XXI. Malaria [MAL = bad; ARIA = air] (Chapter 9) 2008
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: The Middle Passage; 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: Battle of the Little Big Horn; 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?

Word Slide: 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.

Cartwright, F.F., 1972, Disease and History, Dorset Press, New York, p. 140
Answer: Europeans risked death by disease when if they left the sea coast and entered the interior of the African continent.

Picture Slide: John Wayne, 1949, Sands of Iwo Jima
5. Many wars were lost, not because the winners were better soldiers, but because malaria decimated the losing army.

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”

Slide: A honeymoon canoe trip down the Mississippi River in 1933 by the artist Walter Anderson & his bride, Agnes, was cut short by malaria Approaching the Magic Hour, Anderson (1989) pp. 39-40.
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) Medical officer with US Army
      (2) Insisted that US Army take steps to control mosquitoes during a yellow fever epidemic in Havana
      (3) Results could not be ignored by Germ Theory skeptics
         (a) 1900, 1,400 yellow fever cases
         (b) 1901, 37 cases
         (c) 1902, 0 cases
   e. Eliminated malaria as a health problem during the digging of Panama Canal

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: Plasmodium vivax Trophozoites; Plate I textbook

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: Plasmodium falciparum Trophozoites; Plate 3

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

Picture Slide: Plasmodium malariae Trophozoites; Plate 5


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 bloodmeal rich in protein for manufacturing eggs
   b. Males (feathery antennae) do not feed on vertebrates

Picture Slide: Head Structures in Mosquitoes Showing Sex Characters; Borror et al., 1989, Fig. 32-37

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

Picture Slide: 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. Ookinete becomes an OOCYST attached to wall of digestive tract

   Picture Slide: *Plasmodium* Oocyst; Fig. 9.3, p 153 of textbook

   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: *Plasmodium* Sporozoites; Fig. 9.4, p 153 textbook

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

   Picture Slide: *Plasmodium* Exo-erythrocytic Cycle Schizogony Occurring in Host Liver;

   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 *Plasmodium falciparum* Macrogametocyte; Plate 3
   Picture Slide: *Plasmodium falciparum* Macrogametocyte;

G. Ecology of transmission [Intelligent Design?]

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

Picture Slide: Exflagellation


(3) Induced by . . .

(a) Cooling: as would happen if the parasite left a warm-blooded vertebrate and entered the gut of a mosquito

(b) Drop in pH: as would happen if it entered mosquito stomach

(4) Capability to exflagellate (= to mature) lasts about 6 hours

b. Most mosquitoes feed on humans only during a few hours of the day

c. Periodicity is a selective device maximizing the chances that gametocytes will be picked up by feeding mosquitoes

d. How is timing of exflagellation accomplished?

(1) Depending upon the species, periodicity of asexual cycles (= intermittent fevers) are in multiples of 24 hours

(2) Gametocytes become mature approximately 30-35 hours after release of merozoites

(3) Mechanism

(a) Vertebrate body temperature drops slightly when sleeping

(b) Malaria uses rhythmic daily temperature fluctuations of vertebrate host to control its development

2. Gametocytes selectively attract mosquito vectors to infective humans

a. Experiment 1

(1) Compared the biting rates of Anopheles on 3 groups of children

(a) No malaria

(b) Malaria, but no gametocytes (non-infective)

(c) Malaria, with gametocytes (infective)

(2) Results: Infective children (with gametocytes) attracted twice as many mosquito bites as the 2 other groups.

b. Experiment 2

(1) Treated parasitized children and cured them of malaria

(2) Children whose blood was cleared of gametocytes no longer attracted Anopheles mosquitoes

(3) Indication is that malaria gametocytes attract vector (probably through an odor)

Series of 3 slides from Malaria Infection Increases Attractiveness of Humans to Malaria PLoS Biology, 2005, 3(9) p. 1590-93; Title Page, Experimental Setup and Results

H. Symptomology

1. Fevers caused by rupture 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: Hemozoin Depots in Host Liver

I. Defense mechanisms of malaria

1. Circumvention of vertebrate immune system
   a. Many stages avoid detection by immune system because they are inside host cells
   b. Recent evidence suggests that hemozoin paralyzes T-cells that would normally activate the antibody-producing B-cells

Picture Slides; Urban & Todryk, 2006, Malarial pigment paralyzes dendritic cells J. Biology, http://jbiol.com/content/5/2/4

2. Sequestration
   a. Surfaces of infected RBCs have proteins that bind to epithelial cells in host capillaries
   b. Selective advantage to parasite: They do not pass through liver and spleen which remove old and damaged RBCs.
   c. Cost to host: Blocked capillaries damage organs
      (1) CEREBRAL MALARIA = stroke and/or disorientation
      (2) BLACKWATER FEVER = kidney failure

Picture Slide: Histopathology of Malaria Infected RBCs in Placental Tissue; RBCs infected with P. falciparum attached to epithelial cells of placenta; Beeson et al., 2001, Trends in Parasitology 17(7): 332

J. Defense mechanisms of humans

1. Antibodies are made to sequestration proteins

2. Genetic diseases
   a. Malaria has had a tremendous impact upon the human genome (In some areas of Africa approximately 20% of the children die from malaria before the age of five.)
   b. SICKLE CELL ANÉMIA
      (1) Genetic disease common in West Africa
      (2) Hemoglobin S produced which precipitates under certain conditions & cannot carry oxygen
         (a) RBCs become sickle-shaped
         (b) Fatal in homozygous individuals
         (c) Heterozygous individuals carry the trait
            i. Not fatal, but suffer attacks
            ii. Produce both types of hemoglobin
      (3) Mechanism of protection is not well understood

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

   c. THALASSEMIA
(1) Found in populations inhabiting malarious Mediterranean coast (Greece, Sardinia, etc)
(2) Defect in the utilization of iron in hemoglobin synthesis

d. New Guinea and Micronesia
(1) A mutation causes change in membrane of RBCs making them more resistant to invasion by malaria.
(2) Spleen removes RBCs more rapidly than normal RBCs
(3) Carriers suffer from anemia

e. Central Africa
(1) Individuals lack the “Duffy” protein on RBCs
(2) *P. vivax* cannot invade these cells
(3) Function of “Duffy” protein unknown

Slide Sequence: Malaria Eradication Philippines 1968