The typical life history of each of these organisms involves more than 24 morphologic forms. However, for the purposes of this text, only the most commonly encountered forms in human specimens will be discussed. These are listed as follows (in chronologic order): ring form (also known as the early trophozoite), developing trophozoite, immature schizont, mature schizont, microgametocyte, and macrogametocyte. All these morphologic forms occur following the invasion of red blood cells (RBCs). This chapter is organized into two main sections, a discussion of *Plasmodium* species and then *Babesia* species.

PLASMODIUM SPECIES

As noted, there are five species of *Plasmodium* known to be of concern regarding transmission to humans. General information, including a historical perspective and generic description of the six most commonly encountered morphologic forms, is followed by a discussion of each of these species in detail.

Historical Perspective

Historical accounts of events leading to the formation of the United States have cited malaria as being of significance on several occasions. Malaria-infected individuals from southwest England apparently transported *Plasmodium* spp. parasites as they migrated to the New World. Malaria quickly spread throughout the colonies, resulting in a shortage of healthy workers. The demand for replacement workers played a significant role in the emergence of the African slave trade. Interestingly, many of those from West Africa who were brought to America to work did not contract malaria. It has since been determined that they were genetically protected from select species of malaria-causing *Plasmodium* spp. parasites.

Malaria was considered endemic in many of the colonies during the Revolutionary War, particularly in areas with significant water sources in which mosquito vectors thrived and soldiers often camped. A group of British soldiers, under the direction of General Charles Cornwallis, was no exception. After several exposures in areas in which malaria was rampant, almost all the British soldiers contracted malaria and were unable to continue fighting. Ultimately, General Cornwallis surrendered, resulting in a successful end to the war.

By some accounts, malaria was first described by a French army doctor, Charles Louis Alphonse Laveran, in 1880. In 1907, he received the Nobel Prize for Physiology or Medicine for his work on malaria. Since then, numerous physicians and scientists have studied the diseases caused by members of the genera *Plasmodium* and have made great strides toward our understanding of these diseases. Today, malaria lethally affects almost 2.5 million people worldwide. Although North America was declared malaria free in 1970, travel and immigration bring it back to the continent regularly.

Morphology and Life Cycle Notes

Ring Forms (Early Trophozoites). The **ring form**, as the name implies, refers to a ringlike appearance of the malarial parasite following invasion into a previously healthy RBC. The typical ring, when stained with Giemsa stain, consists of a blue cytoplasmic circle connected with or to, depending on the species, a red chromatin dot, also referred to in some texts as a nucleus. The space inside the ring is known as a vacuole.

Developing Trophozoites. The appearance of the **developing trophozoite** varies among the *Plasmodium* species. There are numerous growing stages in this category for each organism. However, remnants of the cytoplasmic circle and chromatin dot, which are in some cases both still intact until late in development, are present in the developing trophozoite form. Pigment, primarily brown in color, is often visible. In general, because the parasite is actively growing during this stage, the amount of RBC space invaded is significantly more than that of the ring form. A representative developing trophozoite will be

described in more detail under the discussion of each malarial parasite.

Immature Schizonts. Although still unorganized, evidence of active chromatin replication is seen in the typical **immature schizont**. Visible cytoplasmic material surrounds the growing chromatin. Pigment granules, often brown in color, are also commonly seen. As the parasite continues to multiply, it expands and occupies more space within the RBC.

Mature Schizonts. **Mature schizonts** are characterized by the emergence of the fully developed stage of the asexual sporozoa trophozoite known as **merozoites**. The number and arrangement of these merozoites vary and are described in detail under the discussion of each malarial species. With the exception of *Plasmodium vivax*, cytoplasmic material is not visible and is presumed to be absent.

Microgametocytes. With the exception of *P. falciparum*, which is crescent-shaped, the typical **microgametocyte** is roundish in shape. This morphologic form consists of a large diffuse chromatin mass that stains pink to purple and is surrounded by a colorless to pale halo. Pigment is usually visible; its distribution and color vary by species.

Macrogametocytes. **Macrogametocytes** range in shape from round to oval, with the exception of *P. falciparum,* which is crescent-shaped. The compact chromatin mass is partially to completely surrounded by cytoplasmic material. Pigment is also present, and its color and distribution in this morphologic form vary by individual *Plasmodium* species. Specific details are described under the discussion of each species.

Life Cycle Notes. Members of the mosquito genus *Anopheles* are responsible for the transmission of malaria to humans via a blood meal. This vector transfers the infective stage of the parasite known as **sporozoites** from its salivary gland into the human bite wound. Following entrance into the body, the sporozoites are carried through the peripheral blood to the parenchymal cells of the liver. It is here that **schizogony** (asexual multiplication) occurs. This **exoerythrocytic cycle,** which literally means reproduction outside of red blood cells (in this case in human liver cells), of growth and reproduction lasts from 8 to 25 days, depending on the specific *Plasmodium* species involved. The infected liver cells eventually rupture and introduce merozoites into the circulating blood. These migrating merozoites target age- and size-specific RBCs to invade and thereby initiate the phase of reproduction involving red blood cells known as the **erythrocytic cycle** of growth. These RBC specifics vary among each species and are described under the life cycle notes of each species. It is in this asexual phase that the plasmodia feed on hemoglobin and pass through the numerous stages of growth, including their six morphologic forms.

On formation of the merozoites, one of three paths may be taken. Some of the RBCs infected with merozoites rupture, releasing these forms to target and infect new RBCs, and this part of the cycle repeats itself. A number of erythrocytic cycles may occur. However, other infected RBCs containing merozoites develop into microgametocytes and macrogametocytes, and still others are destroyed by the immune system of an otherwise healthy individual. Although never demonstrated in human infection, it is presumed that **hypnozoites** (dormant *Plasmodium*-infected liver cells) may form during infection with *P. vivax* or *P. ovale*. These forms, also known as sleeping forms, may be dormant for months to years after the initial infection. The mechanism behind the reactivation of such cells was not well described in any of the references used to prepare this chapter. However, once stimulated, the hypnozoites rupture and introduce merozoites into the circulating blood, thus initiating the erythrocytic cycle and a relapse infection, or **recrudescence**.

Transmission of the parasite back into the vector occurs when the mosquito ingests mature male (micro) and female (macro) sex cells called **gametocytes** during a blood meal, thus initiating the sexual cycle of growth. Male and female gametocytes unite in the mosquito's stomach and form a fertilized cell called a **zygote** (also known as an **ookinete**). The zygote becomes encysted and matures into an **oocyst**. On complete maturation, the oocyst ruptures and releases

numerous sporozoites, which migrate into the salivary gland of the mosquito and are ready to infect another unsuspecting human. Thus, the cycle repeats itself.

In addition to contracting malaria via an *Anopheles* mosquito bite, there are several other modes of transmission for *Plasmodium* species. Transfusion malaria, as the name implies, occurs when uninfected patients receive blood tainted with malaria collected from an infected donor. Malaria may also be spread through the sharing of needles and syringes, a common practice among intravenous drug users; this type of infection is referred to as mainline malaria. Although rarely documented, congenital malaria, which is the passing of the parasite from mother to child, may also occur.

Quick Quiz! 6-1

The infective stage of *Plasmodium* is (are) the: (Objective 6-6)

A. Merozoites
B. Oocyst
C. Sporozoites
D. Gametocytes

Laboratory Diagnosis

Giemsa-stained peripheral blood films are the specimens of choice for the laboratory diagnosis of malaria. Wright's stain may also be used and will result in an accurate diagnosis. However, because Giemsa is the recommended stain for all blood films submitted for parasite study, the specific morphologic discussion of each *Plasmodium* species is based on the use of this stain. Both thick and thin blood films should be made and examined. Thick blood smears serve as screening slides, whereas thin blood smears are used in differentiating the *Plasmodium* species. All blood films should be studied under oil immersion. It is important to note that mixed *Plasmodium* infections may occur, with the most frequently encountered being *P. vivax* and *P. falciparum*. Careful and thorough screening of all smears is crucial to ensure the correct identification, reporting, and ultimately the proper treatment of all *Plasmodium* organisms present.

The timing of blood collection for the study of malaria is crucial to success in retrieving the malarial parasites. The various morphologic forms of parasites visible at any given time depend on the stage of organism development at the time of specimen collection. For example, when the infected RBCs rupture, merozoites are present in the circulating blood. This stage, when found, is difficult to serve as a species identifier. However, gametocytes may be present at this point in time and they are readily discernible. The greatest number of parasites is present in the blood in between characteristic bouts of fever and chills resulting from the release of merozoites and toxic waste products from infected RBCs, known as **paroxysms**. Thus, this is the optimal time to collect peripheral blood samples to determine the presence of *Plasmodium* spp. parasites (Table 6-1).

It is important to note that multiple sets of blood films, which, as noted, consist of thick and thin smears, are necessary to rule out malarial infections. It is recommended that blood be collected every 6 to 12 hours for up to 48 hours before considering a patient to be free of *Plasmodium* spp. parasites.

In addition to blood films, serologic tests and polymerase chain reaction (PCR) techniques for malaria are available. These tests are not that helpful in regard to the actual treatment of malarial infections. However, one benefit of

TABLE 6-1 Occurrence of Cyclic Paroxysms in Common *Plasmodium* Species

Plasmodium Species	Timing of Cyclic Paroxysms
P. vivax	Every 48 hr
P. ovale	Every 48 hr
P. malariae	Every 72 hr
P. falciparum	Every 36-48 hr

serologic testing is that this methodology does appear to help rule out malaria in patients suffering from a fever of unknown origin, and PCR techniques can confirm the malarial speciation, but is usually not necessary. Representative laboratory diagnostic methodologies are presented in Chapter 2, as well as in each individual parasite discussion, as appropriate.

Quick Quiz! 6-2

The best time to collect blood for *Plasmodium* parasites is: (Objective 6-10)

A. Between paroxysms
B. During paroxysms
C. Morning
D. Evening

Pathogenesis and Clinical Symptoms

The typical patient remains asymptomatic following the initial mosquito bite and exoerythrocytic cycle of malarial infection. However, once the erythrocytic phase is initiated and large numbers of rupturing RBCs simultaneously occur, the resulting merozoites and toxic waste byproducts in the blood system produce the first clinical symptom, a paroxysm. Considered in part as an allergic response of the body to the development of the **schizonts** and to the circulating parasitic antigens following the release of merozoites, a paroxysm is characterized by chills (also known as **rigor**), typically lasting for 10 to 15 minutes or longer, followed by 2 to 6 hours or more of a fever. As the fever subsides and returns to normal, the patient experiences profuse sweating and extreme fatigue. The periodicity of paroxysms varies and is defined under the discussion of each *Plasmodium* species; periodicity often accounts for one of the common names associated with each *Plasmodium* species as well. Patients may experience these clinical symptoms as a result of having a recrudescence. A recurrence, or true relapse, occurs when patients become reinfected with rupturing hypnozoites months to years after the initial infection, as is often the case with *P. vivax* and *P. ovale* infections.

Additional malarial symptoms may include headache, lethargy, anorexia, **ischemia** (insufficient blood supply in other body tissues caused by blockage of the capillaries and blood sinuses), nausea, vomiting, and diarrhea. Anemia, central nervous system (CNS) involvement, and nephrotic syndrome may occur in all *Plasmodium* infections. It is interesting to note that malaria may mimic a number of other diseases, including meningitis, pneumonia, gastroenteritis, encephalitis, or hepatitis. Specific clinical symptoms are described under the discussion of each individual organism.

Furthermore, persons exhibiting erythrocyte structural abnormalities such as heterozygous (Gd^{A-}/Gd^{B}) glucose-6-phosphate dehydrogenase (G6PD) deficiency and certain hemoglobinopathies (S, C, E, and thalassemia) tend to have a greater resistance to malarial infections than those who do not possess the abnormalities. Similarly, those individuals who are Duffy blood group–negative also tend to show a greater resistance than those who are positive for the antigens on their red blood cells.

Quick Quiz! 6-3

A paroxysm is: (Objective 6-1)

A. An allergic reaction
B. A periodic episode characterized by fever, chills, sweats, and fatigue
C. Both A and B are correct.
D. None of the above

Classification

Malaria belongs to the phylum Apicomplexa, class Aconoidasida, order Haemosporida, family Plasmodiidae, genus *Plasmodium*. All five of the *Plasmodium* species discussed in this chapter are found in the blood, as indicated in Figure 6-1.

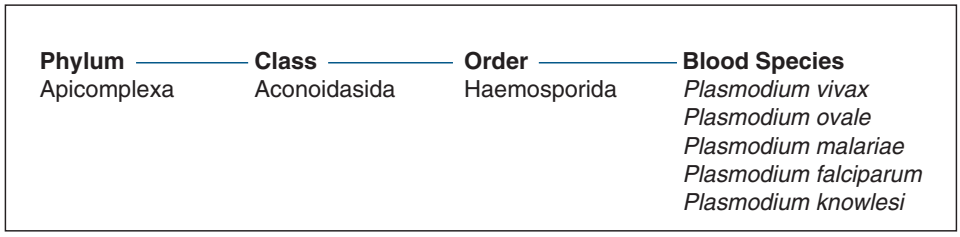

FIGURE 6-1 Parasite classification—*Plasmodium* species.

Plasmodium vivax
(Plaz-mo 'dee-um/vye' vacks)

Common associated disease and condition names: Benign tertian malaria, vivax malaria.

Morphology

Ring Forms. The cytoplasmic ring of the typical *P. vivax* ring form measures approximately one third the diameter of the red blood cell in which it resides (Figs. 6-2 and 6-3; and Table 6-2). A single chromatin dot serves as the connecting point of this delicate ring. A vacuole is visible inside the ring. The parasite may first be visible as a crescent-shaped mass at the outer edge of the red blood cell, a location known as **accolé** or **appliqué.**

Developing Trophozoites. Although remnants of the cytoplasmic ring may be visible, the parasite takes on more of an irregularly shaped ameboid appearance (Figs. 6-2 and 6-3; and Table 6-2). A single, large chromatin dot is present among the cytoplasmic material. The vacuole remains visible and basically intact until the late stage of development. The presence of **hemozoin** (a remnant of the parasite feeding on RBC hemoglobin visible as a brown pigment) becomes apparent in the cytoplasm of the parasite in this stage and increases in amount and visibility as the parasites mature.

Immature Schizonts. The immature schizont form of *P. vivax* is characterized by the presence of multiple chromatin bodies that emerge from progressive chromatin division (Figs. 6-2 and 6-3; and Table 6-2). Cytoplasmic material is present and often contains clumps of hemozoin.

TABLE 6-2 *Plasmodium vivax*: Typical Characteristics at a Glance

Relative age of infected RBCs	Only young and immature cells
Appearance of infected RBCs	Enlarged, distorted
Morphologic Form*	**Typical Characteristics (Based on Giemsa Staining)**
Ring form	Delicate cytoplasmic ring measuring one third of RBC diameter Single chromatin dot Ring surrounds a vacuole Accolé forms possible
Developing trophozoite	Irregular ameboid appearance Ring remnants common Brown pigment becomes apparent, increases in number and visibility as parasites mature
Immature schizont	Multiple chromatin bodies Often contains clumps of brown pigment
Mature schizont	12 to 24 merozoites occupy most of infected red blood cell Merozoites surrounded by cytoplasmic material Brown pigment may be present
Microgametocyte	Large pink to purple chromatin mass surrounded by colorless to pale halo Brown pigment common
Macrogametocyte	Round to oval cytoplasm Eccentric chromatin mass Delicate light-brown pigment—may be visible throughout cell

*All morphologic forms may also contain Schüffner's dots.

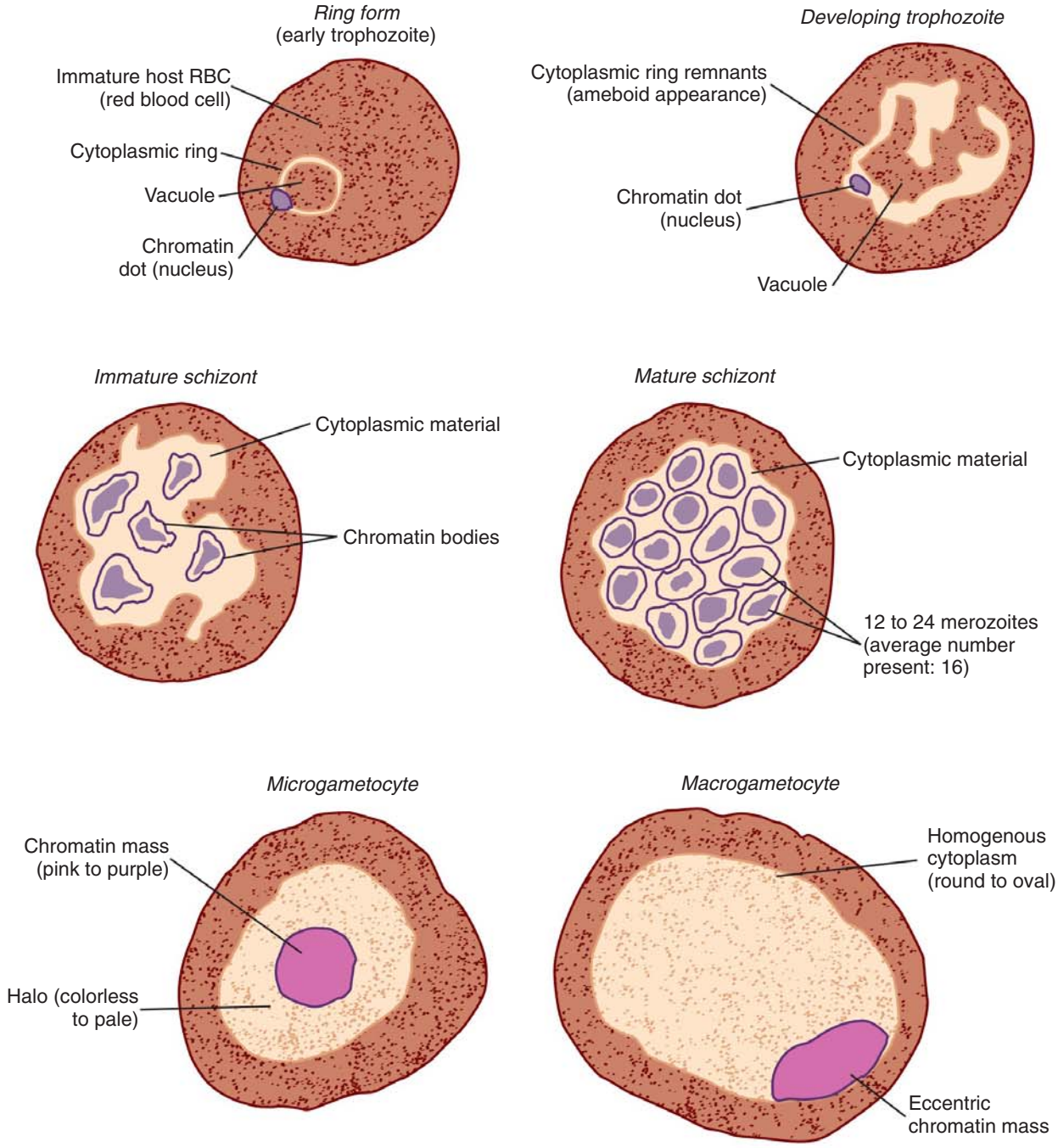

FIGURE 6-2 Commonly seen morphologic forms of *Plasmodium vivax*.

Mature Schizonts. The continuing division of chromatin results in 12 to 24 (average, 16) merozoites. These merozoites, surrounded by cytoplasmic material, occupy most of the RBCs. In some cases, the RBCs can hardly be detected. Brown pigment may also be present.

Microgametocytes. The typical *P. vivax* microgametocyte consists of a large pink to purple chromatin mass, when Giemsa-stained, which is surrounded by a colorless to pale halo. Evenly distributed cytoplasmic hemozoin is usually visible.

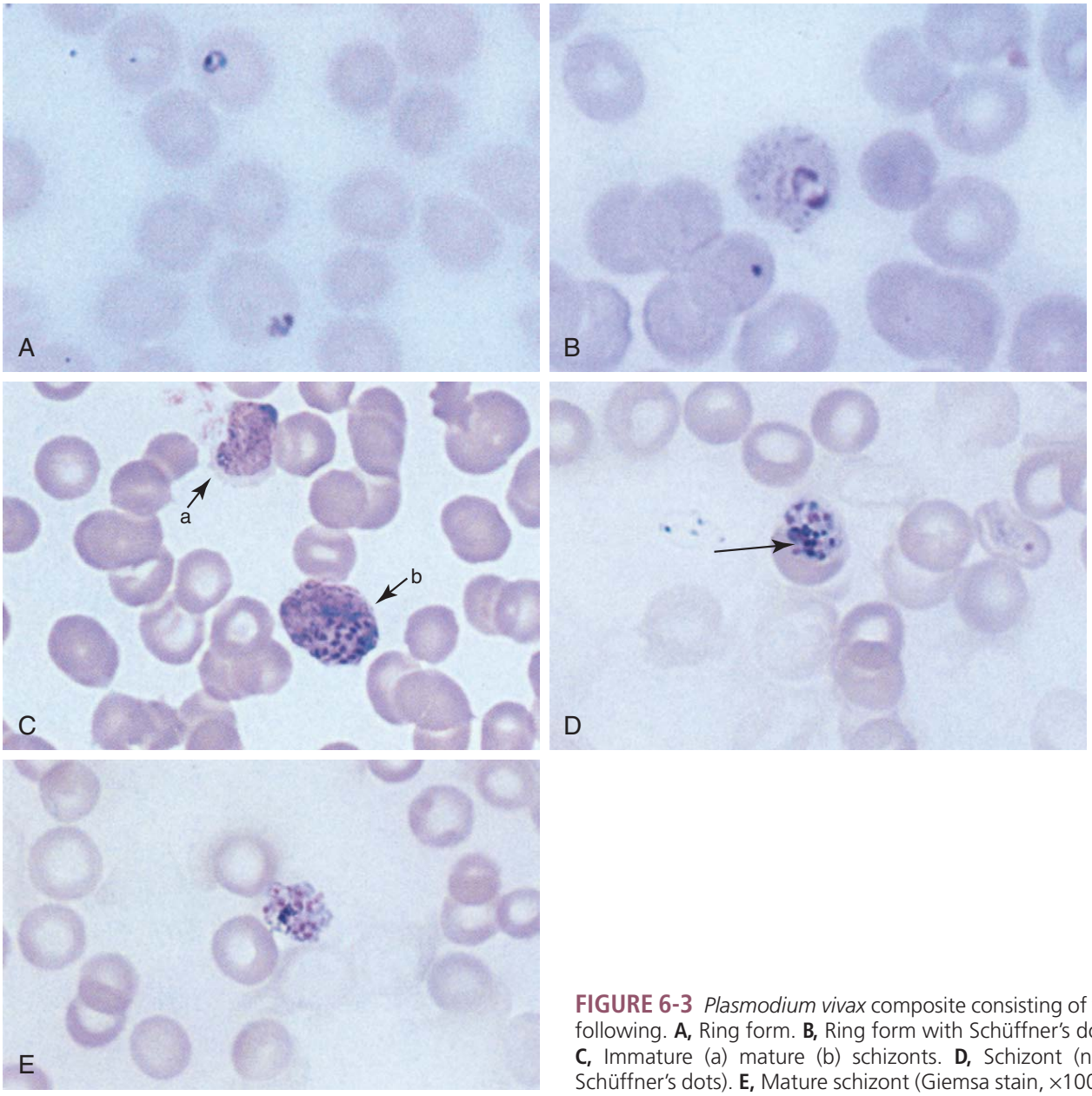

FIGURE 6-3 *Plasmodium vivax* composite consisting of the following. **A,** Ring form. **B,** Ring form with Schüffner's dots. **C,** Immature (a) mature (b) schizonts. **D,** Schizont (note Schüffner's dots). **E,** Mature schizont (Giemsa stain, ×1000).

Macrogametocytes. The average *P. vivax* macrogametocyte is characterized by round to oval homogeneous cytoplasm and an eccentric chromatin mass, often located against the edge of the parasite. Diffuse, delicate, light brown pigment may be visible throughout the parasite.

Other Morphologic Characteristics. Red blood cells infected with *P. vivax* tend to become enlarged and distorted in response to the presence of the growing parasites. The morphologic forms of *P. vivax*, with the exception of early ring forms that are less than 8 to 10 hours

postinfection, may contain tiny granules in the cytoplasm known as **Schüffner's dots** (also referred to as eosinophilic stippling). This characteristic is also typically seen in RBCs infected with *P. ovale*. Although their presence may not be of help in speciating these two *Plasmodium* species, Schüffner's dots may prove to be helpful in preliminarily ruling out the species that do not contain them, *P. malariae* and *P. falciparum*.

Laboratory Diagnosis

All morphologic stages of *P. vivax* may be seen on thick and thin peripheral blood films. However, thin blood films are of the most benefit in species diagnosis. Although the best time to observe numerous infected RBCs is halfway between paroxysms, blood samples may be taken at any time during the illness. The morphologic forms present at a given time reflect the developmental stage occurring at that point in time.

Life Cycle Notes

P. vivax characteristically tends to invade young RBCs. These immature cells are the primary target of invasion because they are typically pliable. This feature allows the RBCs to respond to the presence of the replicating parasite by increasing in size. Thus, distortion of the RBCs occurs.

Epidemiology

P. vivax is the most widely distributed malarial organism. Infections occur worldwide in both the tropics and subtropics. In addition, unlike the other *Plasmodium* species, *P. vivax* is also seen in temperate regions.

Clinical Symptoms

Benign Tertian Malaria. Patients infected with *P. vivax* typically begin to develop the symptoms of **benign tertian malaria** following a 10- to 17-day incubation period postexposure. These vague symptoms mimic those usually seen in cases of the flu, including nausea, vomiting, headache, muscle pains, and photophobia.

As infected RBCs begin to rupture, the resulting merozoites, hemoglobin, and toxic cellular waste products initiate the first in a series of paroxysms. These paroxysms typically occur every 48 hours (thus, the name tertian malaria). Untreated patients may experience and withstand numerous attacks over several years. However, infections that become chronic in nature may result in serious damage to the brain, liver, and kidney. Blockage of these organs occurs when toxic cellular waste products and hemoglobin, as well as clumps of RBCs, accumulate in the corresponding capillary veins, resulting in ischemia or tissue hypoxia. Dormant hypnozoites may cause relapses months to years following the initial infection.

Treatment

Choosing the appropriate treatment for malaria is, relatively speaking, a bit more complex than selecting chemotherapy for other parasitic infections. It is for this reason that malarial treatment will be discussed for the *Plasmodium* species as a group in this section.

There are numerous antimalarial drugs on the market (not all are available in the United States), including quinine, quinidine, chloroquine, amodiaquine, primaquine, pyrimethamine, sulfadoxine, dapsone, mefloquine, tetracycline, doxycycline, halofantrine, atovaquone, proguanil, ginghaosu, artemisinin, artemether, artesunate, pyronaridine, Fenozan B07, trioxanes, nonane endoperoxides, azithromycin, and WRZ38605. It is important to note that these available malarial medications affect the parasite in different ways, depending on the specific morphologic life cycle stages present at the time of administration. In addition, specific *Plasmodium* species respond differently to the presence of these treatments. Drug-resistant malaria has emerged over recent years, and the threat of a continuing increase in these strains remains a concern in the medical community. Physicians must take the known medication information into account, including

the possibility of potential drug toxicity, when selecting the course of treatment for individuals suffering from malaria, as well as the patient's G6PD status.

Prevention and Control

Prevention and control measures designed to halt the spread of *P. vivax* (as well as the other *Plasmodium* species) include personal protection such as netting, screening, protective clothing, and repellents for persons entering known endemic areas. In certain cases, prophylactic treatment may be used based on the geographic location and length of exposure, as well as other factors. Ideally, although difficult to accomplish, mosquito control, or better yet total eradication, would definitely break the organism life cycle in addition to promptly treating infected persons. The avoidance of sharing intravenous needles, as well as thorough screening of donor blood, are additional measures aimed at eliminating the risk of nonmosquito *Plasmodium* species transmission.

A number of studies have focused on developing potential malaria vaccines for *P. vivax* as well as the other *Plasmodium* species. Just as consideration of the specific malarial species and multiple morphologic forms in each organism life cycle is necessary for selecting proper treatment, this information is also important when designing vaccines. Unfortunately, questions have arisen regarding the effectiveness of such a control measure. Additional research is crucial to answer these questions. Although not currently available, the prospects are hopeful that long-awaited and much needed viable vaccines will be developed in the future.

Notes of Interest and New Trends

Methods using recombinant DNA probes and ribosomal RNA probes have been developed and experimentally tested for the diagnosis of malaria. Although they are presently inadequate for diagnostic purposes, they can be useful for screening donor blood and performing epidemiologic studies.

An effective means of preventing the spread of transfusion-acquired malaria has been the implementation of deferring the use of blood donors, including military personnel, who have traveled to known endemic areas, such as Panama and Vietnam. An immunofluorescent test, designed to screen donor units of blood for malaria, has been developed and is available for use.

It has been documented that 131 United States military personnel returned from service in Operation Restore Hope in Somalia infected with mosquito-acquired malaria. Experts agree that the probability of contracting malaria in such conditions has decreased dramatically over the past years because of the increased awareness of proper personal precautions, disease symptoms, and prompt treatment. It is interesting to note that *P. falciparum*, the deadliest *Plasmodium* species, was responsible for 94% of these 131 cases.

Quick Quiz! 6-4

Which morphologic characteristic may help in distinguishing *P. vivax* from *P. falciparum?* (Objective 6-11)

A. Hemozoin
B. Schüffner's dots
C. 72-hour paroxysm
D. None of the above

Quick Quiz! 6-5

P. vivax characteristically invades: (Objective 6-7A)

A. Immature RBCs
B. Senescent RBCs
C. All RBCs
D. Lymphocytes

Quick Quiz! 6-6

The incubation period for *P. vivax* is generally: (Objective 6-8)

A. 6 to 8 days
B. 7 to 10 days
C. 12 to 24 days
D. 10 to 17 days

Plasmodium ovale
(plaz-mo' dee-um/ovay'lee)

Common associated disease and condition names: Benign tertian malaria, ovale malaria.

Morphology

Ring Forms. The typical *P. ovale* ring form is similar in most respects to that of *P. vivax* (Fig. 6-4; Table 6-3). There are only two notable differences. First, the *P. ovale* ring is larger than *P. vivax*. Second, the *P. ovale* ring is thicker and often more ameboid in appearance than the ring of *P. vivax*.

TABLE 6-3 *Plasmodium ovale*: Typical Characteristics at a Glance

Relative age of infected RBCs	Only young and immature cells
Appearance of infected RBCs	Oval and enlarged, distorted with ragged cell walls
Morphologic Form*	**Typical Characteristics (Based on Giemsa Staining)**
Ring form	Resembles that of *P. vivax* Ring larger in size than *P. vivax* Ring thick and often somewhat ameboid in appearance
Developing trophozoite	Ring appearance usually maintained until late in development Ameboid tendencies not as evident as in *P. vivax*
Immature schizont	Progressive dividing chromatin surrounded by cytoplasmic material—often maintains circular shape early in development
Mature schizont	Parasites occupy 75% of RBCs. Rosette arrangement of merozoites (average of eight merozoites typically present)
Microgametocyte, macrogametocyte	Similar to *P. vivax*, only smaller in size

*All forms typically contain Schüffner's dots.

Developing Trophozoites. The *P. ovale* developing trophozoite maintains its ring appearance as it matures (Fig. 6-4; Table 6-3). The ameboid tendencies common in this stage of *P. ovale* are much less evident than those of *P. vivax*.

Immature Schizonts. The typical *P. ovale* immature schizont consists of progressively dividing chromatin material surrounded by cytoplasmic material, which in its earliest stages often maintains a circular shape (Fig. 6-4; Table 6-3).

Mature Schizonts. The *P. ovale* mature schizont is characterized by a rosette arrangement of merozoites (eight on average) (Fig. 6-4; Table 6-3). Late in its development, as much as 75% of the cell is occupied by the parasite.

Microgametocytes. The *P. ovale* microgametocyte resembles *P. vivax*, only smaller (Fig. 6-4; Table 6-3).

Macrogametocytes. As with the microgametocyte, the macrogametocyte of *P. ovale* is similar in appearance to *P. vivax*, only smaller. In Figure 6-4, the *P. ovale* microgametocyte and macrogametocyte are drawn closer in size to those of *P. vivax* to show the similarities in detail of both organisms (Fig. 6-4; Table 6-3).

Other Morphologic Characteristics. In addition to becoming enlarged and distorted, RBCs infected with *P. ovale* often develop ragged cell walls in response to the growing parasite. All morphologic forms of *P. ovale*, including very young ring forms, typically contain Schüffner's dots. These dots are often larger and darker than those seen in *P. vivax*.

Laboratory Diagnosis

All developmental stages of *P. ovale* may be seen in blood film preparations. As with the other *Plasmodium* species, thick and thin blood smears are generally examined, using the thick smears to identify the presence of malarial organisms and the thin smears to speciate them. Because all stages of development may be seen, as in *P. vivax* infections, the *P. ovale* morphologic forms present at a given time represent the specific life cycle phase occurring at the sample collection time.

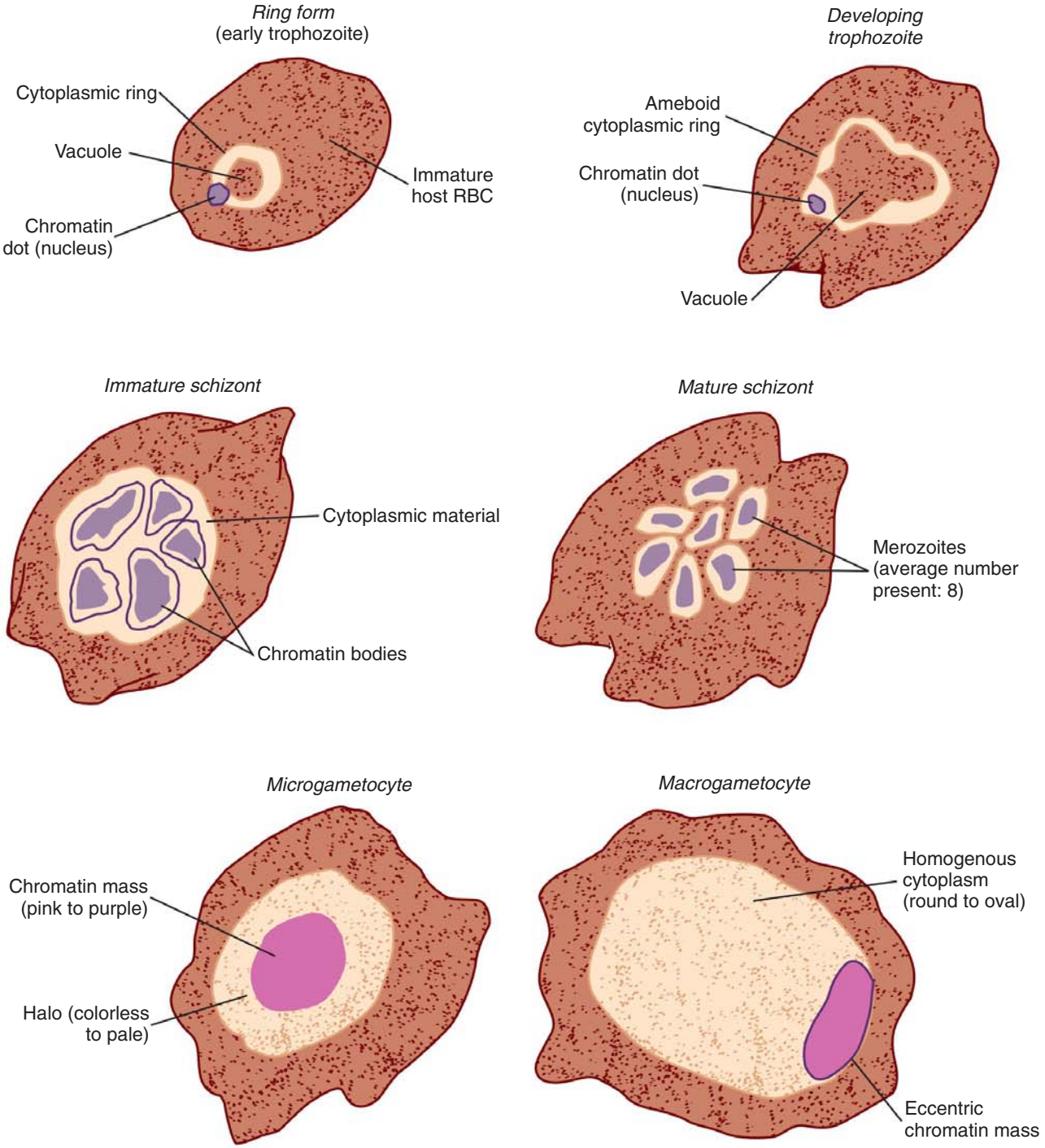

FIGURE 6-4 Commonly seen morphologic forms of *Plasmodium ovale*.

It is important to note that the ring forms, microgametocytes, and macrogametocytes of *P. vivax* and *P. ovale,* are usually difficult to distinguish because of their remarkable similarities. The mature schizont may ultimately be the morphologic form of choice for examination. Because there are definite differences in this form among the two species, the prospects of proper specific identification are much more promising.

Life Cycle Notes

Like *P. vivax*, *P. ovale* targets and subsequently infects young RBCs. These cells have the ability to adapt to the growing parasites by enlarging and assuming an oval shape. This distortion is enhanced by the development of a ragged cell wall.

Epidemiology

P. ovale is primarily found in tropical Africa, where it apparently has surpassed *P. vivax* in frequency of occurrence, as well as in Asia and South America.

Clinical Symptoms

Benign Tertian Malaria and Ovale Malaria. The clinical scenario of *P. ovale*, including initial infection symptoms, time of typical paroxysm cycle (every 48 hours), and relapses caused by the reactivation of hypnozoites, resembles that of *P. vivax*. A notable difference between the two species is that untreated patients with *P. ovale* typically experience infections that last approximately 1 year, whereas similar patients with *P. vivax* may remain infected for several years. In addition, *P. ovale* relapse infections, when they occur, usually result in spontaneous recovery, a characteristic not typically associated with those of *P. vivax*.

Treatment

The known measures for treating infections with *P. ovale* are the same as those discussed in detail for *P. vivax*.

Prevention and Control

The known measures of preventing and controlling *P. ovale* are the same as those discussed in detail for *P. vivax*. These include adequate personal protection, prophylactic therapy when indicated, prompt treatment of infected persons, mosquito control, screening donor blood, and the avoidance of sharing intravenous drug needles.

Quick Quiz! 6-7

Which morphologic form would be the best choice for distinguishing between *P. vivax* and *P. ovale*? (Objective 6-11)

A. Mature schizont
B. Ring form
C. Early trophozoite
D. Immature schizont

Quick Quiz! 6-8

In which geographic regions would the laboratorian most likely suspect *P. ovale* as the infecting agent? (Objective 6-2)

A. Tropical Africa
B. Asia
C. South America
D. All of the above

Quick Quiz! 6-9

Which of the following is considered an antimalarial medication? (Objective 6-9A)

A. Amoxicillin
B. Erythromycin
C. Chloroquine
D. Dicyclomine

Plasmodium malariae

(plaz-mo′ dee-um/ma-lair′ ee-ee)

Common associated disease and condition names: Quartan malaria, malarial malaria.

Morphology

Ring Forms. The typical *P. malariae* ring occupies approximately one sixth of the infected RBC (Fig. 6-5; Table 6-4). It is usually smaller than that of *P. vivax* and is connected

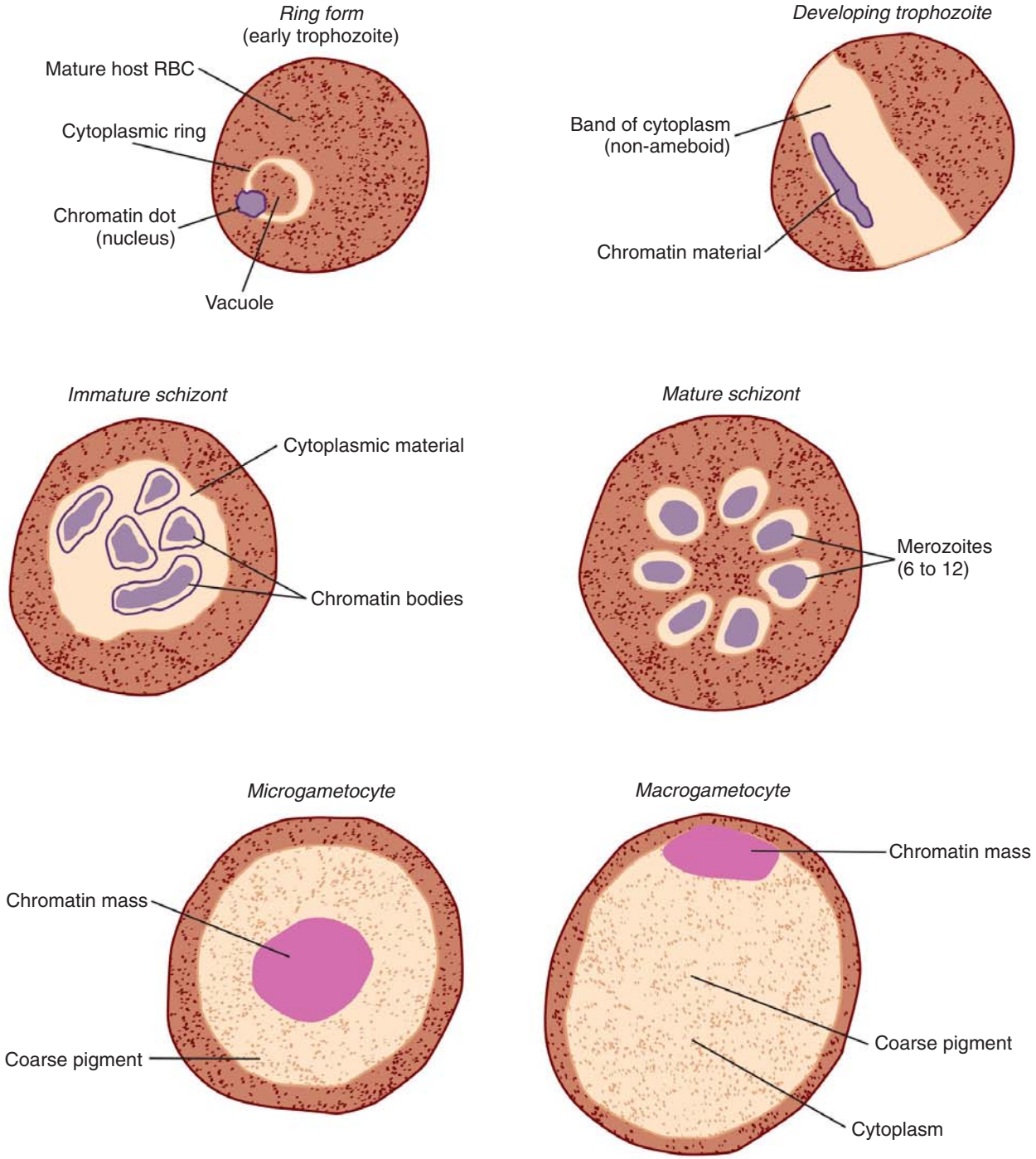

FIGURE 6-5 Commonly seen morphologic forms of *Plasmodium malariae*.

by a heavy chromatin dot. The vacuole may at times appear filled in. Pigment characteristically forms early.

Developing Trophozoites. The key characteristic of this morphologic form that distinguishes it from the other *Plasmodium* species is the formation of a nonameboid solid cytoplasm potentially assuming a band, bar, oval, or roundish shape (Fig. 6-5; Table 6-4). The cytoplasm consists of coarse dark brown pigment often masking

TABLE 6-4 *Plasmodium malariae*: Typical Characteristics at a Glance

Relative age of infected RBCs	Only mature cells
Appearance of infected RBCs	Normal size, no distortion
Morphologic Form*	**Typical Characteristics (Based on Giemsa Stain)**
Ring form	Smaller than *P. vivax* Occupies one sixth of the RBC Heavy chromatin dot Vacuole may appear filled in Pigment characteristically forms early
Developing trophozoite	Nonameboid solid cytoplasm that may assume roundish, oval, band, or bar shape Cytoplasm contains coarse dark brown pigment; may mask chromatin material Vacuoles absent in mature stages
Immature schizont	Similar to that of *P. vivax*, only smaller; may contain large and dark peripheral or central granules
Mature schizont	Typically contains 6 to 12 merozoites arranged in rosettes or irregular clusters Central arrangement of brown-green pigment may be visible Infected RBC may not be seen because developing parasites often fill the cell completely.
Microgametocyte, macrogametocyte	Similar to *P. vivax*, only smaller in size; pigment usually darker and coarser Older forms assume an oval shape.

*The cytoplasm of heavily stained *P. malariae* may contain Ziemann's dots.

the chromatin material. Vacuoles are absent in the mature forms of this stage.

Immature Schizonts. The typical *P. malariae* immature schizont is similar to that of *P. vivax*, with two exceptions (Fig. 6-5; Table 6-4). *P. malariae* immature schizonts are characteristically smaller than those of *P. vivax*. In addition, larger and darker peripheral or central granules may be seen in *P. malariae* immature schizonts.

Mature Schizonts. The mature schizont of *P. malariae* typically contains 6 to 12 merozoites, usually arranged in rosettes or irregular clusters (Fig. 6-5; Table 6-4). A central arrangement of brown-green pigment may often be visible in this stage. In the case of normal-sized RBCs, the cell itself may not be seen because the parasites tend to fill the cell completely. Figure 6-4 shows infection of a larger than normal-sized red blood cell.

Microgametocytes. The average *P. malariae* microgametocyte is similar to that of *P. vivax*, with only one notable exception—the pigment is darker and coarser than the pigment of *P. vivax* (Fig. 6-5; Table 6-4). Older forms of the *P. malariae* microgametocytes are typically oval in shape.

Macrogametocytes. The *P. malariae* macrogametocyte resembles that of *P. vivax*. As with the *P. malariae* microgametocyte, the macrogametocyte pigment is darker and coarser than the pigment seen in *P. vivax*. Older forms of this stage also tend to assume an oval shape.

Other Morphologic Characteristics. *P. malariae* multiplies within the confines of mature RBCs. Enlargement and distortion of these cells does not occur because the mature RBC cell wall is no longer pliable. Unlike both *P. vivax* and *P. ovale*, *P. malariae* does not contain Schüffner's dots. The lack of this feature is important to note when speciating the *Plasmodium* organisms. However, the cytoplasm of heavily stained *P. malariae* may contain fine dustlike dots known as **Ziemann's dots**.

Laboratory Diagnosis

Because *P. malariae* passes through the ring stage quickly, this stage is not commonly seen. The most frequently encountered growth stages of *P.*

malariae seen are the developing trophozoite and the immature and mature schizonts. Although gametocytes may occasionally be seen, they are not readily distinguishable from those of *P. vivax* and thus are of little help in diagnosing *P. malariae* infections. Searching thick and thin Giemsa-stained peripheral blood films will reveal these morphologic forms in patients infected with *P. malariae*. As with the other *Plasmodium* species, detection of infection may be accomplished by reviewing thick blood smears, but the speciation is best determined with the use of thin blood smears.

Life Cycle Notes

P. malariae primarily infects mature RBCs. This particular group of RBCs has well-established cell walls that are not conducive to expansion. Infection with the parasite, therefore, does not result in cell distortion or enlargement. The parasite responds by forming bands and other shapes as necessary to maintain itself.

Epidemiology

P. malariae is found in subtropic and temperate regions of the world. These infections appear to occur less frequently than those with both *P. vivax* and *P. falciparum*.

Clinical Symptoms

Quartan or Malarial Malaria. Patients suffering from **quartan malaria** (also known as **malarial malaria**) infections caused by the presence of *P. malariae* typically experience an incubation period of 18 to 40 days followed by the onset of flulike symptoms. Cyclic paroxysms occur every 72 hours (thus, the name quartan malaria). Spontaneous recovery may result after the initial infection. There are no known relapses because dormant hypnozoites are not associated with *P. malariae* infections. However, repeated attacks may occur for 20 years or more and may be moderate to severe in nature.

Treatment

The known measures for treating infections with *P. malariae* are the same as those discussed for *P. vivax*.

Prevention and Control

The prevention and control measures necessary to eradicate *P. malariae* are similar to those of *P. vivax*. Prophylactic therapy, when appropriate, proper clothing, netting, and screening, as well as the use of insect repellents, offer protection to humans entering known endemic areas. The control of mosquito breeding areas and thorough screening of donor blood units and the avoidance of sharing intravenous drug needles are all essential measures required to halt the spread of *P. malariae*.

Quick Quiz! 6-10

Which morphologic form is not typically seen in infections of *P. malariae*? (Objective 6-7B)

A. Mature schizont
B. Ring form
C. Immature schizont
D. Macrogametocyte

Quick Quiz! 6-11

Which of the following are morphologic features of *P. malariae*? (Objective 6-12A)

A. Schüffner's dots
B. Ziemann's dots
C. Maurer's dots
D. None of the above

Quick Quiz! 6-12

Which of the following is not a prevention and control measure for malaria? (Objective 6-9B)

A. Wearing the hair up
B. Following prophylactic therapy when traveling to malaria-endemic areas
C. Bed netting
D. Proper clothing, such as long-sleeved shirt and long pants

Plasmodium falciparum
(plaz-mo′dee-um/fal-sip′uh-rum)

Common associated disease and condition names: Black water fever, malignant tertian malaria, aestivoautumnal malaria, subtertian malaria, falciparum malaria.

Morphology

Ring Forms. The typical small, delicate ring form of *P. falciparum* consists of scanty cytoplasm connected to one (circle configuration) or two (headphone configuration) small chromatin dots (Figs. 6-6 and 6-7; Table 6-5). A small vacuole is usually visible. Multiple rings in an RBC are frequently seen. *P. falciparum* has the ability to produce accolé (appliqué) forms as well as slender variations.

Developing Trophozoites. The *P. falciparum* developing trophozoite typically consists of one or two rings that each possess a heavy cytoplasmic ring—that is, the cytoplasm is thicker than in the preceding ring form stage (Figs. 6-6 and 6-7; Table 6-5). Fine pigment granules may also be visible. Mature stages of this form are not routinely seen in the peripheral blood.

Immature Schizonts. The immature schizont phase of *P. falciparum* is not routinely seen in the peripheral blood (Figs. 6-6 and 6-7; Table 6-5). This form is characterized by multiple chromatin bodies surrounded by cytoplasm and is only visible in those with severe infections.

Mature Schizonts. As with the immature schizont, the mature schizont is only visible in the peripheral blood of patients with severe *P. falciparum* infection (Figs. 6-6 and 6-7; Table 6-5). Although the typical mature schizont contains 24 merozoites, 8 to 36 merozoites in a cluster arrangement may be present in this stage.

Microgametocytes. The typical *P. falciparum* microgametocyte assumes a characteristic sausage or crescent shape (Figs. 6-6 and 6-7; Table 6-5). Dispersed central chromatin and nearby black chromatin are usually visible.

Macrogametocytes. The macrogametocyte of *P. falciparum* is typically sausage- or crescent-shaped, just like the corresponding microgametocyte form described earlier (Figs. 6-6 and 6-7; Table 6-5). Because of this similarity in shape, it is difficult to distinguish the macrogametocyte from the microgametocyte. The macrogametocyte chromatin is usually more compact than the chromatin of the microgametocyte.

TABLE 6-5 *Plasmodium falciparum*: Typical Characteristics at a Glance

Relative age of infected RBCs*	May infect cells of all ages
Appearance of infected RBCs	Normal size, no distortion
Morphologic Form	**Typical Characteristics (Based on Giemsa Stain)**
Ring form	Circle configuration (one chromatin dot) or headphone configuration (two chromatin dots) Scanty cytoplasm Small vacuole usually visible Multiple rings common Accolé forms possible
Developing trophozoite	Heavy rings common Fine pigment granules Mature forms only seen in severe infections
Immature schizont	Multiple chromatin bodies surrounded by cytoplasm Only detected in severe infections
Mature schizont	Typically consists of 8-36 merozoites (average, 24) in cluster arrangement Only detected in severe infections
Microgametocyte	Sausage- or crescent-shaped Dispersed central chromatin with nearby black pigment usually visible
Macrogametocyte	Sausage- or crescent-shaped Compact chromatin Black pigment surrounding chromatin may be visible

*The cytoplasm of red blood cells infected with *P. falciparum* may contain Maurer's dots.

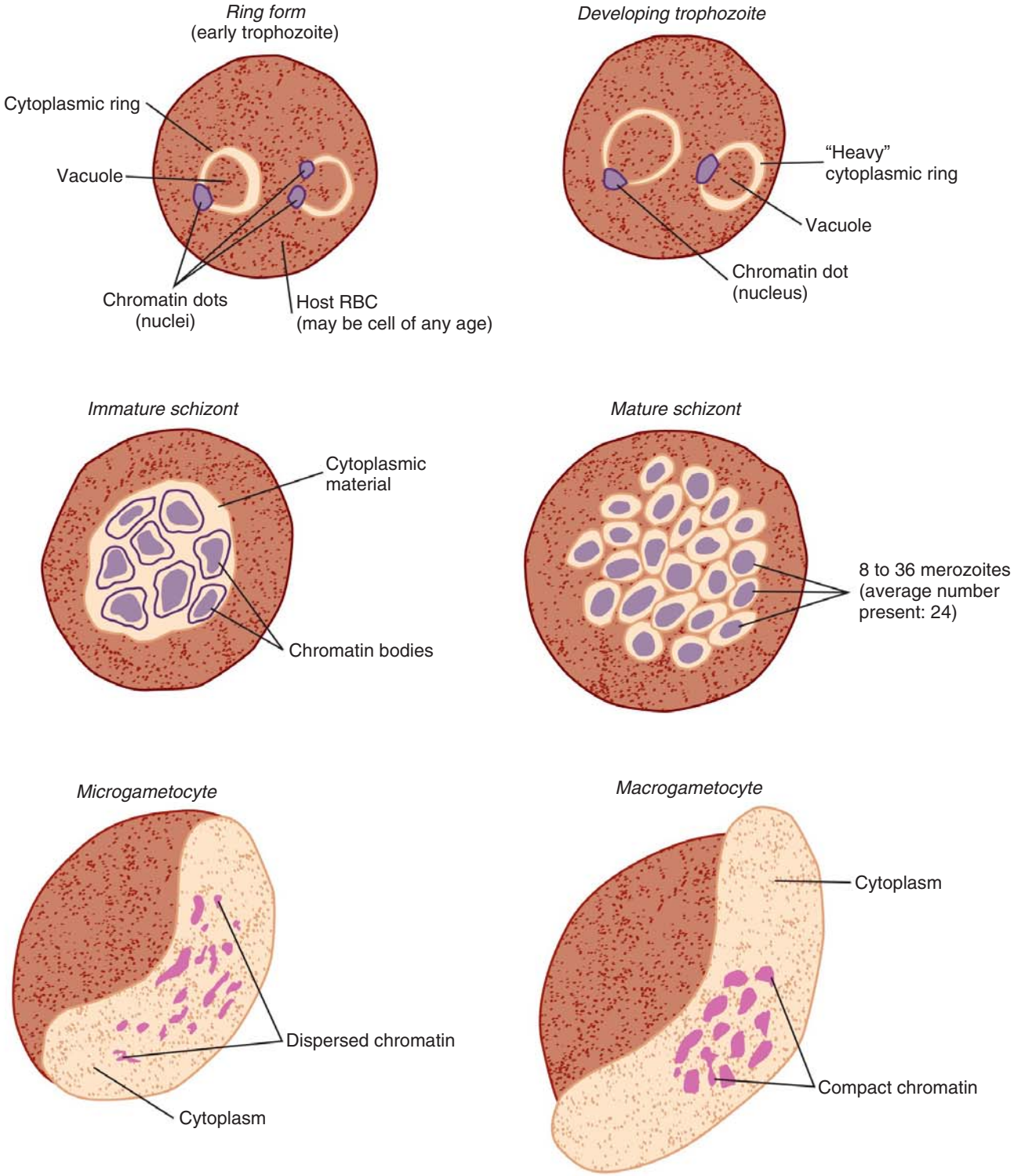

FIGURE 6-6 Commonly seen morphologic forms of *Plasmodium falciparum*.

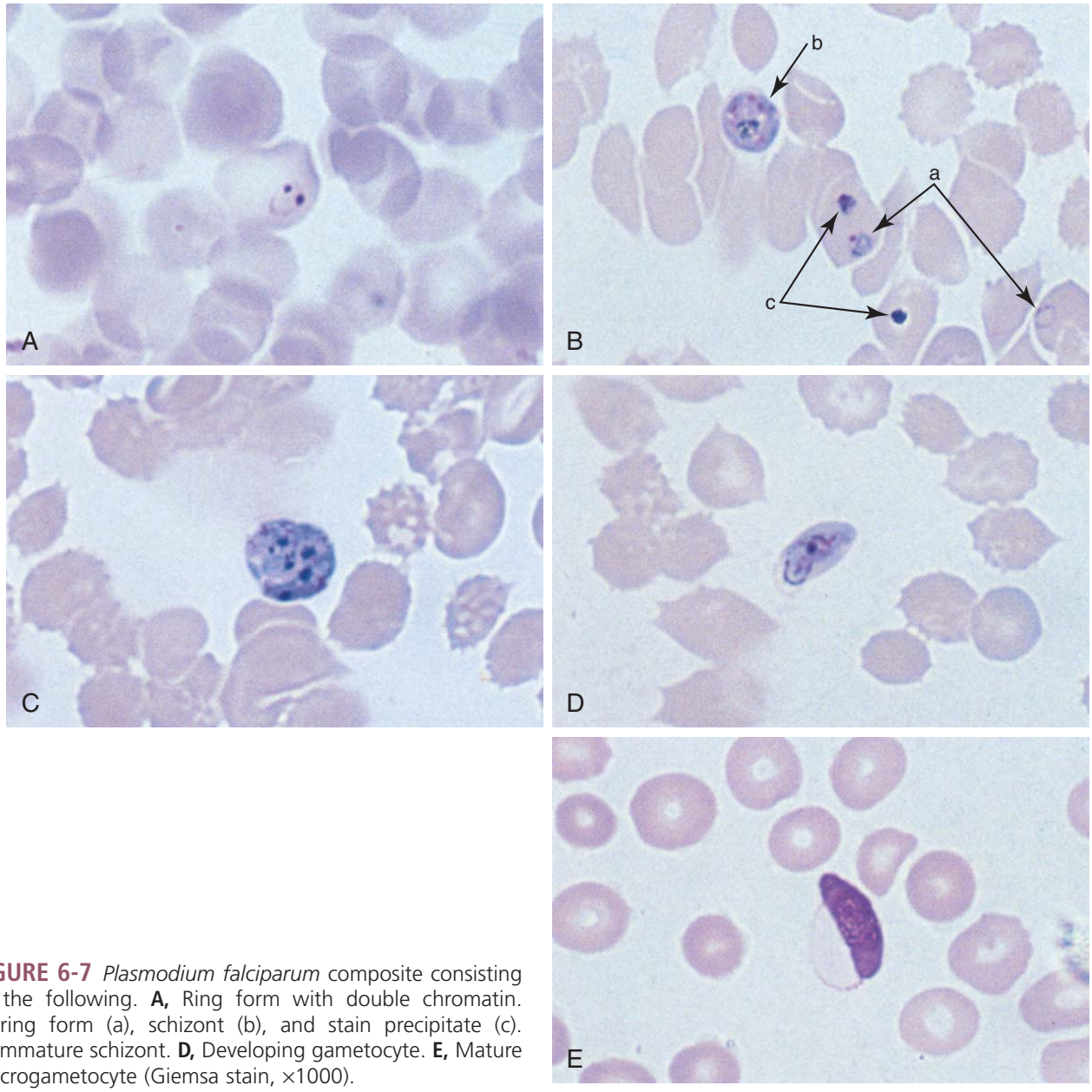

FIGURE 6-7 *Plasmodium falciparum* composite consisting of the following. **A,** Ring form with double chromatin. **B,** ring form (a), schizont (b), and stain precipitate (c). **C,** Immature schizont. **D,** Developing gametocyte. **E,** Mature macrogametocyte (Giemsa stain, ×1000).

Black pigment surrounding the chromatin may also be visible.

Other Morphologic Characteristics. *P. falciparum* may infect RBCs at any age. However, young infected cells do not enlarge and become distorted, as they do when infected with *P. vivax* or *P. ovale*. The morphologic forms of *P. falciparum* do not contain Schüffner's dots or Ziemann's dots. Rather, these growth stages may contain dark-staining, irregular to comma-shaped cytoplasmic dots called **Maurer's dots**, a feature that when present, may be helpful in differentiating the specific malarial species.

Laboratory Diagnosis

Peripheral blood smears from patients suffering with a mild to moderate *P. falciparum* infection typically reveal only the ring forms and gametocyte forms. The trophozoites and schizonts are

usually only visible in the peripheral blood of patients with severe infection. Thick smears primarily serve as screening slides, whereas thin smears are used for the speciation of *P. falciparum*.

Because *P. falciparum* may infect RBCs at any age, severe infections and multiple infections may result. Although *P. falciparum* may invade young pliable RBCs, these cells usually do not appear enlarged or distorted, as is the case with *P. vivax* and *P. ovale* infections. Unlike the other *Plasmodium* species, the development of all growth stages of *P. falciparum,* after the formation of the ring form, occurs in the capillaries of the viscera. It is for this reason that typically only the young ring forms and gametocytes are seen in the peripheral blood. Hypnozoites are not produced in the liver of patients with *P. falciparum* infections, and relapses are not known to occur. However, recrudescence may occur, and these attacks may ultimately prove fatal.

Life Cycle Notes

Plasmodium falciparum invades red blood cells of any age and may infect up to 50% of the red blood cell population at any one time throughout the course of the infection. Schizogony generally occurs in the capillaries and blood sinuses of internal organs during infection with this parasite.

Furthermore, infections with *P. falciparum* generally tend to occur in the warmer months of late summer and early autumn—thus, the name **aestivoautumnal malaria.** *P. falciparum* needs the warmer months for reproduction within the *Anopheles* mosquito, which explains this seasonal factor.

Epidemiology

The geographic distribution of *P. falciparum* appears to be limited to the tropical and subtropical regions of the world.

Clinical Symptoms

Black Water Fever and Malignant Tertian Malaria. Following a relatively short incubation period of 7 to 10 days, as compared with infections caused by the other *Plasmodium* species, which may last for months to years, patients infected with *P. falciparum* exhibit early flulike symptoms. Daily episodes of chills and fever, as well as severe diarrhea, nausea, and vomiting, rapidly develop followed by cyclic paroxysms, which occur every 36 to 48 hours. A fulminating disease results and the intestinal symptoms (nausea, vomiting, and diarrhea) mimic those seen in malignant infections—hence, the name **malignant tertian malaria**.

P. falciparum typically produces the most deadly form of malaria in untreated patients. This is in part because all ages of RBCs may be infected, thus producing large amounts of toxic cellular debris and capillary plugs consisting of massed red cells, platelets, malarial pigments, and leukocytes. *P. falciparum* may enter the kidney, brain, and/or liver. Kidney involvement, known as **black water fever,** usually results in marked **hemoglobinuria** (the presence of hemoglobin in the urine) caused by *P. falciparum*-induced red cell destruction. Acute renal failure, tubular necrosis, nephrotic syndrome, and death may result. The brain frequently becomes involved when plugs form in the associated capillaries. Patients often slip into a coma, followed by death. Abdominal pain, the vomiting of bile, rapid dehydration, and severe diarrhea are typically noted during *P. falciparum* liver involvement.

Treatment

The known measures for treating infections with *P. falciparum* are the same as those discussed for *P. vivax*. It is important to note that the malaria should be treated first and then the secondary complicating health problems caused by the malaria.

Prevention and Control

Because of the potential severity of infections with *P. falciparum*, prompt treatment of known infected individuals is crucial to halt the spread

of the disease. Other prevention and control measures include prophylactic therapy, when appropriate, proper personal protection when entering known endemic areas, mosquito control by chemically destroying their breeding areas, thorough screening of donor blood units, and the avoidance of sharing intravenous drug needles.

The quest to develop a vaccine targeted against malaria has been underway since the mid 1980s. A collaborative effort of the following entities recently resulted in the development of a vaccine against malignant tertian malaria known as RTS,S/AS01: GlaxoSmithKline Biologicals', a global program known as the PATH Malaria Vaccine Initiative (VMI), research organizations in Africa and elsewhere, and the Bill and Melinda Gates foundation which provides funding support. Clinical trials in children ages 5 to 17 months in areas of Africa using other effective malaria prevention and treatment interventions to date show remarkable success. Children who received the vaccine had approximately half the number of clinical outbreaks versus those who did not receive the vaccine. The next phase of clinical trials to be conducted is slated to occur in children 6 to 12 weeks of age.

Notes of Interest and New Trends

Numerous serologic studies that have focused on the detection of antigens and antibodies in specimens of patients with *P. falciparum* have been conducted in recent years. Tests using human serum and plasma, identification reagents, cultures of *P. falciparum*, and urine samples have all been developed. Although serologic tests are presently available for *P. falciparum*, they are hard to obtain and thus are not useful for monitoring therapy in a patient. However, they are useful in ruling out malaria in a patient with fever of unknown origin.

Methodology has been developed and tested to identify high and low numbers of *P. falciparum* by DNA hybridization. It is primarily used as an epidemiologic tool at the present time, but this technology may also prove to be of benefit in the future for diagnostic purposes and screening donor blood supplies.

Quick Quiz! 6-13

What age of red blood cell does *P. falciparum* typically invade? (Objective 6-7A)

A. Mature red blood cells
B. Immature red blood cells
C. All red blood cells, regardless of age
D. Does not invade red blood cells

Quick Quiz! 6-14

P. falciparum is commonly found in the United States. (Objective 6-2)

A. True
B. False

Quick Quiz! 6-15

Black water fever can be described by which of the following: (Objective 6-1)

A. Marked hemoglobinuria
B. Kidney involvement in *P. falciparum* infections
C. Caused by *P. falciparum*–induced red blood cell destruction
D. All of the above

Plasmodium knowlesi
(plaz-mo'dee-um/)

Once thought to be solely a parasite of Old World Monkeys, *P. knowlesi* has recently been identified in humans suffering from malaria in Malaysia and other parts of Southeast Asia. On more than one occasion the infection proved fatal. Although there is still much to learn about *P. knowlesi,* the incidence of corresponding life-threatening malarial illness is predicted to rise and as such it is worthy of brief discussion in this chapter.

P. knowlesi morphologically resembles *P. malariae* to the extent that there is documented evidence that misdiagnosis by microscopic methods has occurred. Depending on the morphologic forms present, *P. knowlesi* may resemble *P. falciparum*. DNA extraction and nested-PCR examination of samples have been known to reveal the differences between the two *Plasmodium* species. On the contrary,

cross-reactivity with *P. vivax* appears to interfere with PCR testing. Clinical features of infected individuals range from respiratory distress, acute renal or multi-organ failure, to shock. Treatments vary depending on disease severity. Infected patients with no complications have been treated with quinine, chloroquine or artemether-lumefantrine. Inraveous quinine, artesunate or a combination of chloroquine-primiquine have proven to be effective treatments for patients with severe disease. Artemisinin has shown be quite effective when used as treatment for both mild and severe forms of malaria due to *P. knowlesi*.

BABESIA SPECIES

As noted, there are numerous species of *Babesia* and, of those, four are known to be of concern regarding transmission to humans. Following an introduction to *Babesia* species that includes a historical perspective and descriptions of the most commonly found morphologic forms, two of the most commonly encountered *Babesia* parasites will be discussed.

Historical Perspective

Apicomplexan parasites belonging to the genus *Babesia* are often seen infecting animals, wild and domestic. Babesial organisms were first described in the 1880s as being responsible for **Texas cattle fever** or **red water fever**; this parasitic infection almost decimated the cattle production industry. However, in recent years, several species have demonstrated an ability to cause illness in humans, who are usually considered as an accidental host. The two babesial organisms most commonly isolated from clinical specimens are *B. microti* (*Theileria microti*) and *B. divergens*; other species have demonstrated an ability to cause disease, but are a rarer occurrence. It is important to point out here that some sources suggest that due to ribosomal RNA comparisons *B. microi* fits more into a related genus known as *Theileria* and thus now call it *Theileria microti*. Until this change is universally accepted in the parasitology community, the current name of *B. microti* will be used in this text.

TABLE 6-6 *Babesia* Species Trophozoite: Typical Characteristics at a Glance

Parameter	Description
Appearance	Resembles a ring form Does not contain Schüffner's, Ziemann's, or Maurer's dots
Ring characteristics when stained with Giemsa	Blue cytoplasmic circle connected with or to red chromatin dot Vacuole usually present

TABLE 6-7 *Babesia* Species Merozoite: Typical Characteristics at a Glance

Parameter	Description
Appearance	Resembles four trophozoites attached by their respective chromatin dots in the shape of a Maltese cross

Morphology and Life Cycle Notes

The typical life history of each of these organisms involves several morphologic forms. However, for the purposes of this text, only the two forms most commonly encountered in human specimens will be discussed, the trophozoite and merozoite. Other morphologic forms are responsible for invading the RBCs, but are generally never seen at the point of laboratory diagnosis.

Trophozoite. The trophozoite (Table 6-6) develops after the sporozoite infects the red blood cell. This form resembles the ring form of *Plasmodium* infections. The typical ring, when stained with Giemsa, consists of a blue cytoplasmic circle connected with or to a red chromatin dot, also referred to by some as a nucleus. The space inside the ring is known as a vacuole. The ring form is the most commonly seen diagnostic feature of babesiosis and can be differentiated from malarial organisms by the absence of malarial pigments (hemozoin) and of Schüffner's, Ziemann's, or Maurer's dots (Table 6-7).

Merozoite. The merozoite develops within the red blood cell as the trophozoite matures. The merozoite resembles four trophozoites attached together by their respective chromatin dots in the

shape of a cross, often referred to as resembling a Maltese cross. Merozoites undergo binary fission in the human host to produce more sporozoites.

Babesiosis has a sexual and asexual phase in its life cycle. The sexual phase occurs within its vector, the tick, and the asexual phase occurs within its host (e.g., mice, deer, cattle, dogs, humans). It is generally transmitted through the bite of an infected tick of the genus *Ixodes*. The uninfected host must be in contact with the tick's saliva for 12 hours or longer before this parasite can be transmitted. The infected tick transmits sporozoites into the uninfected host. The sporozoites invade the red blood cells and develop into trophozoites. Multiple sporozoites can infect a RBC, so multiple trophozoites can be seen within the infected RBC. The trophozoites continue to develop into merozoites. The merozoites mature and develop into gametocytes inside their normal animal host, but are not generally seen in the accidental human host. In the human host, the merozoites undergo binary fission to produce more sporozoites; when the number of sporozoites exceeds the red blood cell's capacity, it ruptures, releasing sporozoites to infect more red blood cells. An ixodid tick bites an infected host and the gametocytes travel to the gut, where they unite to form an ookinete. The ookinete travels to the salivary glands where **sporogony**—the process of spore and sporozoite production via sexual reproduction—takes place, resulting in numerous sporozoites that can be transmitted to a new host.

Quick Quiz! 6-16

Humans are an accidental host of *Babesia* species. (Objective 6-6)
A. True
B. False

Laboratory Diagnosis

Giemsa-stained peripheral blood films are the specimens of choice for the laboratory diagnosis of babesiosis. Wright's stain may also be used and will result in an accurate diagnosis. However, because Giemsa is the recommended stain for all blood films submitted for parasite study, the specific morphologic discussion of *Babesia* is based on the use of this stain. Thick and thin blood films should be made and examined. Thick blood smears serve as screening slides; thin blood smears are used for differentiating *Babesia* from *Plasmodium* spp. All blood films should be studied under oil immersion. Careful and thorough screening of all smears is crucial to ensure the correct identification, reporting, and ultimately the proper treatment of the organisms present. The timing of blood collection for the study of *Babesia* is not crucial to success in retrieving the *Babesia* parasites; they have not shown periodicity, as have the malarial organisms.

In addition to blood films, serologic tests and PCR techniques for babesiosis are available. These tests are generally best used for diagnosing patients with a low parasitemia or in donor blood supply screening and epidemiologic studies. Serologic and PCR testing are also valuable for the speciation of *Babesia,* because this is a limitation of blood film tests. Representative laboratory diagnostic methodologies are described in Chapter 2 as well as within each individual parasite discussion, as appropriate.

Quick Quiz! 6-17

The specimen of choice for the recovery of *Babesia* is: (Objective 6-10)
A. Tissue
B. Cerebral spinal fluid (CSF)
C. Stool
D. Blood

Pathogenesis and Clinical Symptoms of *Babesia*

The typical patient presenting with babesiosis was exposed 1 to 4 weeks prior to the onset of symptoms. Babesiosis is generally a self-limiting infection. Its onset is usually gradual and characterized by prodrome-like symptoms—fever,

headache, chills, sweating, arthralgias, myalgias, fatigue, and weakness. The fever shows no periodicity. Hepatosplenomegaly and mild to severe hemolytic anemia have been recorded. Elevated bilirubin and transaminase levels have also been demonstrated.

Babesiosis tends to be worse for the splenectomized and immunocompromised patient. Rare asymptomatic infections have also been recorded. Infections tend to present in late summer to early fall and generally correlate with the breeding cycle of the ixodid tick. It is also not uncommon to see a patient coinfected with Lyme disease and/or human granulocytic ehrlichiosis.

Quick Quiz! 6-18

Babesiosis is characterized by all the following except: (Objective 6-8)

A. Trophozoites resembling the ring form seen in *Plasmodium* infections
B. A mild to severe hemolytic anemia
C. Fever periodicity
D. None of the above

Babesia Classification

Babesia species belongs to the phylum Apicomplexa, class Aconoidasida, order Piroplasmida, family Babesiidae. The *Babesia* species discussed in this chapter occur in the blood, as indicated in Figure 6-8.

Babesia microti
(baa″beez-ee′yuh/my″crō-tee)

Common associated disease and condition names: Presently, no common name exists.

Babesia divergens
(baa″beez-ee′yuh/di′′vər-jənz)

Common associated disease and condition names: Presently, no common name exists.

Morphology

The morphologic features of *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Laboratory Diagnosis

The laboratory diagnostic procedures for identifying *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Life Cycle Notes

The life cycle of *B. microti* and *B. divergens* are described in the general notes concerning babesiosis.

Epidemiology

B. microti is commonly found in areas of southern New England, such as Nantucket, Martha's Vineyard, Shelter Island, Long Island, and Connecticut. It has also been isolated in clinical specimens in patients in New Jersey, Wisconsin, Missouri, Georgia, North Carolina, and Mexico. The vector most commonly associated with the transmission of *B. microti* is *Ixodes dammini*. The principal reservoir host for this infection is the white-footed mouse, *Peromyscus leucopus*.

B. divergens is commonly found in European countries, particularly those in the former Yugoslavia, Russia, Ireland, and Scotland. The vector most commonly associated with the transmission

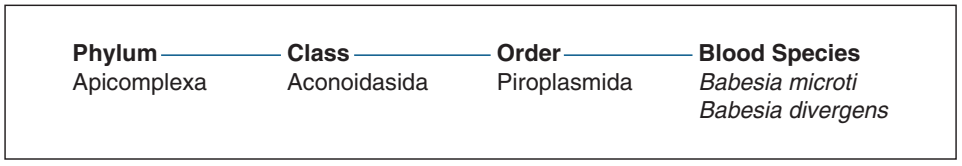

FIGURE 6-8 Parasite classification—*Babesia* species.

of *B. divergens* is *Ixodes ricinus*. The principal reservoir hosts are cattle and rabbits. *B. divergens* has also been described in the Nantucket area, primarily in the rabbits and birds of the region.

Babesiosis has also been demonstrated to be a transfusion-transmissible disease and has the potential to be transmitted congenitally and by the sharing of intravenous drug needles.

Clinical Symptoms

The clinical symptoms for *B. microti* and *B. divergens* infections have been described earlier ("Pathogenesis and Clinical Symptoms"). *B. divergens* tends to be the more severe of the two parasitic infections and is frequently fatal if left untreated. *B. microti* tends to be rather benign and self-limiting. Disease with either of these organisms is often more severe for older adult, immunosuppressed, and/or splenectomized patients.

Treatment

The treatment of babesiosis often involves a combination of drugs. The most common combinations are clindamycin and quinine or atovaquone and azithromycin. Diminazene and pentamidine, in combination or singly, and pyrimethamine and quinine, in combination or singly, have also shown promise, but the side effects of some of these medications may be less than desirable. Patient age, immune status, G6PD status, and other clinical symptoms will play a role in the physician's choice as to which therapy is best for the patient.

Prevention and Control

The best prevention measure is to avoid tick-infested areas. However, examining the body for ticks immediately after leaving such an area and rapid removal of the tick are crucial. The tick must feed for at least 12 hours before it is able to transmit the parasite. Using insect repellents and eradicating the tick population are also helpful for disease prevention and control.

Quick Quiz! 6-19

Which of the following are laboratory diagnostic procedures is recommended for specifically identifying *T. microti*? (Objective 6-10)

A. Thick and thin blood films
B. Serologic testing
C. PCR techniques
D. Both B and C are correct.
E. None of the above

Quick Quiz! 6-20

Which of the following is not a location known for infection by *T. microti*? (Objective 6-2)

A. California
B. North Carolina
C. Mexico
D. Nantucket

Quick Quiz! 6-21

For which patient would babesiosis be more severe? (Objective 6-8)

A. The splenectomized
B. The patient with *Babesia divergens*
C. Older adults
D. All of the above

LOOKING BACK

As with all parasites, the proper identification of malaria and babesiosis is crucial to ensure that the patient is adequately treated when necessary. *Plasmodium* and *Babesia* spp. have morphologic forms that may look similar. However, because not all species typically show all the morphologic forms in the peripheral blood, coupled with the fact that other morphologic forms look different (e.g., mature schizonts, gametocytes) and whether pigment is produced, allow accurate speciation of the malarial organism and differentiation of malaria from babesiosis. Thorough screening of all smears is essential; this practice ensures that even low numbers of organisms will be detected.