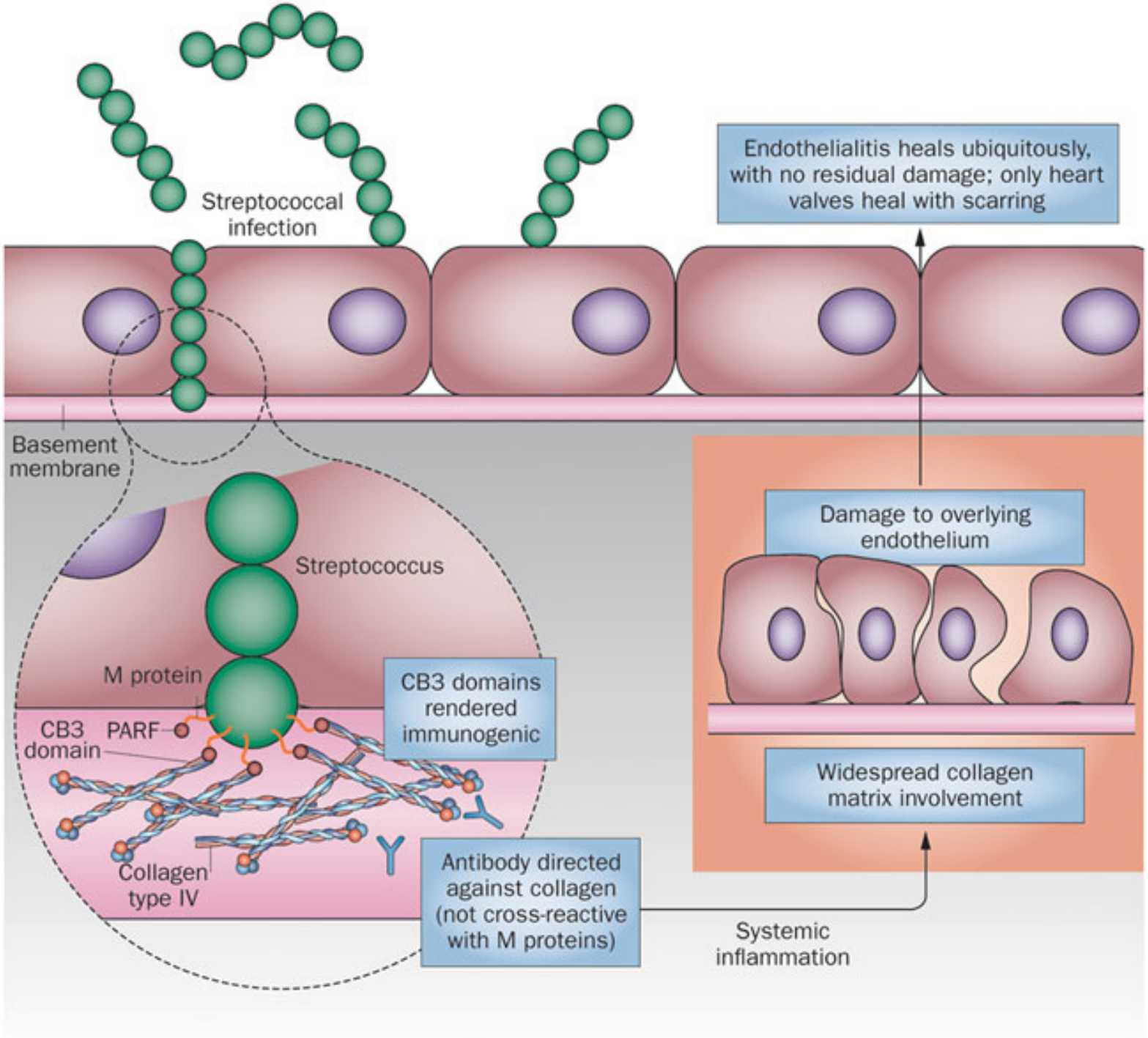


- Re-infection furthers damage heart valves // may progress to valve failure and death

- Early twentieth century rheumatic fever killed more school age children than all other diseases



- Since then problem has lessen // believed due to change in M protein serotype


Endothelialitis heals ubiquitously, with no residual damage; only heart valves heal with scarring
Streptococcal infection
Basement membrane
Streptococcus
M protein
CB3 domains rendered immunogenic
CB3 domain
PARF
Collagen type IV
Antibody directed against collagen (not cross-reactive with M proteins)
Damage to overlying endothelium
Widespread collagen matrix involvement
Systemic inflammation

Anthrax

- Bacillus anthracis – endospore forming, aerobic, gram-positive bacteria causes anthrax
- Grows in soil with specific moisture requirements
- When stressed forms endospores // can survive 60 years as endospore
- Grazing animals consume endospores with grasses
- After endospore becomes a vegetative bacteria // causes fatal sepsis

Anthrax

- Macrophage ingest endospores where spores germinate into bacteria
- Kill macrophage and release bacteria into blood // rapid growth and produce toxins
- Bacillus anthracis // unusual capsule of amino acid residue // capsule does not stimulate immune response
- Produce two toxins and third component (protective antigen) that allow toxins to attach to host cells and enter

Anthrax

- Edema toxin – local edema // interferes with phagocytosis
- Lethal toxin – targets and kills macrophage // disables important cell in acquired immunity
- Anthrax proliferates without effective inhibition // huge population of bacteria secreting toxins kills the host

Anthrax Types

- Cutaneous anthrax – 90% of cases
- Endospore enters lesion in skin // forms papule then depressed black eschar (scab) ulcerated area
- Most cases restricted to skin if it does not advance into blood
- Fever and general malaise
- Mortality up to 20% if not treated

Anthrax Types

- Gastrointestinal anthrax // ingestion of undercook foods containing anthrax endospores
  - Abdominal pain, nausea, bloody diarrhea // Mortality more than 50%
- Inhalation (pulmonary) anthrax // endospores inhales likely to enter bloodstream
  - Symptoms of mild fever, coughing, some chest pain // if not treated in first few days
  - Illness progresses to septic shock // kills patient in 2 to 3 days // mortality approaching 100%
  - Anthrax can be weaponized // used in war

Gangrene

- Clostridium perfringens species most likely to cause gangrene // gram-positive, endospore-forming anaerobe
- Bacteria in soil as well as in humans and domesticated animals intestinal tracts
- After ischemia and necrosis especially in skeletal muscle occurs // C. perfringens grows – metabolize carbohydrates to produce carbon dioxide and hydrogen – swells tissue
- Bacterial toxins breakdown collagen and other proteins allowing infection to rapidly move through tissue

Gangrene

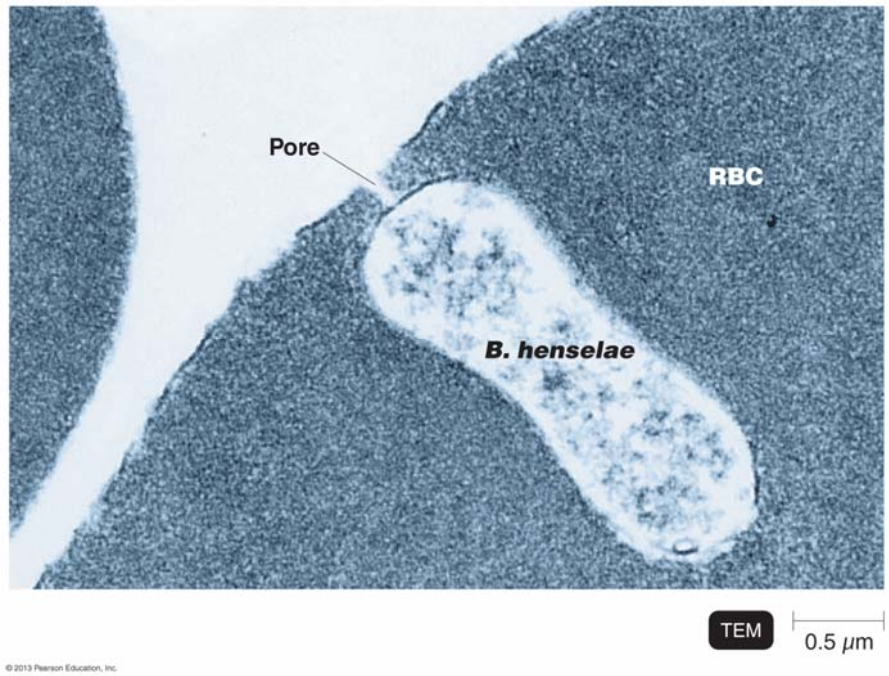
- C. perfringens reside in genital tract of 5% women // improper abortions allow microbe to invade uterine wall // infection can lead to gas gangrene

- Surgical removal of necrotic tissue and amputation are most common treatment

- Hyperbaric chamber – pressurized oxygen treatment may stop obligately anaerobic Clostridia

Cat Scratch Disease

- Bartonella henselae – aerobic, gram-negative bacteria causes 22,000 cases per year (more than better known Lyme disease)
- Bacteria live inside cat's RBC // connect to RBC extracellular nutrients via a pore
- 50% domesticated cats and feral cats carry bacteria



- Fleas bites cat and extract blood // fleas defecate and cat pick up feces on their claws – scratches person to infects person with bacteria
- Papule at site of scratch within 3 to 4 days // advance to lymph nodes with swelling associated with fever and malaise for couple weeks – self limiting

Vector Transmitted Diseases

- Plague
- Lyme Disease
- Typhus
- Rocky Mountain Spotted Fever

Plague

- Yersinia pestis – gram-negative bacillus
- Normally, disease of rats transmitted to humans by fleas (Xenopsylla cheopis) // endemic in ground squirels and prairie dogs
- Bacteria causes biofilm in flea esophagus // flea continues to try to feed which spreads disease
- Bacteria in humans enter blood stream and proliferate in lymph nodes
- Swelled lymph nodes call buboes (bubonic plague) // able to grow inside macrophage

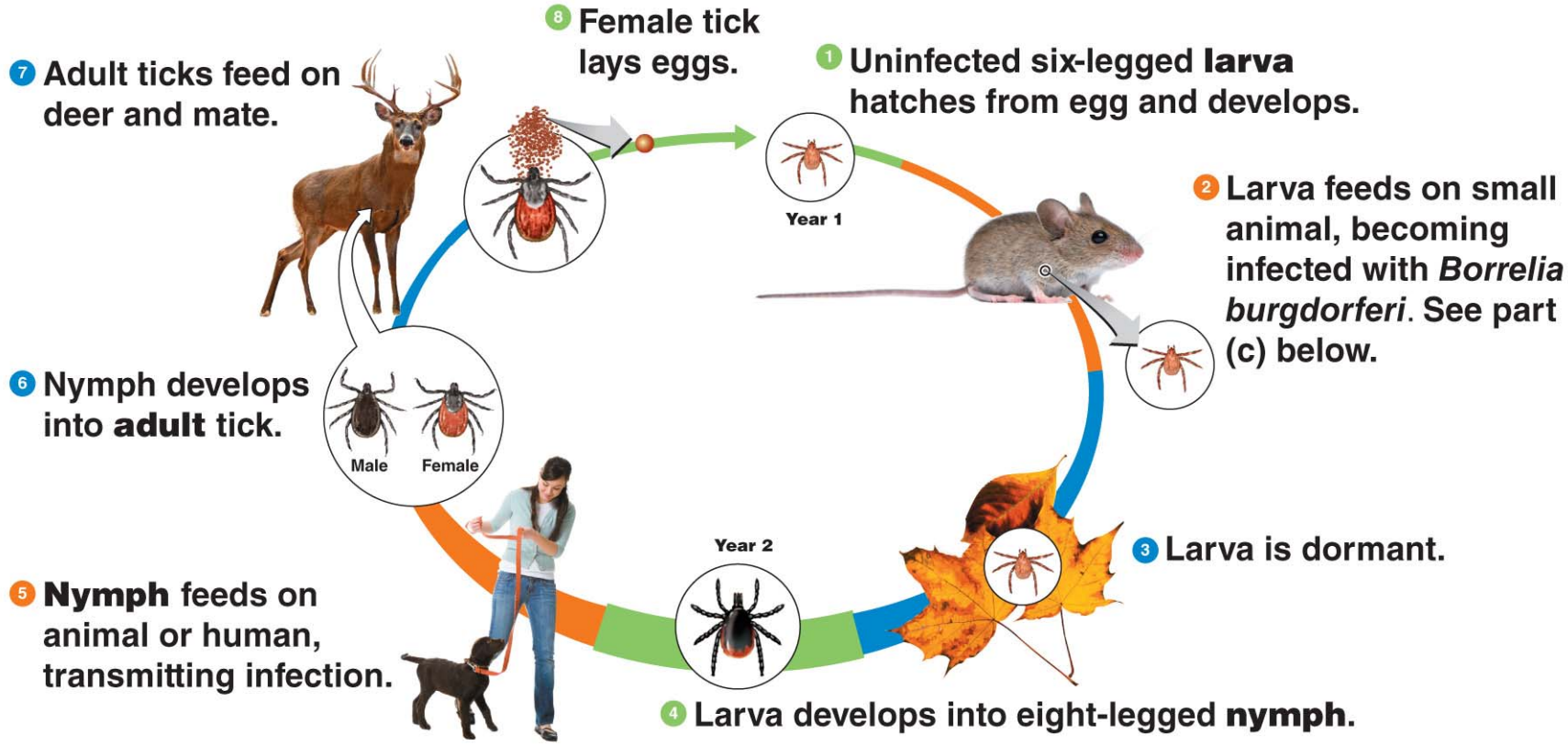
Plague

- Septicemic plague – enters blood to cause septic shock
- Pneumonic plague – mortality rate 100% if not recognized and treated within 12 to 15 hours
- Repeated pandemics between 542 and 767 // killed more than 25% in fourteenth and fifteenth centuries // plague responsible for social changes in European society
- Last major outbreak in Los Angeles in 1924 - 1925
- Vaccine available // exposed treated with prophylactic antibiotics – streptomycin and tetracycline

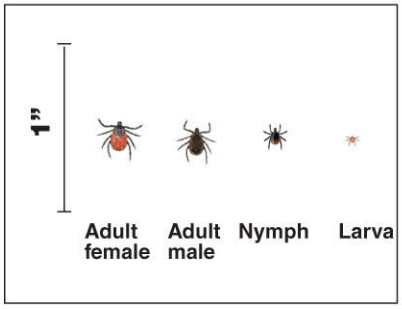
Lyme Disease

- Borrelia burgdorferi – spirochete // now known as most common tickborne disease in United States
- 1975 cluster of infections misdiagnosed as rheumatoid arthritis in Lyme, Connecticut
- Not contagious between family members // suggested transmitted by tick
- Field mice animal reservoir // ticks feed on infected mice and transfer to humans // deer maintain infected fleas because fleas mate on deer

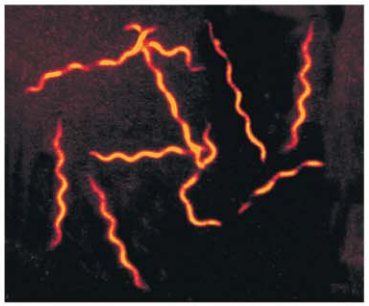
- First symptom rash at bite site
- Flue like symptoms follow in couple weeks // antibiotics effective
- Not treated // second phase – heart problems, facial paralysis, oppressive fatigue, encephalitis
- Third phase // months to years later – joint damage // similar to later stages of syphilis



(a) The tick, *Ixodes scapularis*, has a 2-year life cycle in which it requires three blood meals. The tick is infected by its first blood meal and can pass on the infection to a human in its second.



(b) Comparison of actual tick sizes.



(c) The cause of Lyme disease, *Borrelia burgdorferi.*

KEY
- Spring
- Summer
- Fall and Winter

Typhus

- Rickettsia – obligate intracellular parasite of eukaryotes // cause various types of typhus
- Rickettsia prowazekii = bacteria that causes epidemic typhus (louse borne typhus)
- Rickettsia spread by arthropods (e.g. lice) // the bacteria infect and multiply in epithelial cells of vascular system // inflammation cause local blockage and rupture of blood vessels
- R. prowazekki grows in gastrointestinal tract of the louse // when louse bites human to feed it defecates – human itches bite and forces bacteria into wound

Typhus

- High and prolonged fever last at least two weeks // while Rickettsia invade blood vessels // affects brain
- Mortality high when untreated // Tetracycline effective // vaccines now available
- Historically – killed more solders than combat
- Anne Frank, teenage writer of the famed World War II diary died from Typhus in concentration camp

Spotted Fevers (Rocky Mountain Spotted Fever)

- Rickettsia ricettsii – best known Rickettsia disease in United States
- Actually more common in southeastern US
- In endemic areas // 1 out of 1,000 ticks infected
- Different ticks (dog ticks vs wood ticks) carriers in different regions of US
- Measles like rash (palms and hands), fever, and headache // 3% mortality rate due to kidney and heart failure
- Tetracycline effective if administered early enough
- No vaccine available

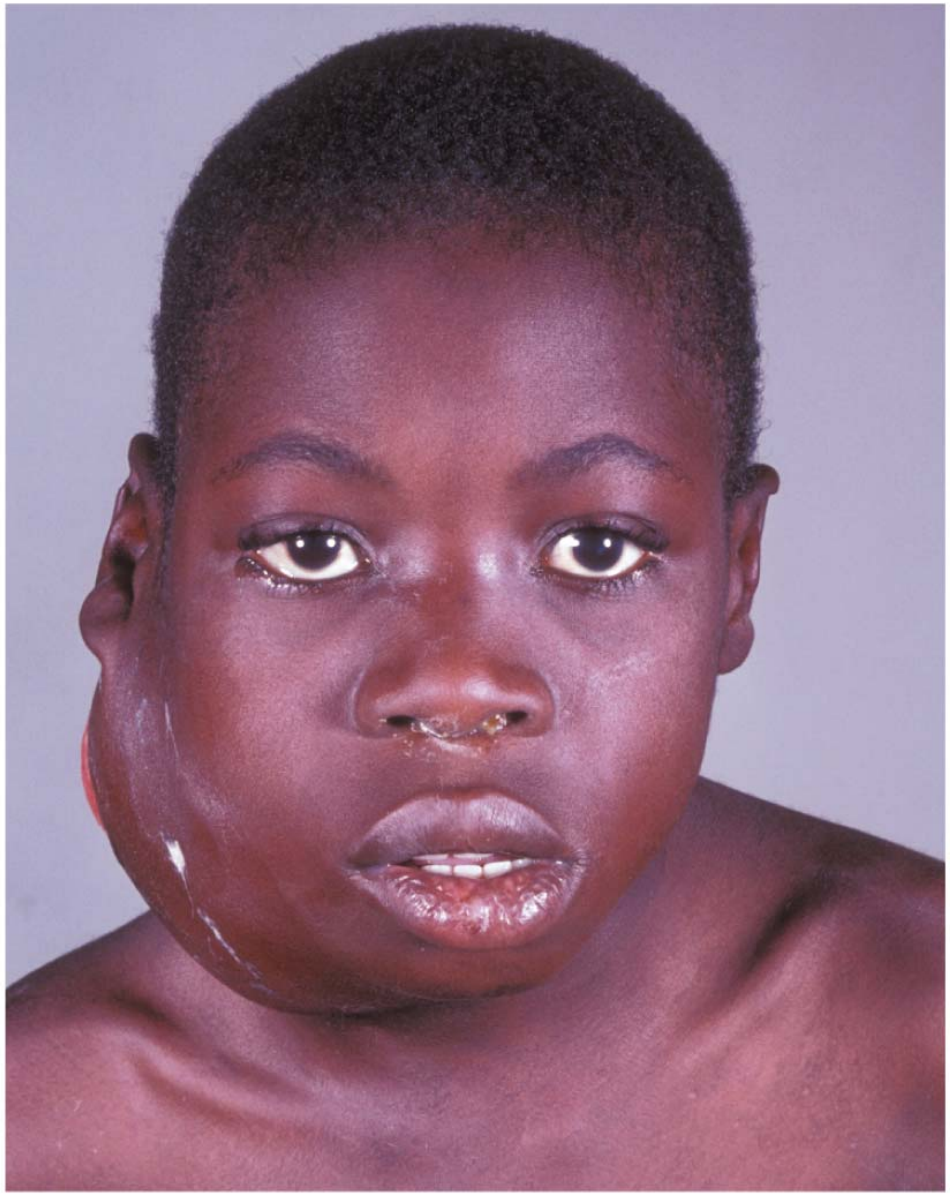
Viral Diseases

- Burkitt's Lymphoma
- Infectious Mononucleosis
- Chikungunya Fever
- Hemorrhagic Fevers
  - Yellow Fever
  - Dengue
  - Ebola

Burkitt's Lymphoma

- Common childhood cancer in Africa // fast growing tumor in jaw
- Historically important // Virologist Tony Epstein and student Yvonne Barr – biopsies on patient found virus was cause – first time cancer associated with virus (Epstein Barr Virus or human herpes virus 4)
- Malaria impairs immune system so it does not eliminate the virus // results in Burkitt's lymphoma
- EB virus so adaptive to humans it is our most effective parasite // universally present worldwide
- Rarely causes disease

Burkitt's Lymphoma

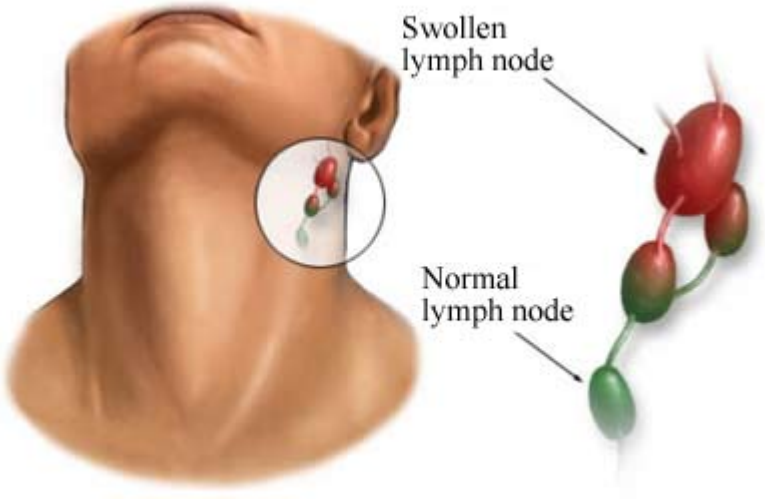


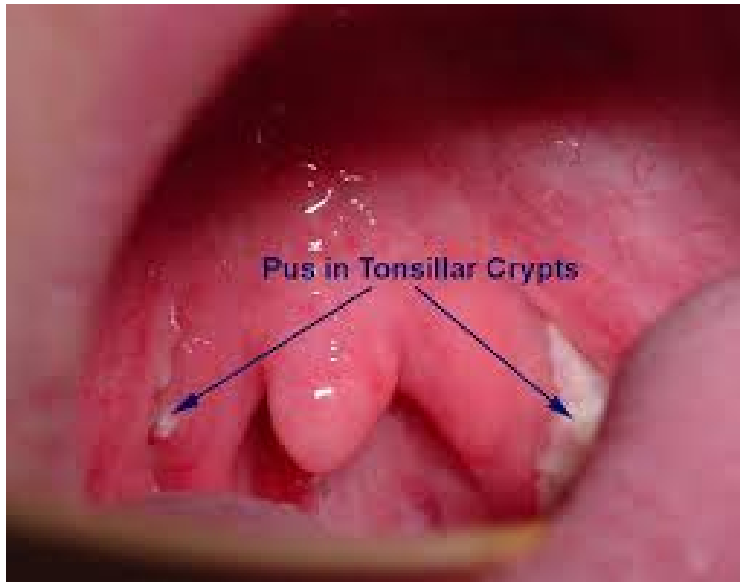
Infectious Mononucleosis

- Disease symptoms fever, sore throat, swollen lymph nodes in the neck and general weakness
- Serological test indicates EB virus // same virus which causes Burkitt's lymphoma in Africa also causes infectious mononucleosis
- EB infection occurs in early childhood in developing countries // 95% of adults have acquired antibodies
- In US childhood infections usually asymptomatic // if delayed until adulthood more symptomatic related to intense immunological response // peak age 15 to 25
- Rarely cause death // results from ruptured spleen
- Recovery occurs in a few weeks

Infectious Mononucleosis

- Persistent infection in the mouth and throat
- Route of infection from saliva (kissing or drinking from same glass) // incubation period 4 to 7 weeks
- Resting B cells in lymphoid tissue site of EB virus replication
- Symptoms are attributed to response of T cells





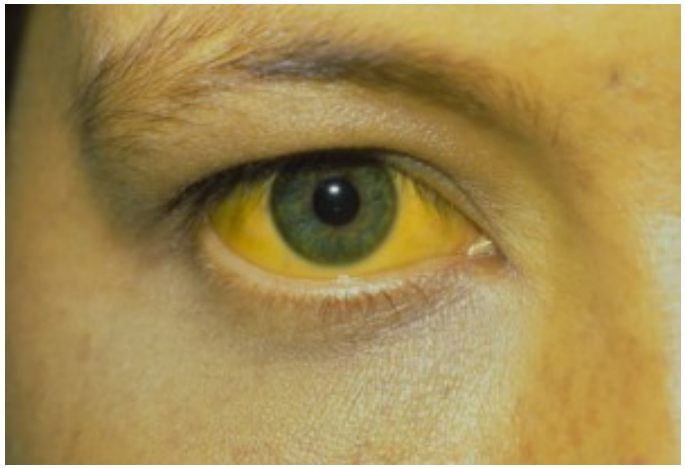
Chikungunya Fever

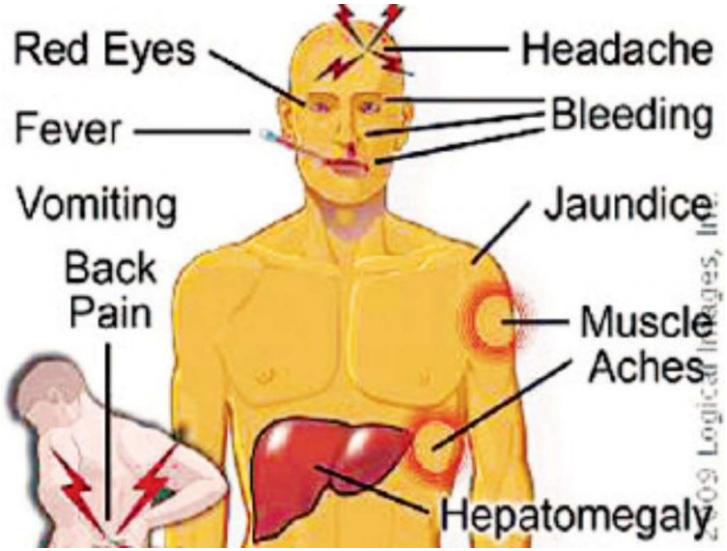
- Caused by a mutation in virus which causes the western and eastern equine encephalitis
- Virus adapted to multiply in the Aedes aegypti mosquito (note: also vector for Zeka virus)
- Symptoms are high fever, severe crippling joint pains with or without rash and blisters // last for weeks to months
- A. albopictus also vector and this mosquito well adapted to urban communities and cold climate

These mosquitoes can be identified by the white stripes on their black bodies and legs. They are aggressive daytime biters, with peak feeding activity at dawn and dusk.

Yellow Fever

- Fever, chills, headache, nausea, and vomiting // followed by jaundice
- Yellow color from liver damage // billirubin builds up in blood because liver can not secrete bile pigments into gal bladder
- Aedes aegypti mosquito vector // endemic in tropics
- Mortality rate 20% // No specific treatment
- Vaccine is attenuated viral strain // very effective

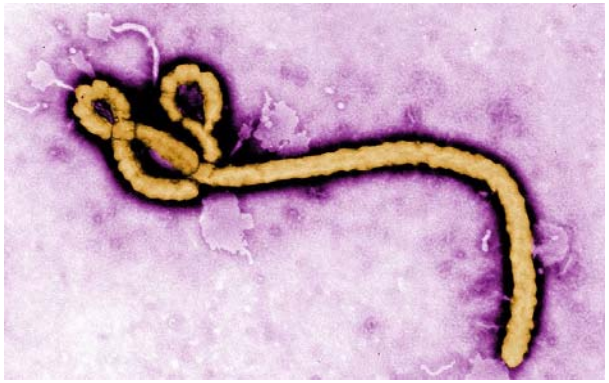




Dengue

- Similar to yellow fever but milder // also transmitted by mosquito
- Fever, rash, severe muscle and joint pain (nickname = breakbone fever)
- Caribbean reporting increasing numbers of dengue fever
- Dengue hemorrhagic fever // severe form – antibodies from previous infection combine with virus and cause shock // kills children in a few hours

Ebola



- Ebolavirus damages the walls of blood vessels // interferes with blood coagulation
- Blood leaks into tissue and from orifices
- Mortality approaching 90%
- Natural animal resource is African fruit bat
- Once human infected shed virus in body secretions and blood
- Local burial customs of washing deceased body contributed to spread of disease

Protozoan Diseases

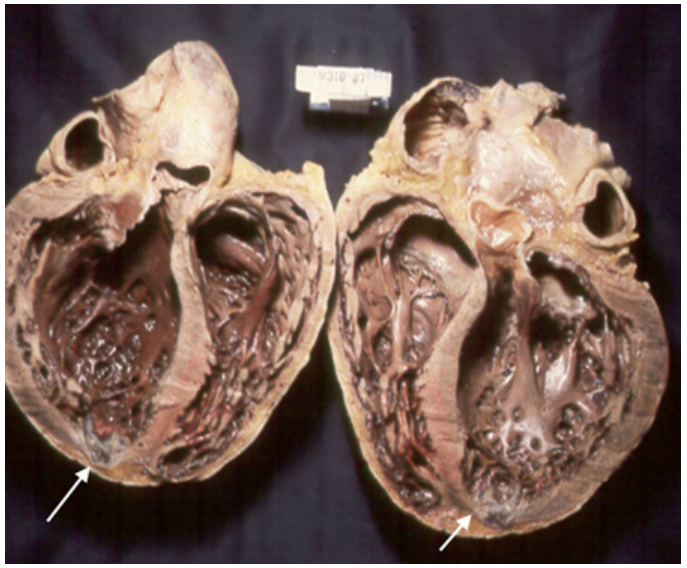
- Chagas' Disease
- Toxoplasmosis
- Malaria

Chagas' Disease

- Trypanosoma cruzi – flagellated protozoan
- Endemic in South America and Central America // infects 18 million and kills 50,000 annually
- Reservoir is wide variety of wild animals including rodents, armadillos // arthopod vector is the "kissing bug" – so named because it bites people near their mouth
- Protozoa deposited on human skin when kissing bug bites and defecates // human itches bite and rubs protozoa into wound

Chagas' Disease

- Acute stage fever and swollen glands
- 20% - 30% infected cases develop 20 years later nerve damage regulating peristalsis in esophagus and colon – unable to transport food in GI tract // megaesophagus and megacolon
- 40% infected cases result in damage to heart
- Disease difficult to treat with chemotherapy because protozoa multiply intracellularly



Toxoplasmosis

- Toxoplasma gondii – spore forming protozoan

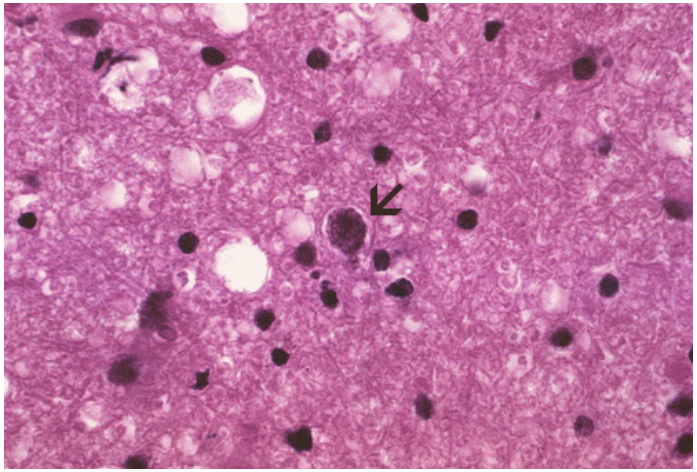
- Cats are an essential part of the T. gondii life cycle // large number of cats infected but cause no illness in cat (rodents infected with T. gondii lose their normal avoidance behavior towards cats!)

- Microbe goes through only sexual phase in the intestinal tracct of cats // millions of oocysts shed in feces for 7 to 12 days contaminating soil and water // ingested by other animals (including humans)

- Immune system becomes increasing effective // chronic phase infected host cell forms “tissue cyst” // persist for years especially in the brain

Toxoplasmosis

- Consuming undercooked food infects people with tachyzoites or tissue cysts
- Primary danger is congenital infection of a fetus // still births, severe brain damage or vision problems
- 400,000 congenital infections per year



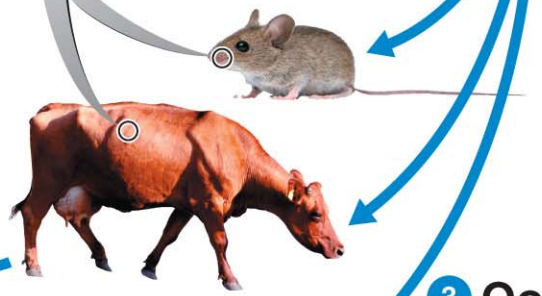
1 Immature oocyst is shed in cat feces.

Sporogony

2 Mature oocysts develop by sporogony and contain two sporocysts, each with four infective sporozoites.

3 Oocysts can infect many hosts, including mice, domestic animals, and humans, via ingestion.

Intermediate hosts



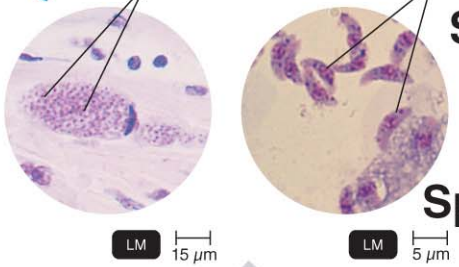
If humans eat undercooked meat containing tissue cysts, they may become infected.

If a pregnant woman accidentally ingests oocysts (contacted when changing a cat litter box), prenatal infection of the fetus may occur.

Definitive host

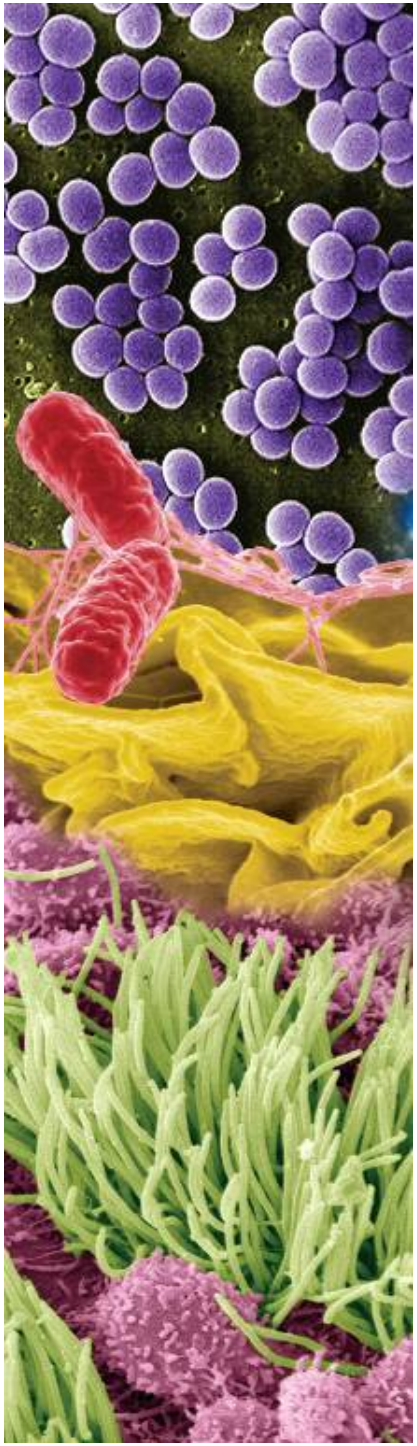
Bradyzoites in tissue cyst

Tachyzoites



4 Sporozoites from ingested oocysts invade animal tissue and develop into bradyzoites within tissue cysts or into tissue-invading tachyzoites.

5 Cat ingests bradyzoites in tissue cysts of animals, usually mice.



Malaria

Malaria has been one of the greatest afflictions throughout human history

same ranking as bubonic plague, influenza, and tuberculosis

dominant protozoan disease

Threatens 40% of the world's population every year

name comes from the Italian words **mal** (bad) and **aria** (air)

Malaria // Signs and Symptoms

10-day incubation period, first symptoms are malaise, fatigue, vague aches, and nausea /// with or without diarrhea // followed by chills, fever, and sweating

symptoms occur at 48- or 72-hour intervals, as the result of synchronous red blood cell rupture

Interval, length, and regularity of symptoms reflect the type of malaria // Falciparum malaria: persistent fever, cough, and weakness for weeks without relief

Malaria *II* Signs and Symptoms

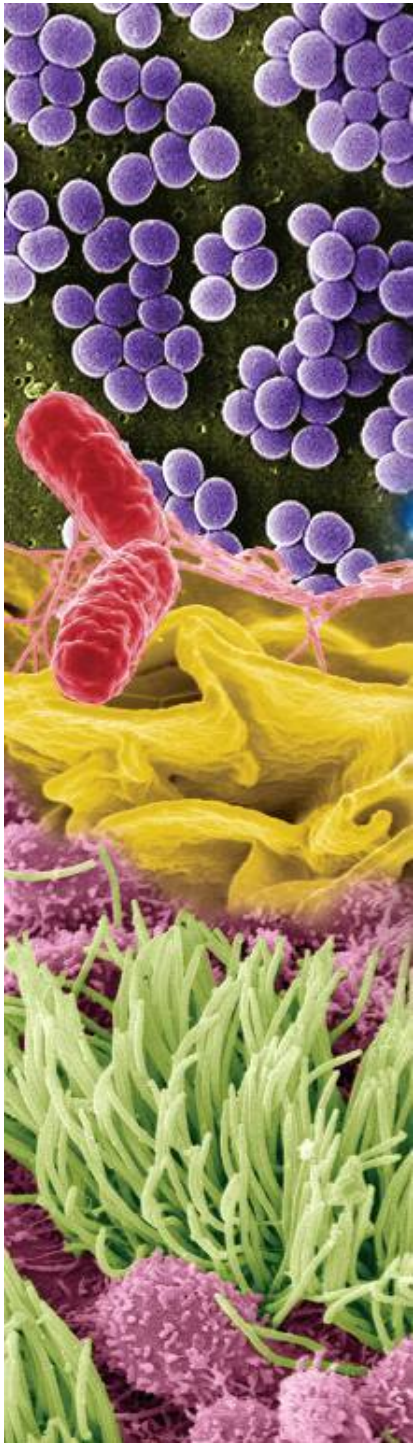
Complications of falciparum malaria /// hemolytic anemia from lysed red blood cells

organ enlargement and rupture due to cellular debris that accumulates in the spleen, liver, and kidneys

Cerebral malaria: one of the most serious complications of falciparum malaria

small blood vessels in the brain become obstructed due to RBCs adhering to blood vessel walls

decrease in oxygen in the brain can cause coma and death



Malaria *II* Signs and Symptoms

In general, malaria has the highest death rate in the acute phase, especially in children

Malaria caused by *Plasmodium vivax* and *P. ovale* are subject to relapses

infected liver cells harbor dormant protozoans for up to 5 years

Causative Agent

Plasmodium species are protozoans in the sporozoan group

Four species: *P. malariae, P. vivax, P. falciparum,* and *P. ovale,* each showing variations in pattern and severity of disease

humans are the primary vertebrate hosts

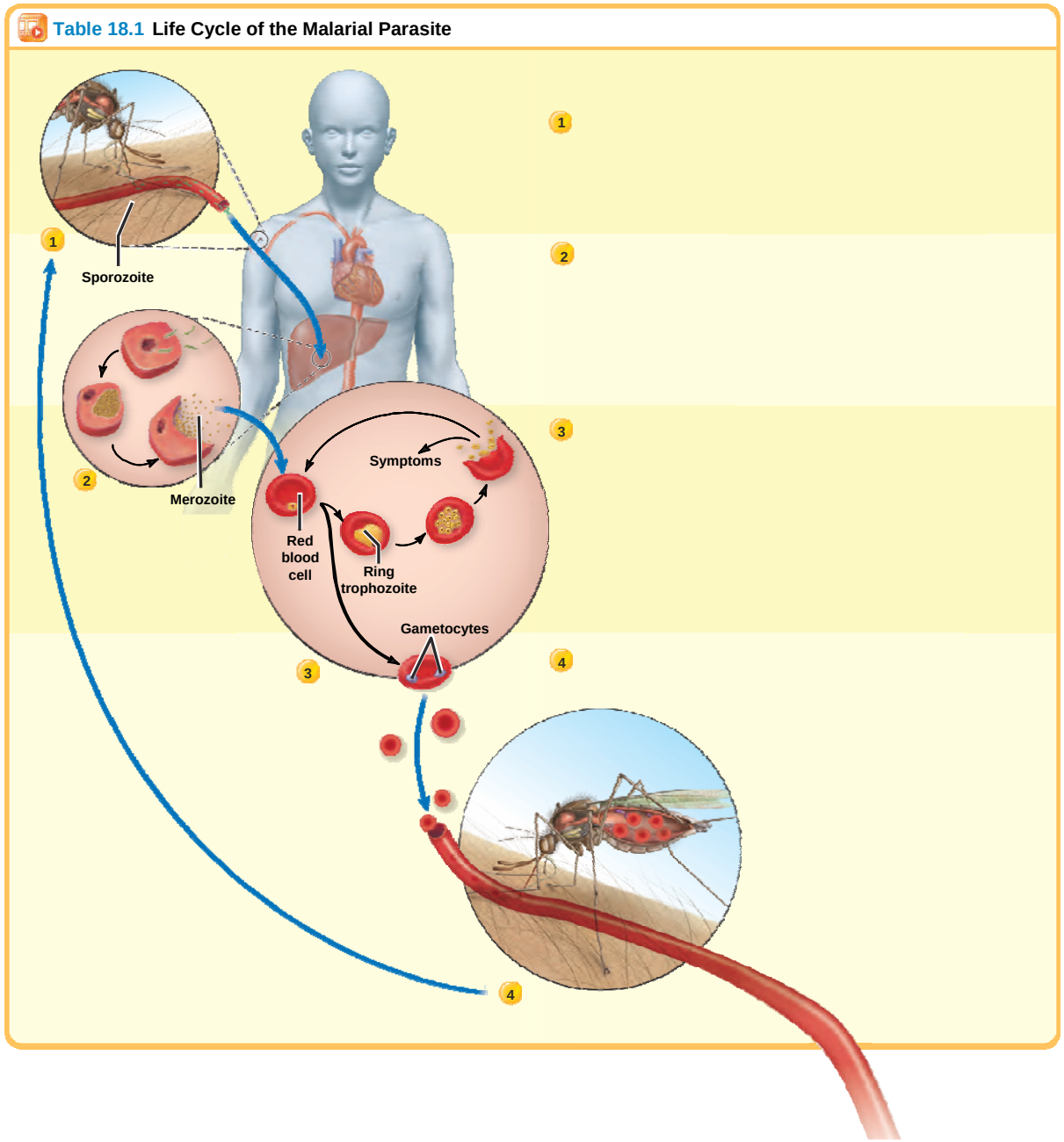
Malaria // Causative Agent (cont.)

Development of the malarial parasite is divided into two distinct phases

asexual phase: carried out in the human

sexual phase, carried out in the mosquito

Life Cycle of the Malarial Parasite

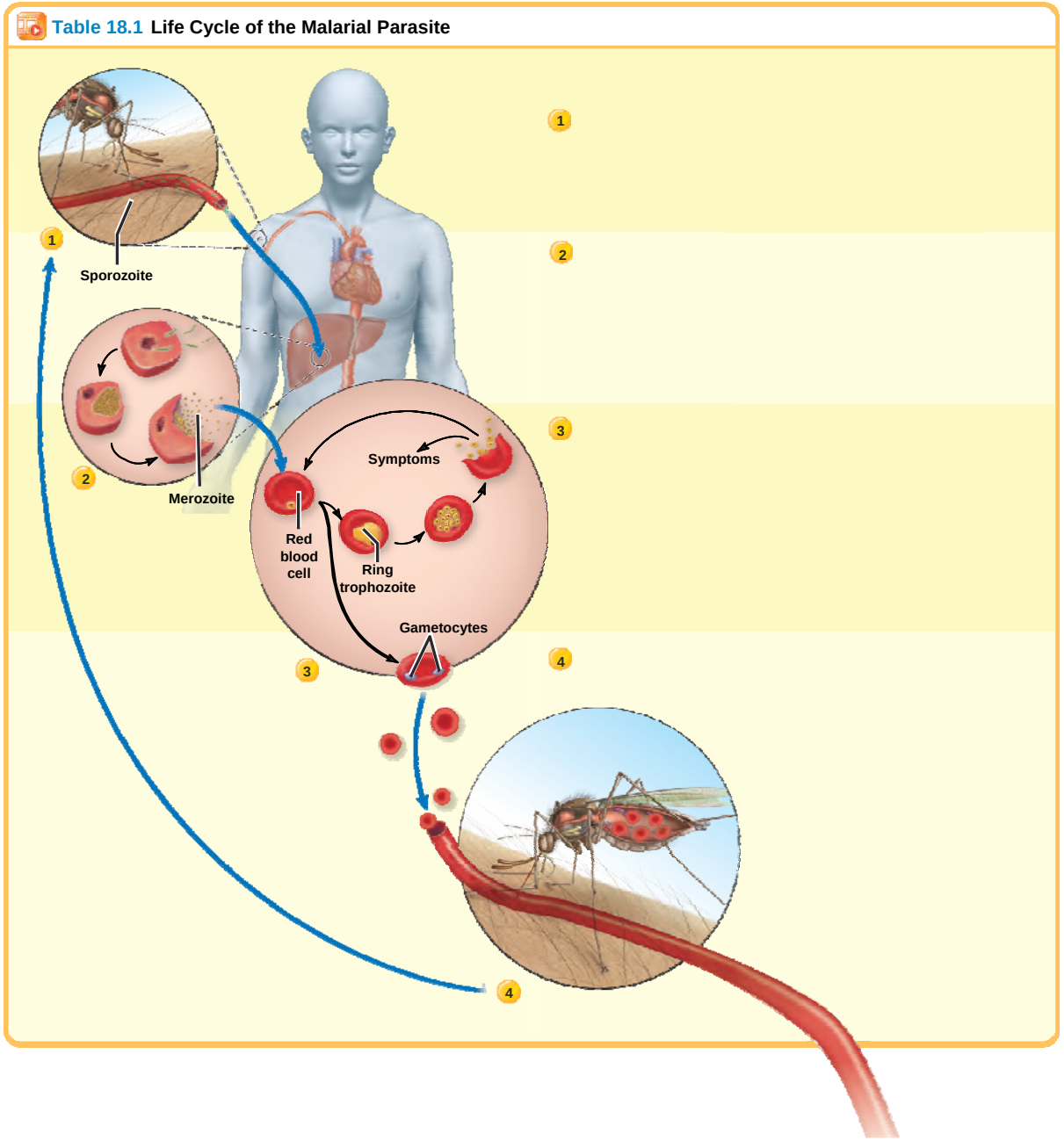


#1

The asexual phase (and infection) begins when an infected female Anopheles mosquito injects saliva containing anticoagulant into a capillary in preparation for taking a blood meal.

In the process, she inoculates the blood with motile, spindle-shaped asexual cells called sporozoites (Gr. sporo, seed, and zoon, animal).

Life Cycle of the Malarial Parasite



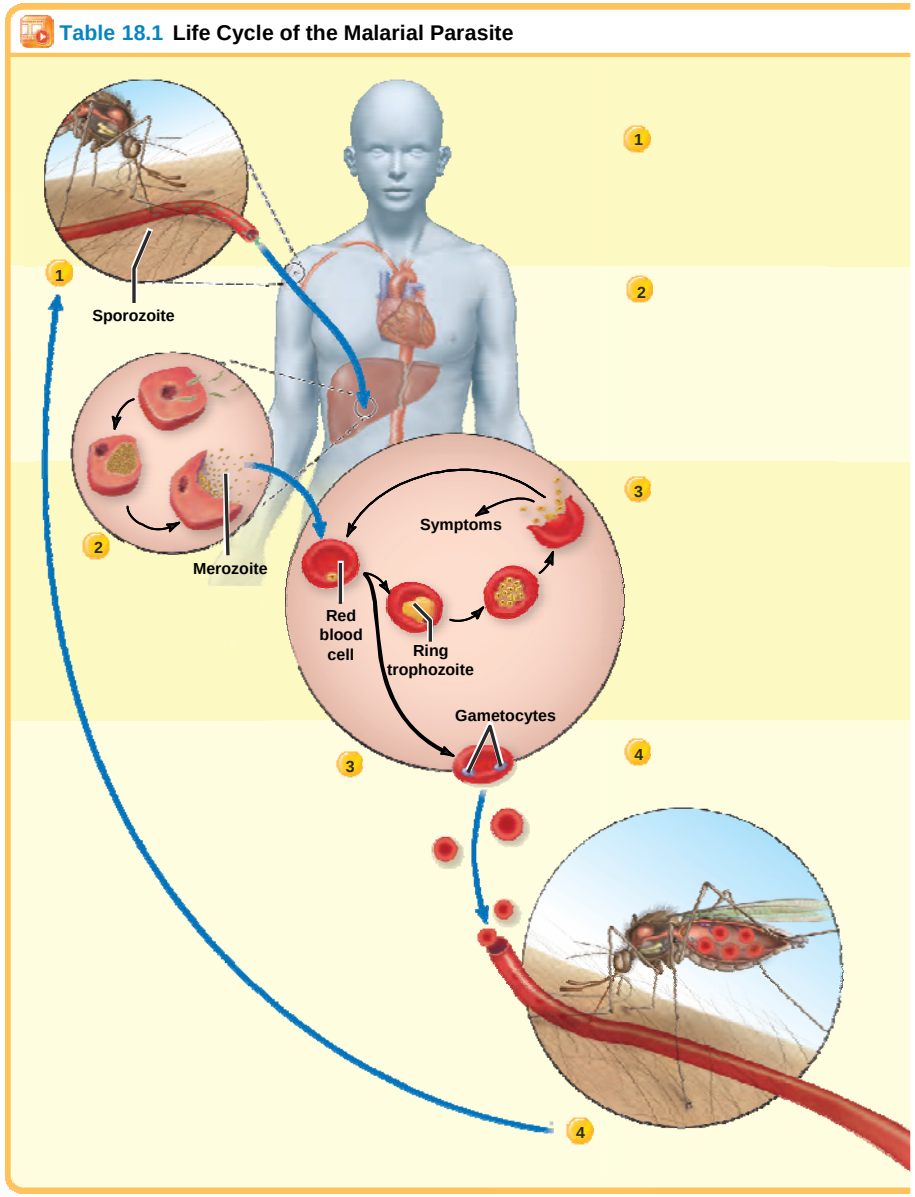
#2

The sporozoites circulate through the body and migrate to the liver in a short time. Within liver cells, the sporozoites undergo asexual division called schizogony (Gr. schizo, to divide, and gone, seed), which generates numerous daughter parasites, or merozoites.

This phase of pre-erythrocytic development lasts from 5 to 16 days, depending upon the species of Plasmodium.

Its end is marked by eruption of the liver cell, which releases from 2,000 to 40,000 mature merozoites into the circulation.

Life Cycle of the Malarial Parasite



#3

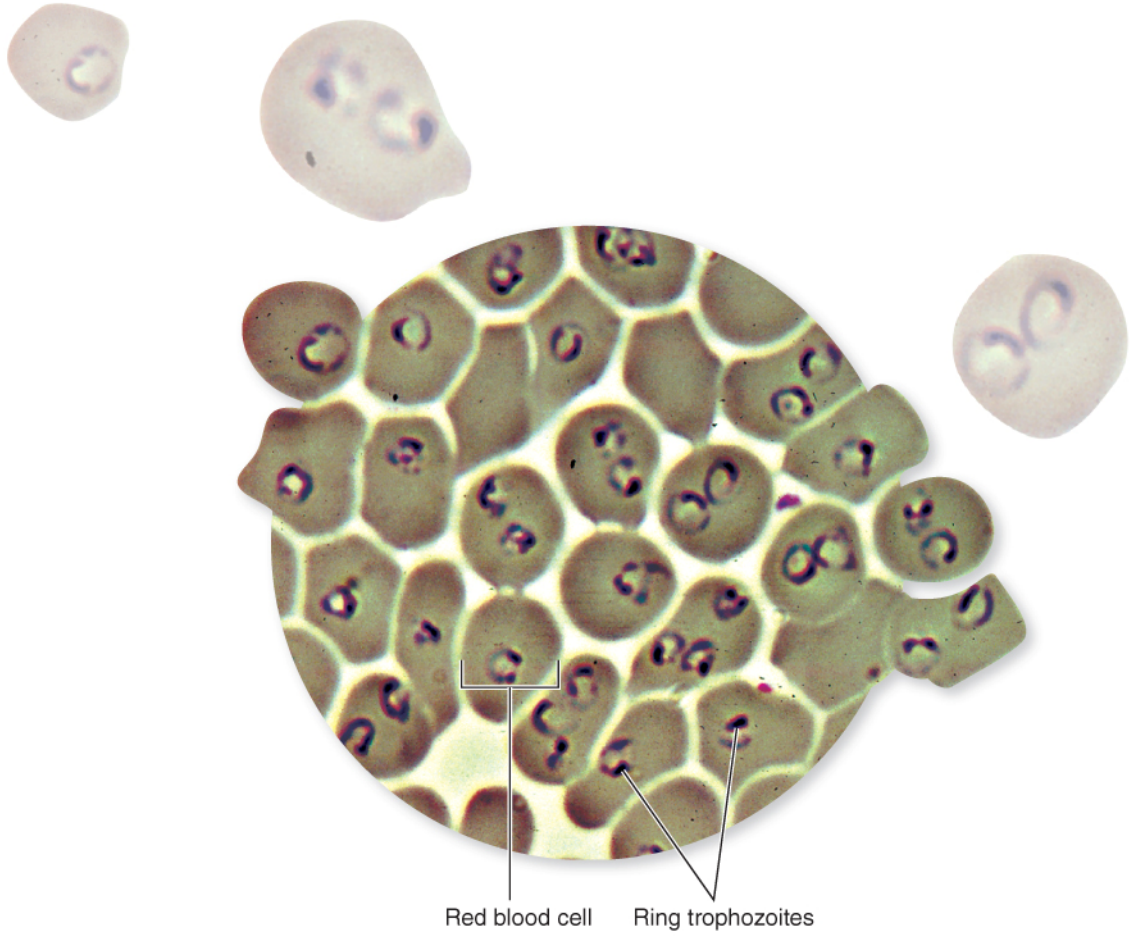
During the erythrocytic phase, merozoites attach to special receptors on RBCs and invade them, converting in a short time to ring-shaped trophozoites.

This stage feeds upon hemoglobin, grows, and undergoes multiple divisions to produce a cell called a schizont, which is filled with more merozoites.

Bursting RBCs liberate merozoites to infect more red cells.

Eventually, certain merozoites differentiate into two types of specialized gametes called macrogametocytes (female) and microgametoctyes (male).

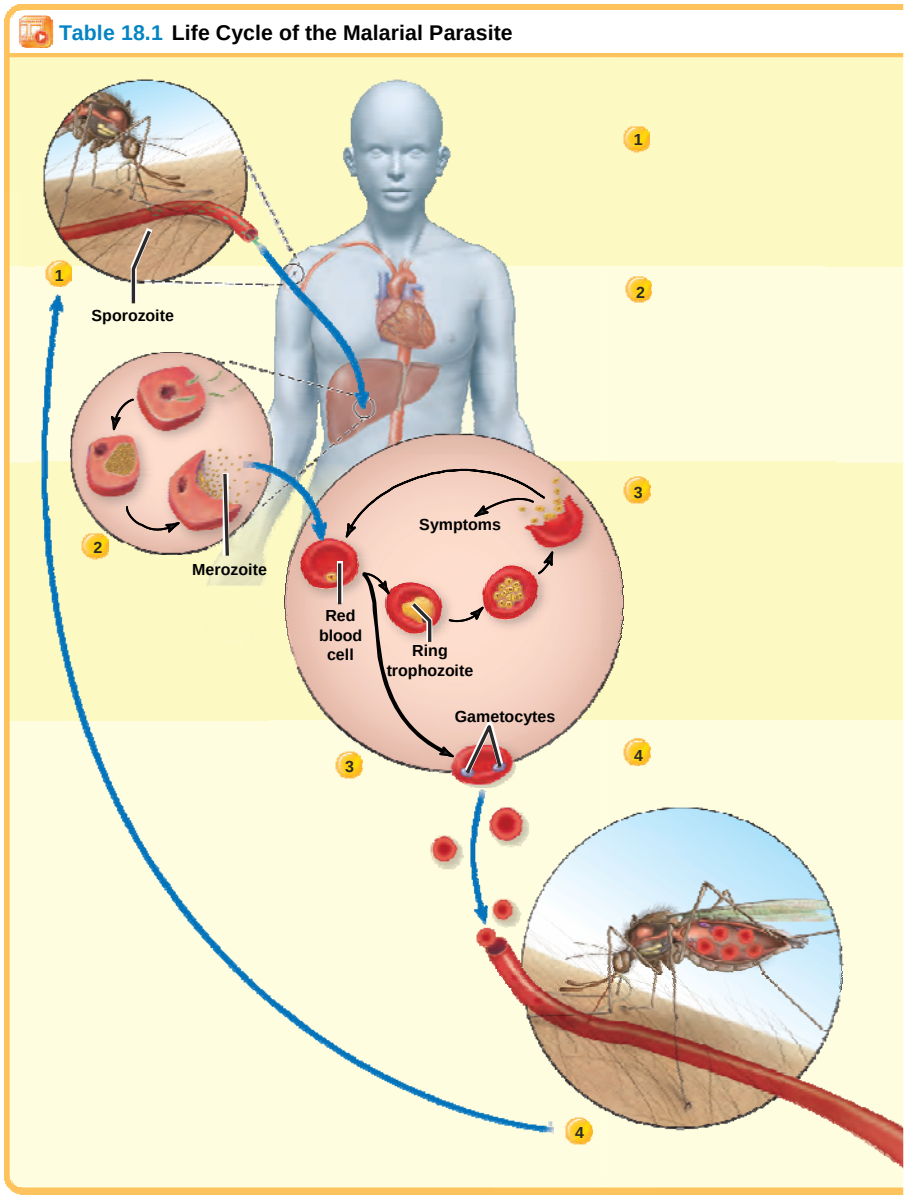
Because the human does not provide a suitable environment for the next phase of development, this is the end of the cycle in humans.



Ring trophozoite stage in
Plasmodium falciparum infection

Courtesy of Stephen B. Aley, PhD., University of Texas at El Paso

Life Cycle of the Malarial Parasite



#4

The sexual phase (sporogony) occurs when a mosquito draws infected red blood cells into her stomach.

In the stomach, the microgametocyte releases gametes that fertilize the larger macrogametocytes.

The resultant diploid cell (ookinete) implants into the stomach wall of the mosquito, becoming an oocyst, which undergoes multiple mitotic divisions, ultimately releasing sporozoites that migrate to the salivary glands and lodge there.

This event completes the sexual cycle and makes the sporozoites available for infecting the next victim.

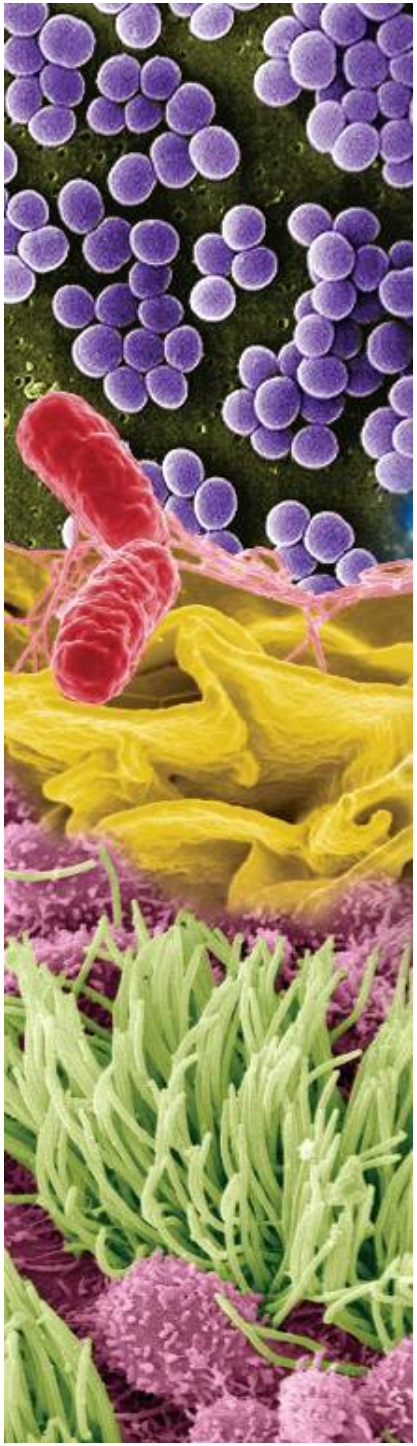
Malaria // Pathogenesis and Virulence Factors

Invasion of merozoites into RBCs leads to the release of fever-inducing chemicals into the bloodstream // chills and fevers often occur in a cyclic pattern

Plasmodium also metabolizes glucose at a very high rate, /// leading to hypoglycemia in the human host

Damage to RBCs results in anemia

Accumulation of malarial products in the liver and the immune stimulation in the spleen can lead to enlargement of these organs



Malaria // Transmission and Epidemiology

Primarily spread by the female *Anopheles* Mosquito

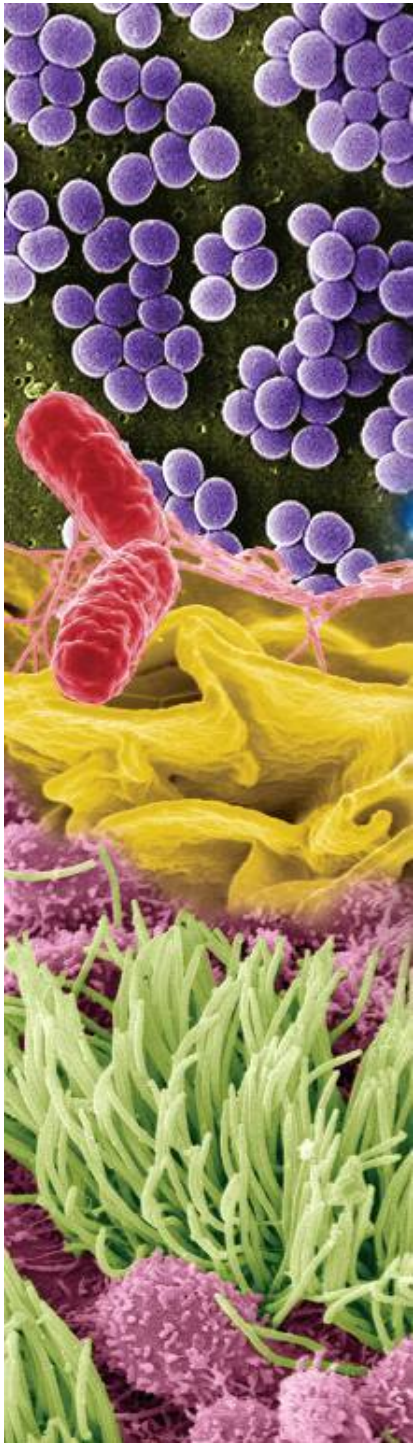
malaria was once distributed throughout the world

mosquito control in temperate areas has restricted it to a belt around the equator

300 – 500 million new cases are still reported each year, 90% of them in Africa

<u>most frequent victims are children and young adults; 2 million die annually</u>

a form of the protozoan causes damage to the placenta and leads to excess mortality in fetuses and newborns



Malaria // Transmission and Epidemiology

Total case rate in the U.S. is 1,000 – 2,000 new cases a year

most occur in immigrants or travelers to endemic areas

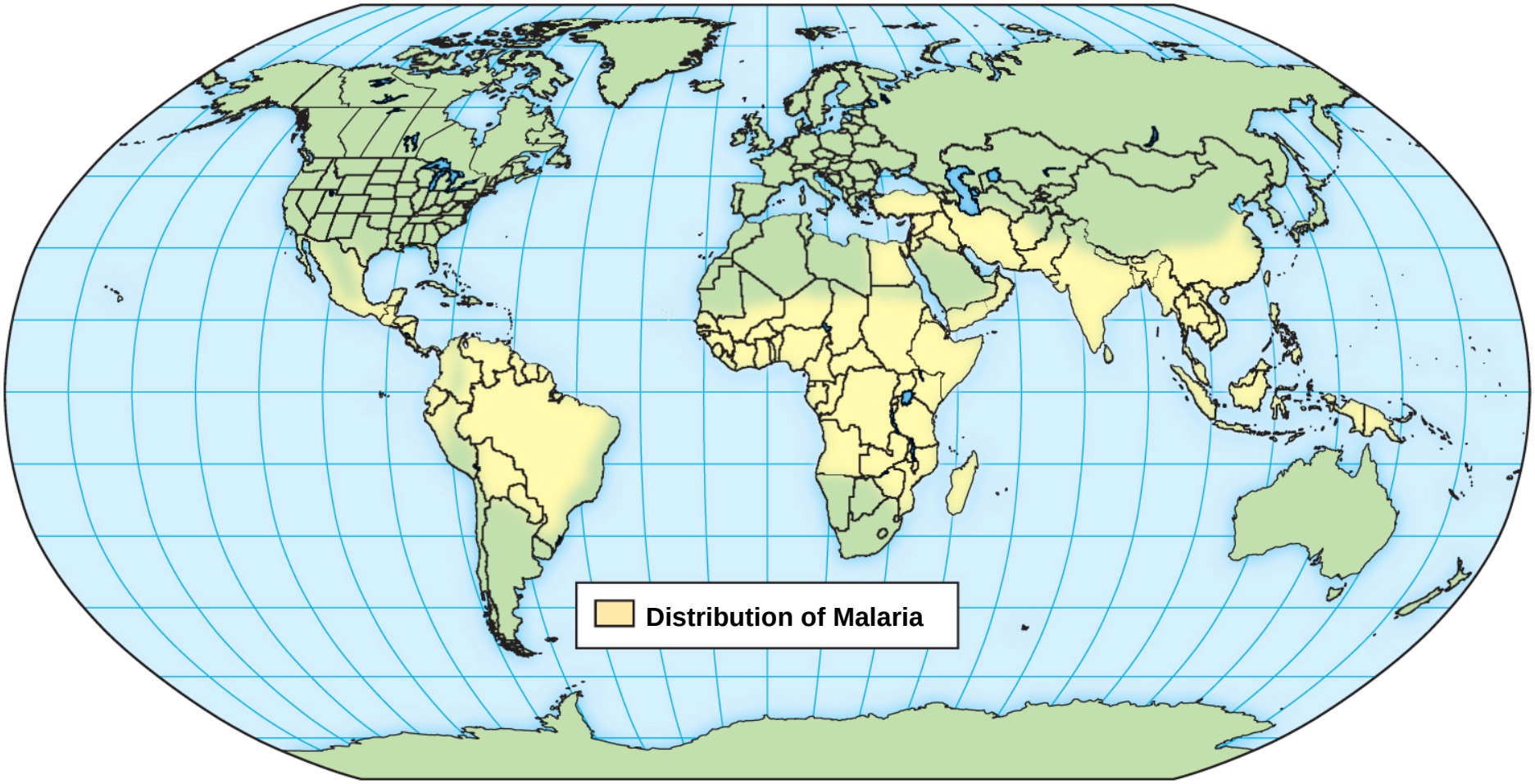
Culture and Diagnosis

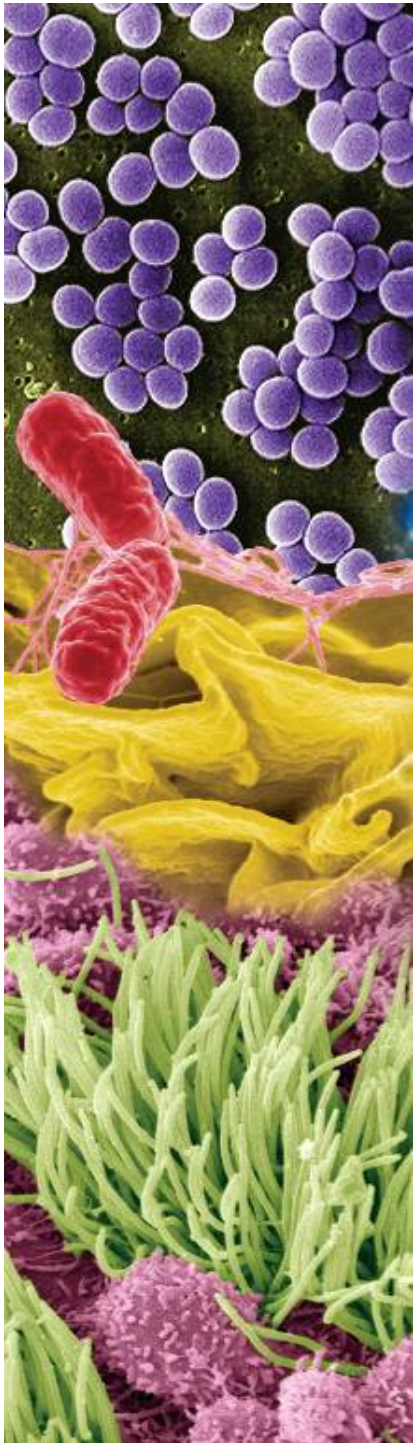
Definitive diagnosis by the discovery of a typical *stage of Plasmodium in stained blood smears*

newer serological procedures have made diagnosis more accurate while requiring less skill to perform

other indications are knowledge of the patient's residence or travel in endemic areas and symptoms of recurring chills, fever, and sweating

The Malaria Belt





Malaria // Prevention

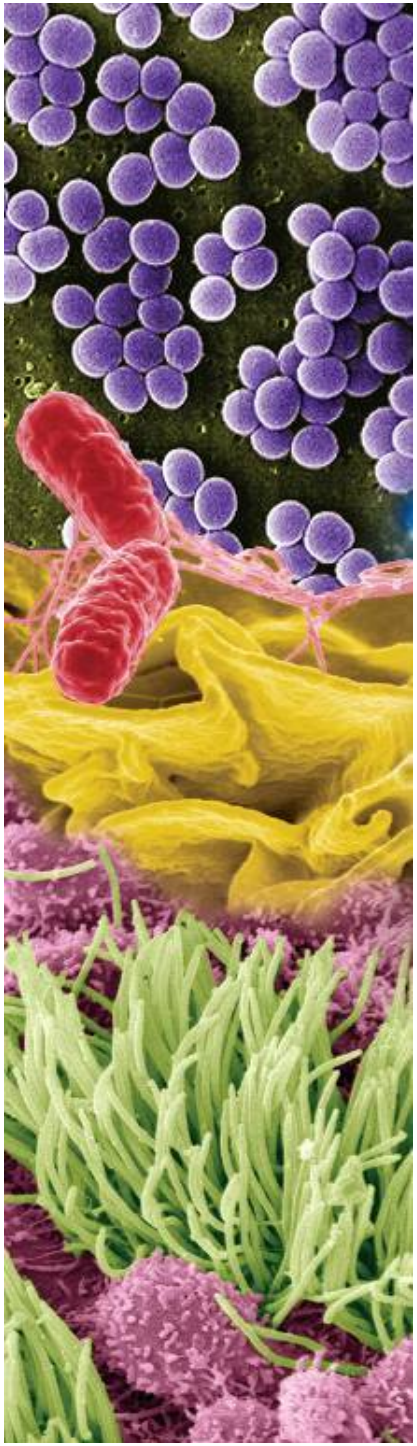
World health officials have tried for decades to eradicate malaria

- most recent attempt is by the United Nations-backed Global Malaria Action Plan, which hopes to cut malaria by 75% between 2000 and 2015 and reduce deaths to zero

Prevention is attempted through long-term mosquito abatement and human chemoprophylaxis

- elimination of standing water that can serve as breeding sites

- spraying of insecticides to reduce populations of adult mosquitoes

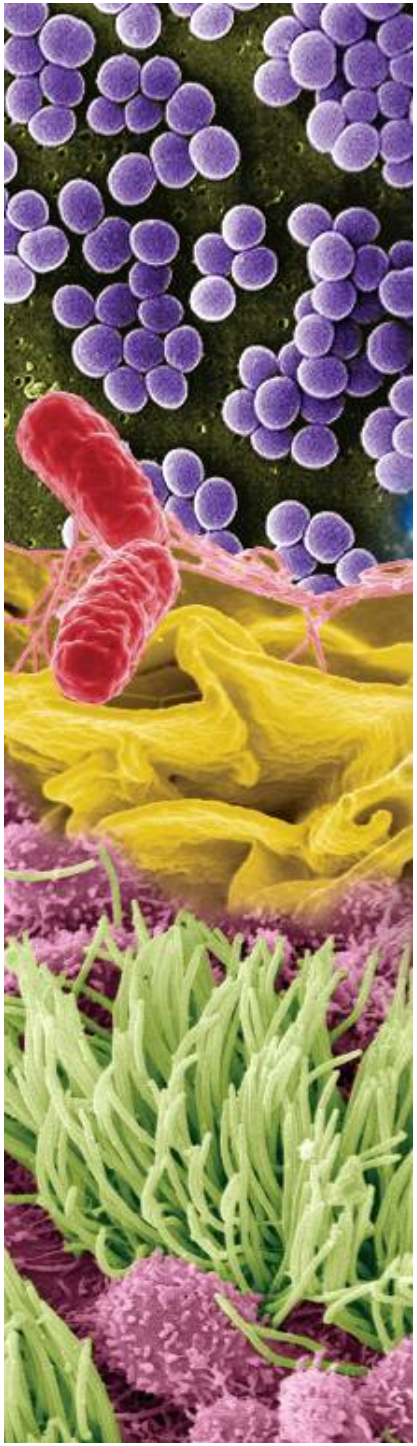


Malaria // Prevention

Scientists have attempted introducing sterile male mosquitoes into endemic areas to reduce mosquito populations

Humans reduce their risk by

- using netting, screens, and repellants
- remaining indoors at night
- taking weekly doses of antimalarial drugs
- Western travelers to endemic areas are usually prescribed antimalarials for the duration of their trip



Malaria // Prevention (cont'd)

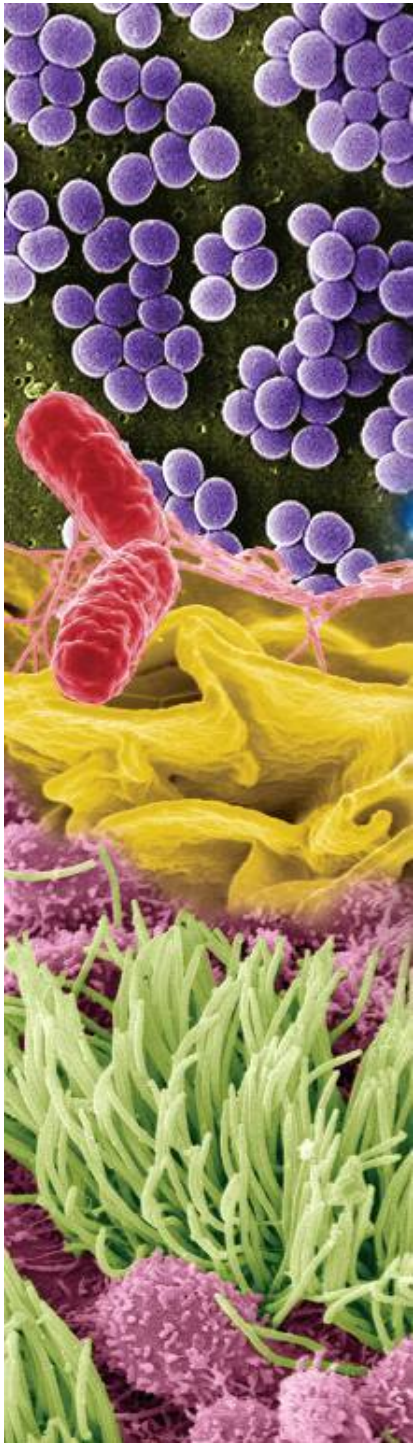
People with a recent history of malaria are not allowed to give blood

WHO and other international organizations focus efforts to distribute bed nets and to teach people how to dip the nets into insecticide

use of bed nets has reduced childhood mortality from malaria by 20%

bed-net use has tripled in 16 of 20 sub-Saharan African countries since 2000

even with massive efforts undertaken by the WHO, the prevalence of malaria in endemic areas is still high



Malaria // Prevention (cont'd)

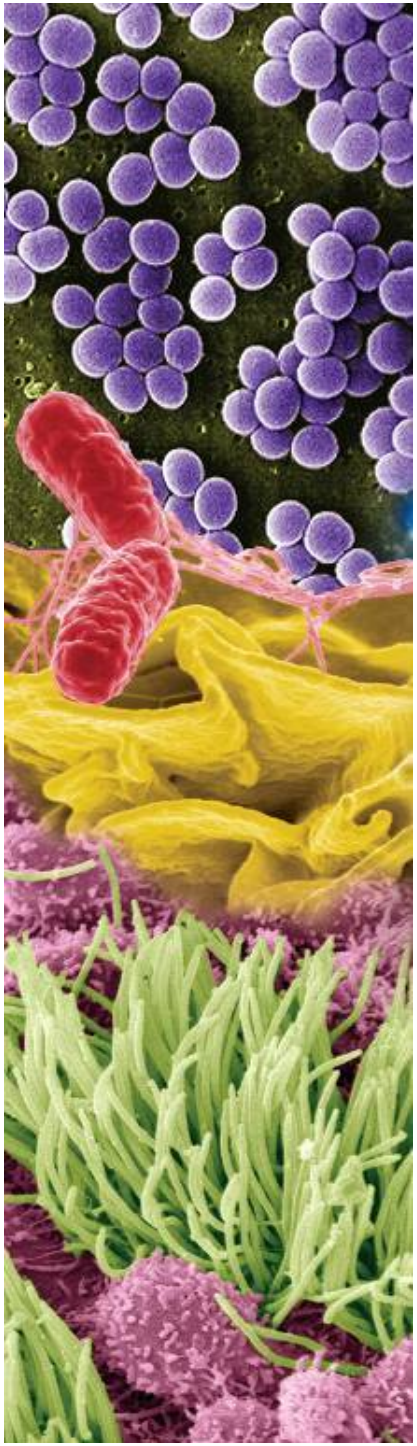
The best protection could come from a malaria vaccine

scientists have struggled for decades to develop one

a successful malaria vaccine must be capable of striking a diverse and rapidly changing target

scientists estimate the parasite has 5,300 antigens

another potentially powerful strategy is the use of interfering RNAs in the mosquitoes to render them resistant to Plasmodium infection



Malaria // Treatment

Quinine has long been a mainstay of malaria Treatment

- chloroquine, the least toxic type, is used in nonresistant forms of the disease

- mefloquine or pyrimethamine plus sulfadoxine (Fansidar) are used where resistant strains of *P. falciparum* and *P. vivax* predominate

Artemisinin, a plant compound, has been most effective, although resistance has been found in Cambodia

- the WHO recommends only administering arteminsinin in combination with other antimalarials to prevent resistance development

Malaria

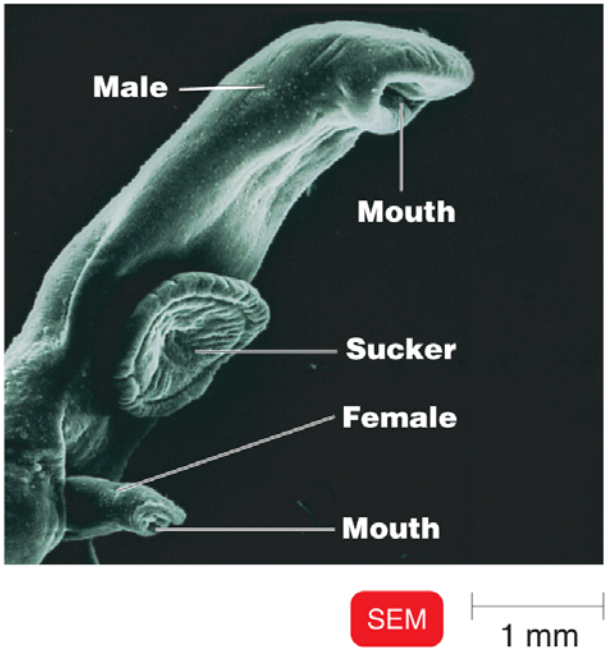
Causative Organism(s)	Plasmodium falciparum, P. vivax, P. ovale, P. malariae
Most Common Modes of Transmission	Biological vector (mosquito), vertical
Virulence Factors	Multiple life stages; multiple antigenic types; ability to scavenge glucose, cytoadherence
Culture/ Diagnosis	Blood smear; serological methods
Prevention	Mosquito control; use of bed nets; no vaccine yet available; prophylactic antiprotozoal agents
Treatment	Chloroquine, mefloquine, artemisinin, pyrimethamine plus sulfadoxine (Fansidar), quinine, or proguanil

Helminthic Disease

- Schistosomiasis

Schistosomiasis

- Caused by small fluke
- Debilitating disease // second only to malaria
- Adult helminths are 15 to 20 mm long // female lives in a groove in the body of the male
- Lay eggs that lodge in tissue // eggs cause defense reactions which cause local tissue damage // formation of granulomas
- Eggs shed from humans in feces to infect other animals
- Adult worms not affected by host immune system



(a) Male and female schistosomes. The female lives in a groove on the ventral (lower) surface of the male schistosome ("split-body"), is continuously fertilized, and continuously lays eggs. The sucker is used by the male to attach to the host.

1 Adult female flukes lay eggs.

Definitive host

Female (size: 15–20 mm)

Adult flukes

Eggs

Male

2 Eggs reach body of water after being excreted in human feces or urine.

Egg (0.15 mm)

3 Eggs hatch into free-swimming larvae (miracidia).

Miracidium (0.2 mm)

4 Miracidium penetrates snail.

Intermediate host

5 Miracidium reproduces in snail, forming several cercariae.

6 Cercariae are released from the snail.

Cercaria (0.33 mm)

7 Free-swimming cercariae penetrate human skin, losing tail.

Cercaria (0.13 mm)

8 Cercariae travel through circulatory system to intestinal blood vessels, where they mature into adults.

(b) Life cycle of *Schistosoma*, cause of schistosomiasis.