Plasmodium Life Cycle

The malaria parasite exhibits a complex life cycle involving an insect vector (mosquito) and a vertebrate host (human). Four Plasmodium species infect humans: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. All four species exhibit a similar life cycle with only minor variations.

The infection is initiated when **sporozoites** are injected with the saliva of a feeding mosquito. Sporozoites are carried by the circulatory system to the liver and invade hepatocytes (1). The intracellular parasite undergoes an asexual replication known as **exoerythrocytic schizogony** within the hepatocyte (2-4). Exoerythrocytic schizogony culminates in the production of **merozoites** which are released into the bloodstream (5). A proportion of the liver-stage parasites from *P. vivax* and *P. ovale* go through a dormant period (not shown) instead of immediately undergoing asexual replication (i.e., stay temporarily at step 2). These **hypnozoites** will reactivate several weeks to months (or years) after the primary infection and are responsible for relapses.
Merozoites invade erythrocytes (6) and undergo a trophic period in which the parasite enlarges (7-8). The early trophozoite is often referred to as 'ring form' because of its morphology. Trophozoite enlargement is accompanied by an active metabolism including the ingestion of host cytoplasm and the proteolysis of hemoglobin into amino acids. The end of the trophic period is manifested by multiple rounds of nuclear division without cytokinesis resulting in a schizont (9). Merozoites bud from the mature schizont, also called a segmenter (10), and the merozoites are released following rupture of the infected erythrocyte (11). Invasion of erythrocytes reinitiates another round of the blood-stage replicative cycle (6-11).

The blood stage is responsible for the pathology associated with malaria (see following pages). The intermittent fever paroxysms are due to the synchronous lysis of the infected erythrocytes. \textit{P. malariae} exhibits a 72 hour periodicity, whereas the other three species exhibit 48 hour cycles. However, \textit{P. falciparum} often exhibits a continuous fever rather than the periodic paroxysms. \textit{P. falciparum} also is responsible for more morbidity and mortality than the other species. This increase virulence is due in part to the higher levels of parasitemia associated with \textit{P. falciparum} infections. In addition, more complications are associated with \textit{P. falciparum} because of the sequestration of the trophozoite- and schizont-infected erythrocytes in the deep tissues.

As an alternative to the asexual replicative cycle, the parasite can differentiate into sexual forms known as \textit{macro-} or \textit{microgametocytes} (12). The gametocytes are large parasites which fill up the erythrocyte, but only contain one nucleus. Ingestion of gametocytes by the mosquito vector induces gametogenesis (i.e., the production of gametes) and escape from the host erythrocyte. Factors which participate in the induction of gametogenesis include: a drop in temperature, an increase in carbon dioxide, and mosquito metabolites. Microgametes, formed by a process known as exflagellation (13), are flagellated forms which will fertilize the macrogamete (14) leading to a zygote (15).

The zygote develops into a motile ookinete (16) which penetrates the gut epithelial cells and develops into an oocyst (17). The oocyst undergoes multiple rounds of asexual replication (18) resulting in the production of sporozoites (19). Rupture of the mature oocyst releases the sporozoites into the hemocoel (i.e., body cavity) of the mosquito (20). The sporozoites migrate to and invade the salivary glands, thus completing the life cycle.

In summary, malaria parasites undergo three distinct asexual replicative stages (exoerythrocytic schizogony, blood stage schizogony, and sporogony) resulting in the production of invasive forms (merozoites and sporozoites). A sexual reproduction occurs with the switch from vertebrate to invertebrate host and leads to the formation of the invasive ookinete. All invasive stages are characterized by the apical organelles typical of apicomplexan species.
Malaria

**General Clinical Features**
- characterized by acute febrile attacks (malaria paroxysms)
- due to blood stage (not liver stage or gametocytes)
- manifestations and severity depend on species and host status
  - immunity, general health, nutritional state, genetics
- recrudescences or relapses can occur over months or years
- can develop severe complications (especially *P. falciparum*)

**Features of the Paroxysm**
- paroxysms associated with synchronous release of merozoites, antigens, etc (ie, pyrogenic material)
  - high levels of tumor necrosis factor-α correlated with paroxysm
- between paroxysms temperature is normal and patient feels well
- *P. falciparum* may not exhibit classic paroxysms (continuous fever)
- paroxysms become less severe and irregular as infection progresses
- semi-immune may exhibit little (1-2 days fever) or no symptoms
<table>
<thead>
<tr>
<th></th>
<th>vivax</th>
<th>ovale</th>
<th>malariae</th>
<th>falciparum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation Period (days)</strong></td>
<td>8-27</td>
<td>8-27</td>
<td>16-&gt;40</td>
<td>6-25</td>
</tr>
<tr>
<td><strong>Severity of Initial Paroxysms</strong></td>
<td>moderate to severe</td>
<td>mild</td>
<td>mild to moderate</td>
<td>severe</td>
</tr>
<tr>
<td><strong>Average Parasitemia</strong> (per mm³)</td>
<td>20,000</td>
<td>9,000</td>
<td>6,000</td>
<td>50,000-500,000</td>
</tr>
<tr>
<td><strong>Maximum Parasitemia</strong> (per mm³)</td>
<td>50,000</td>
<td>30,000</td>
<td>20,000</td>
<td>2,500,000</td>
</tr>
<tr>
<td><strong>Typical Symptom Duration</strong> (untreated)</td>
<td>3-8 weeks</td>
<td>2-3 weeks</td>
<td>3-24 weeks</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td><strong>Maximum Infection Duration</strong> (untreated)</td>
<td>5-8 years*</td>
<td>12-20 months*</td>
<td>20-50 years</td>
<td>6-17 months</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Other Complications</strong></td>
<td>renal</td>
<td>cerebral**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Incubation period defined as time from sporozoite infection until appearance of symptoms. *Includes relapses (≠ recrudescence) due to dormant 'hypnozoite' stage in liver. **Many other organs in addition to the brain are also affected in severe malaria.

Supplemental materials to the lectures given by Dr. Wiser in Malaria (TRMD 782) can be found at: [http://www.tulane.edu/~wiser/malaria/](http://www.tulane.edu/~wiser/malaria/).