XXI  Malaria [MAL = bad; ARIA = air] 2005

A. Order Haemosporida, Family Plasmodiidae
   1. Live in vertebrate tissues and blood
   2. SCHIZOGONY (asexual reproduction) in vertebrates
   3. SPOROGONY (sexual reproduction) in insects
   4. GAMETOGONY (asexual reproduction) in vertebrates

B. Effect upon human culture
   1. Control of malaria has been a major contributor to the world’s population explosion.
      a. Death rate has been significantly reduced
      b. Estimated that before WWII, 1/2 the deaths in the world were attributable to malaria
      c. Today malaria kills about 1.5 million people (mostly children) annually

Picture Slide #1: The Middle Passage by Tom Feelings;
http://www.juneteenth.com/survival.htm
   2. Slavery in the New World
      a. Why didn’t colonialists enslave Native Americans?
      b. Native Americans had no resistance to European and African diseases.
      c. Utilization of Native American physical labor was not efficient, because so many sickened and died after contact with Europeans.
      d. The slave trade imported Africans because they were resistant to malaria and other diseases

Picture Slide #2: Battle of the Little Big Horn By Kicking Bear (Mato Wanartaka), 1898, watercolor on muslin; http://www.getty.edu/artsednet/images/P/kicking-xl.jpeg
   3. Diseases (especially smallpox), not military defeats, killed most of the Native Americans during colonial expansion.
      a. Mississippi Mound people interacted with the first European explorers, but their settlements had been completely abandoned by the time later explorers arrived.
      b. Repeatedly, deadly epidemics would occur among Indian groups soon after contact with Europeans
      c. This was interpreted as “Manifest Destiny”, evidence that it was “God’s will” that the land belonged to white settlers.

4. Question: Why did not Europeans emigrate to and colonize the African continent as they did the New World?

Comment Slide #1
   Description of the expedition led by H.D. Trotter in 1841.
   “They travelled in three iron-built steamboats, Albert, Wilberforce, and London, which reached a point on the Niger about 100 miles from the sea on 26 August. Fever broke out at the beginning of September ‘and ceased not until it had paralysed the whole expedition’. They pushed on, but sickness became so prevalent that Wilberforce and London were sent back to the coast on 19 September, laden with their own sick and those
from *Albert*. *Albert* steamed further up the river but was forced to return on 4 October, reaching the coast ten days later, having been on the river for nine weeks. Of the 145 Europeans, 130 fell sick of fever and 50 died. Eleven of the twenty-five British coloureds were attacked by fever, but all of these recovered. None of the 133 Africans recruited from Sierra Leone fell sick.


Answer: Europeans risked death by disease when if they left the sea coast and entered the interior of the African continent.

Picture Slide #3: John Wayne, 1949 in *Sands of Iwo Jima*,
http://www.susan.neat.btinternet.co.uk/tt.htm

5. Many wars were lost, not because the winners were better soldiers, but because malaria decimated the losing army.
   a. Malaria halted Alexander the Great’s progress to the East
   b. Caused collapse of many of the Crusades
   c. In the WWII Pacific Theater, five times as many casualties were due to malaria as combat.

   (1) Battle of Bataan
      a) MacArthur decided to defend peninsula not Manila
      b) Troops brought in arms, but overlooked medicine
      c) Quinine ran out, while plenty of ammunition remained
      d) Japanese brought in fresh “healthy” troops
      e) At surrender, 85% of every U.S. regiment had acute malaria

   (2) On Guadalcanal 1942, case rate was 1800 per 1000
   (3) At WWII’s end, case rate had dropped to 10-50 per 1,000

C. Malaria in the United States
   1. Not here before the Europeans arrived
   2. 1814-1847, Charity Hospital, New Orleans 43% patients were classed as “fevers” and 20% as “intermittent fevers”
   3. National Malaria Society
      a. DDT spraying program
      b. 90% reduction in civilian malaria cases in US between 1935 and 1945
      c. Voluntarily disbanded in 1951
      d. Nucleus for Center for Disease Control (= CDC) in Atlanta, GA
   4. *Anopheles* mosquito is still present in southern US
      a. Malaria was reduced below a critical level
      b. Not enough mosquitoes were biting infected people to complete the life cycle
      c. Possibility exists that troops returning from malarious areas could re-introduce disease to region
   5. William Crawford Gorgas (p. 149)
      a. Born 1854, Mount Vernon, AL
b Finished medical school 1880 when germ theory of disease still in doubt
c 1897, William Ross saw malaria in mosquito
d Spanish American War
(1) US Army occupied Havana, Cuba
(2) Yellow fever epidemic
   (a) 1900, 1,400 cases
   (b) 1901, 37 cases
   (c) 1902, 0 cases
e Eliminated malaria during digging of Panama Canal

6. Josiah C. Nott
   a. Mobile Physician during & after Civil War
   b. Started medical school (now run by Univ. South Alabama) with 1st 15 graduates in 1860.
   c. Speculated that yellow fever might be spread by mosquitoes
   d. Letter to editor (1856) in *The Mobile Register*
      (1) Expressed doubt that burning tar & spreading lime in streets would prevent outbreaks of yellow fever
      (2) Advocated draining of nearby swamps in order to eliminate the noxious vapors that caused malaria

   “--- Yellow fever is only an occasional disease, but intermittent and remittent fevers, and many other forms of malarial disease never fail to appear in the hot months, and experience has taught many salutary lessons respecting these.

   Moisture is well known to be a leading element in foul and unhealthy air. It is necessary to the putrifaction [sic] and decomposition of vegetable and animal matter, and it is mainly through the vapor of water that poisonous effluvia find their way into the atmosphere that surrounds us. This being admitted, it is clear that the most important step towards health is a perfect system of *drainage and grading* for both city and suburbs.”

J.C. Nott 1856 *The Mobile Register*

D. Four species infect humans (Table 9-1; p. 151)
   1. *Plasmodium vivax*
      a “Benign tertian” malaria
         (1) Hosts often survive
         (2) Fevers every third day
      b Most common and widely distributed
         (1) 43% of world’s cases
         (2) Common in Asia
      c. Particularly likely to cause relapses
      d. Recognition
         (1) Only young red blood cells (RBCs) or reticulocytes are invaded
         (2) RING STAGE
             (a) Stained cytoplasm forms blue rings in RBCs
             (b) Large
         (3) Trophozoites are amoeboid inside RBCs hence “vivax”
Picture Slide #4: Plate 1: *Plasmodium vivax* Trophozoites; Early Trophozoite or “Ring” Stage & Mature Trophozoite or “Ameboid” Stage

2. *Plasmodium falciparum*
   a. “Malignant tertian” malaria
      (1) Most dangerous, 25% victims die
      (2) Survivors unlikely to have relapses
      (3) About 50% of world’s cases
   b. Recognition
      (1) Merozoites invade RBCs of any age
      (2) High levels of infection seen on slides
      (3) Small
      (4) Multiple infections of a single RBC are common

Picture Slide #5: Plate 3: *Plasmodium falciparum* Trophozoites; Early Trophozoite Double Infection & Mature Trophozoite

3. *Plasmodium malariae*
   a. “Quartian” malaria
   b. 7% of world’s cases
   c. Not deadly, but difficult to get rid of
      (1) One relapse occurred 53 years after initial infection
      (2) Most important cause of blood transfusion malaria
   d. Recognition
      (1) Only mature RBCs infected
      (2) Density in blood is low
      (a) Old RBCs removed more quickly than young ones from blood
      (b) 1 in 20,000 RBCs infected
      (3) Ring forms look like “bands”

Picture Slide #6; Plate 5: *Plasmodium malariae* Trophozoites: Early Trophozoite “Band” Form & Mature Trophozoite

4. *Plasmodium ovale*
   a. “Mild tertian” malaria
   b. Rare
   c. Similar to *P. vivax*, but schizont is oval

E. Mosquito vector
1. Only female mosquitoes of the genus *Anopheles* transmit malaria
   a. Females require protein rich in bloodmeal for manufacturing eggs
   b. Males (feathery antennae) do not feed on vertebrates

Picture Slide #7: Head Structures of Mosquitoes, Borror et al., 1989, Fig. 32-37

2. Anopheline mosquitoes bite and rest at an angle to the substrate

Picture Slide #8: Resting Positions of Mosquitoes; Borror et al., 1989, Fig. 32-38

F. Life cycle (Fig. 9.1, p. 150 & lab handout)
1. Stages within the mosquito
   a. Malarial gametes ingested when mosquito feeds on an infected vertebrate
   b. Male & female gametes fuse in stomach & gut of mosquito
      (1) Zygote is a motile OOKINETE
      (2) Sexual reproduction
      (3) Technically, mosquito is the definitive host for malaria
   c. Ookinetes become an OOCYST attached to wall of digestive tract
   Picture Slide #9: *Plasmodium* Oocyst; Fig. 9.3, p 153

   d. SPOROZOITES produced in oocysts
      (1) SPOROGONY
      (2) Asexual reproduction
   e. Sporozoites enter salivary glands of mosquito
   f. Sporozoites injected into vertebrate host at next blood meal
   Picture Slide #10: *Plasmodium* Sporozoites; Fig. 9.4, p 153

2. Stages within human host
   a. Exo-erythrocytic cycle
      (1) Sporozoites first invade host liver cells
      (2) Some may remain dormant in liver and cause relapses years later
      (3) Others undergo pre-erythrocyte SCHIZOGONY
         (a) First the nucleus divides into several (can be as many as 16-32) portions, then the organism divides
         (b) Produce MEROZOITES by asexual reproduction

   b. Erythrocytic cycle
      (1) Merozoites invade RBCs (= erythrocytes) becoming “signet ring” stage
         (a) Nucleus is stained red
         (b) Cytoplasm is stained blue
      (2) Merozoites undergo two types of schizogony
         (a) MEROGONY
             1) Form more merozoites
             2) Erythrocytic cycle repeated
         (b) GAMETOGONY
             1) Form gametes
             2) Gametes ingested by mosquito
   Picture Slide #12: Plate 3 *Plasmodium falciparum* Macrogametocyte;
   Picture Slide #13: Plate 3 *Plasmodium falciparum* Macrogametocyte

G. Ecology of transmission
1. Maturation of male gametocyte occurs by EXFLAGELLATION
   a. Becomes whip-like (no true flagellum is formed)
   b. Swims and fuses with female gametocyte

   Picture Slide #14: Exflagellation

   c. Induced by . . .
      (1) Cooling: as would happen if the parasite left a warm-blooded vertebrate and entered the gut of a mosquito
      (2) Drop in pH: as would happen if it entered mosquito stomach

   d. Capability to exflagellate (= to mature) only lasts about 6 hours

2. Most mosquitoes feed on humans only during a few hours of the day
   a. Usually at dusk
   b. Sometimes during the night

3. Timing of maturation of malarial gametocytes matches feeding times of mosquito vector

4. How is timing of capability to exflagellate accomplished?
   a. Depending upon the species, periodicity of asexual cycles (= intermittent fevers) are in multiples of 24 hours
   b. Gametocytes become mature approximately 30-35 hours after release of merozoites
   c. Periodicity is a selective device maximizing the chances that any one gametocyte will be picked up by a feeding mosquito

5. How is 24 hour cycle maintained by malaria parasite?
   a. Vertebrate body temperature drops slightly when sleeping
   b. Malarial parasites use rhythmic daily temperature fluctuations of vertebrate host to control their own development [Intelligent Design?] 

H. Symptomology
1. Fevers caused by ruptures of RBCs when merozoites released
2. HEMOZOIN
   a. Hemoglobin iron precipitates in an insoluble pigment produced by parasite
   b. Deposited in liver, spleen & brain
   c. Host anemia develops due to lack of iron

   Picture Slide #15: Hemozoin Deposits in Host Liver;

I. Defense mechanisms of humans
1. Most stages within host cells and are “invisible” to host’s immune system
2. Sickle cell anemia
   a. Genetic disease common in West Africa
   b. Hemoglobin S produced which precipitates under certain conditions & cannot carry oxygen
      (1) RBCs become sickle-shaped
(2) Fatal in homozygous individuals
(3) Heterozygous individuals carry the trait
   (a) Not fatal, but suffer attacks
   (b) Produce both types of hemoglobin
(4) Heterozygous individuals more resistant to malaria than those homozygous for normal hemoglobin
c. Mechanism of protection not well understood

Picture Slide #16: Sickle Cell Anemia; Manual of Hematology, 1980, Upjohn, p. 18

3. Genetic diseases involving other mutations in hemoglobin occur in other regions of the world and provide resistance to malaria
4. Vaccine Research
   a. Sporozoite vaccine
      (1) Would prevent people from acquiring infection
      (2) Sporozoites not around very long before beginning exo-erythrocytic cycle
      (3) Isolated circumsporozoite surface protein (= CSP) from P. falciparum
      (4) Idea is to inject CSP into subjects to stimulate production of antibodies to sporozoites
   b. Merozoite vaccine
      (1) Merozoites cause symptoms
      (2) A promising protein has been found on surface of erythrocytes infected with ring-stage malaria
   c. Gametocyte vaccine
      (1) Most important in stopping new infections from occurring
      (2) Would do nothing to help victim already with the disease
   d. A “cocktail” of vaccines against more than one stage of the disease will probably be used

Picture Slide #17: Antigens & Vaccines under Development against Malaria

J. Sequestration defense of malaria
1. Surface of infected RBCs have proteins that bind to epithelial cells in host capillaries

Picture Slide #18: RBCs infected with malaria attached to epithelial cell of placenta
Beeson et al., 2001, Trends in Parasitology 17(7): 332

2. Selective Advantage to Parasite: They do not pass through liver and spleen which remove old and damaged RBCs.
3. Cost to host: Blocked capillaries damage organs
   a. CEREBRAL MALARIA = stroke and/or disorientation
   b. BLACKWATER FEVER = kidney failure

Picture Slide #19: Cerebral Malaria;
K. Other important members of the suborder Haemosporina

1. *Haemoproteus*
   a. Infects domestic ducks and turkeys
   b. Vectors are louse flies (Hippoboscidae)
   c. Life cycle
      (1) Gametocytes in erythrocytes
      (2) Schizonts in endothelial cells lining blood vessels
   d. *Haemoproteus columbae* in pigeon

2. *Leucocytozoon*
   a. Infects birds
   b. Vectors are blackflies (*Simulium*)

K. Order Piroplasmida

1. Description
   a. Pyriform, ameboid parasites of RBCs
   b. Apical complex is reduced

2. Vectors are ticks

3. *Babesia bigemina*
   a. Important livestock disease
   b. Cattle tick fever