VI. Malaria

A. Effect upon human culture
   1. Control of malaria has contributed to world's population explosion
   2. Africans brought to U.S. because they were resistant to malaria & other diseases
   3. Many wars/battles lost, not because winners were better soldiers, but because losing army had been decimated by malaria

B. Malaria in U.S.
   1. Not here before Europeans
   2. National Malaria Society
      a. Eradicated malaria in U.S.
      b. Became the CDC
   3. *Anopheles* mosquito (vector) still present in South

C. Four species infect humans
   1. *Plasmodium vivax*
      a. "Benign tertian malaria"
      b. Fevers every 3rd day
      c. Particularly likely to cause relapses
   2. *P. falciparum*
      a. "Malignant tertian" malaria
      b. Most dangerous
      c. 50% world's cases
   3. *P. malariae*
      a. "Quartan malaria"
      b. Not deadly, but difficult to get rid of
   4. *P. ovale*
      a. "Mild tertian"
      b. Rare

D. Mosquito vector
   1. Only female mosquitoes of the genus *Anopheles* transmit malaria
   2. Anopheline mosquitoes bite & rest at an angle to substrate

E. Life-cycle
   1. Stages within mosquito
      a. Gametes ingested
      b. Gametocytes fuse in stomach
      c. Sexual reproduction
      d. Technically mosquito is the final & humans the intermediate host
      e. SPOROZOITES in salivary glands of female mosquito are injected into host during a blood meal
   2. Stages within human host
      a. Exoerythrocytic cycle
         (1) Sporozoites invade liver cells
         (2) Some remain dormant in liver and cause relapses years later
(3) Others undergo pre-erythrocyte SCHIZOGONY (asexual reproduction: neither meiosis nor mitosis) in liver cells producing MEROZOITES

b. Erythrocytic cycle
(1) Merozoites invade erythrocytes
(2) Become “active” trophozoites which upon staining give the appearance of forming a ring “ring stage”
(3) Trophozoites undergo 2 types of schizogeny
   (a) Merogony
      i) More merozoites
      ii) Repeat erythrocytic cycle
   (b) GAMOGONY
      i) Form gametes
      ii) Ingested by mosquito

F. Symptomatology
1. Fevers
   a. RBCs rupture & merozoites released
   b. Blood plasma viscosity increases due to protein & wastes
2. Anemia
   a. Lack of iron
   b. Parasite binds iron into an insoluble pigment called HEMOZOIN
3. Vascular obstruction
   a. RBCs w/ parasite become “sticky” and adhere to endothelial cells lining capillaries & post-capillary venules
   b. Organs damaged due to blocked vessels
      (1) Cerebral malaria
      (2) “Blackwater fever”
         (a) Iron (blood) in urine
         (b) Kidney damage

G. Defense mechanisms of malaria
1. Most stages w/ in host cells and “invisible” to immune system
2. Sequestration
   a. Adherence of Plasmodium to endothelial lining of capillaries
      (1) Attachment occurs at “knobby” protrusions
      (2) Parasite induces changes in surface proteins; [NEO-ANTIGENS] convert a non-adhesive RBC into an adhesive one.
      (3) Receptors on endothelial cells are not uniformly distributed
         (a) Examples
            i) CD36
            ii) Intercellular adhesion molecule 1 = ICAM-1
         (b) Many are up-regulated by immune system cytokines
            i) Tumor necrosis factor α
ii) Interferon γ

(4) Receptors on parasite RBCs
   (a) PfEMP-1
      i) Surface antigen of *P. falciparum*
      ii) May be the RBC receptor for endothelial cells
   (b) Sequestrin

(5) 2% of parasites were changing their surface phenotype every generation

b. Hypothesized that sequestration in capillaries prevents entry of infected RBCs into spleen where they would be destroyed
   (1) Spleen enlarges and acts as a blood “filter”
   (2) Macrophages consume damaged and big cells.

c. Conditions resulting in cerebral malaria
   (1) Parasite changing surface antigens
   (2) Exposure to malaria affects the kind & amounts of cytokines in host
   (3) Expected that more adhesive & pathological variants will occur in humans that are semi-immune

H. Vaccines
1. Antisporozoite vaccine
   a. Would prevent people from getting infection = Pre-erythrocytic immunity
   b. Sporozoites not around very long before beginning exoerythrocytic cycle
   c. Circumsporozoite (CS) protein of *P. falciparum* is the target
      (1) Coats sporozoite
      (2) Repeating epitopes in tandem

2. Merozoite antigens
   a. Merozoite causes symptoms
   b. Many proteins off malaria coat have been isolated
   c. Sequestration proteins are promising targets
   d. Immunity
      (1) Has occurred in monkeys
      (2) In humans it has delayed illness, but not stopped it.

3. Gametocyte vaccines
   a. Most important in stopping new infections from occurring
   b. Does nothing to help victim harboring disease
   c. Will be given with vaccines against other stages when developed

4. Probably vaccines against several stages (= a “cocktail”) will need to be developed

I. Ecology of transmission
1. Maturation of male gametocyte
   a. When cooled (as happens when leaving warm-blooded vertebrate
and enters gut of mosquito) or when pH drops (as in mosquito stomach), mature male gametocyte will undergo EXFLAGELLATION.

1. Becomes whiplike (no real flagellum formed)
2. Swims and finds female gametocyte

b. Ability to exflagellate (maturity) lasts about 6 hours

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


4. How is timing of exflagellation accomplished?
   a. Periodicity of asexual cycle (intermittent fevers) are in multiples of 24 hours depending upon species.
   b. Gametocytes develop about 30-35 hrs after release of merozoites (beginning of gamogony).
   c. Periodicity is a selective device maximizing the chances that mature gametocytes will be picked up by feeding mosquitos.

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 cycle

J. Sickle cell anemia
1. Genetic disease common to people of East Africa
2. Produce hemoglobin S which precipitates under certain conditions and cannot carry oxygen
   a. RBCs become sickle shaped
   b. Fatal in individuals homozygous for sickle cell gene
   c. Heterozygous individuals "carry the trait"
      1. Not fatal
      2. Carry both types of hemoglobin
      3. Do suffer attacks

3. Heterozygous individuals more resistant to malaria than individuals homozygous for normal hemoglobin

4. Mechanism of protection not understood
   a. Level of potassium in RBCs is below that required by parasite
   b. Production of a toxic heme group (ferriprotoporphyrin IX)
   c. Lack of oxygen during sickle-cell incidents kills parasite

K. Drug treatments
   1. Primaquine
      a. Attacks exoerythrocytic malaria
      b. Taken long after symptoms gone
   2. Chloroquine
      a. Attacks erythrocytic malaria stages
b. Drug most often used
c. Mode of action [Olliaro & Goldberg (1995)]
   (1) Not fully understood, but does interfere with activities of digestive vacuole.
      (a) Interferes with lysosomal digestion of hemoglobin
      (b) Prevent detoxification of heme groups into hemozoin
         i) Free heme released during hemoglobin digestion, potentially toxic
         ii) Normally heme groups crystallized into hemozoin
         iii) Accumulation of free heme damages membranes
      (c) Inhibits proteinase digestion of hemoglobin & parasite starves
   (2) Future drugs
      (a) Proteinase inhibitors that prevent digestion of hemoglobin
d. Compromised as resistant strains have appeared [Discussed in The Coming Plague]
3. Verapamil
   a. Calcium channel blocker used in treatment of hypertension
   b. Blocks chloroquine resistance by stopping efflux of chloroquine from cells
4. Artemisinin
   a. Binds to hemozoin
   b. May also increase oxidative stress
5. Malaria requires iron for ferroproteins: Iron chelating agents may kill malaria