Cyclospora* and *Cryptosporidium

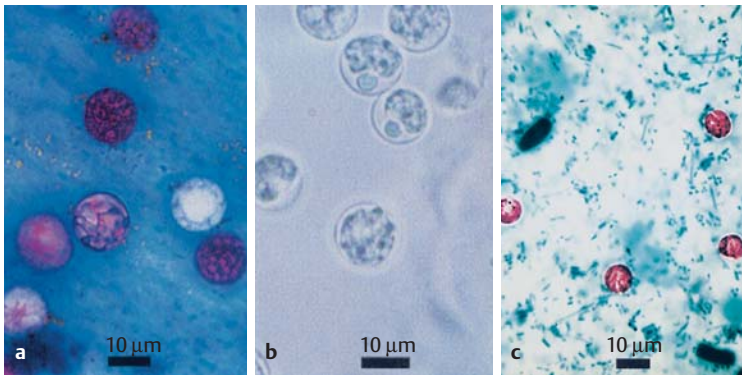


Fig. 9.**14** **a** Oocysts of *Cyclospora cayetanensis* in stool smear, modified Ziehl-Neelsen staining. **b** Oocysts of *Cyclospora*, unstained, after isolation from stool. **c** Oocysts from *Cryptosporidium parvum* in stool smear. Staining as in **a**. (**b** and **c** from: *Bench Aids for the Diagnosis of Intestinal Parasites.* Geneva: WHO; 1995.)

Diagnosis and therapy. Detection of oocysts in stool specimens using concentration methods or in stained stool smears (for instance modified Ziehl-Neelsen staining or modified carbol-fuchsin staining). *Cyclospora* oocysts are easily confused with the oocysts of cryptosporidia (Fig. 9.**14**); they show autofluorescence in UV light and no reaction with monoclonal antibodies to *Cryptosporidium*. The drug of choice is cotrimoxazole.

9

Sarcocystis

Causative agent of sarcocystosis

Parasites, life cycle, and epidemiology. *Sarcocystis hominis* and *S. suihominis* are known as human intestinal parasites. Infection results from ingestion of raw or insufficiently heated meat from cattle or pigs, which frequently contains muscle cysts of these species. In the small intestine, bradyzoites are released from the muscle cysts. The bradyzoites undergo gamogony without an asexual reproductive phase in the lamina propria of the intestine. This process produces thin-walled oocysts that sporulate in the intestinal wall. Once the frail oocyst wall has burst, free sporocysts containing four sporozoites each are excreted with stool in most cases. The sporozoites are infectious for intermediate hosts. Prepatent periods of 14–18 and

11–13 days are reported for *S. hominis* and *S. suihominis*, respectively. Examination of large population groups in Germany (n = approx. 1500) and France (n = 3500) revealed 1.6% and 2% *Sarcocystis* excreters, respectively.

Clinical manifestations, diagnosis, therapy, and prevention. Both species can cause short-lived (six to 48 hours) symptoms within 24 hours of eating meat containing cysts, for example nausea, vomiting, and diarrhea as well as a mild fever. *S. suihominis* is more pathogenic than *S. hominis*.

An intestinal infection with *Sarcocystis* can be diagnosed by detection of sporocysts (14 × 9 µm), or more rarely oocysts (approx. 20 × 13 µm) (Fig. 9.**11k**, p. 504) in stool using the SAFC or the flotation method (p. 621). The two *Sarcocystis* species cannot be differentiated. An effective therapy has not yet been developed. Prevention consists in boiling or deep-freezing (–20 °C for three days) of pork and beef.

Cryptosporidium

Causative agent of cryptosporidiosis

■ Cryptosporidiosis in humans is predominantly caused by *Cryptosporidium hominis* (= human genotype of *C. parvum*) and the bovine genotype of *C. parvum*. Humans are infected by peroral ingestion of infective oocysts. In immunocompetent persons, the infection remains inapparent or manifests as a self-limiting diarrhea. Persistent, choleralike, life-threatening diarrheas are observed in AIDS patients. ■

Parasite species and occurrence. At least 10 species of the genus *Cryptosporidium* and several genotypes are currently known that occur mainly as parasites of the intestine (and rarely of other organs) in humans and numerous species of mammalian animals, birds, and reptiles. *Cryptosporidium hominis* is a parasite of humans and monkeys, the bovine genotype of *C. parvum* infects many species of mammalian animals (ruminants, dogs, cats, rabbits, rodents, etc.) and humans. Other species originating from animals have been found occasionally in AIDS patients, including *Cryptosporidium canis* (host: dog) *Cryptosporidium felis* (host: cat), *Cryptosporidium meleagridis* and *Cryptosporidium baileyi* (hosts: birds).

Cryptosporidiosis occurs worldwide. The mean prevalences in humans differ in developed and developing countries and are about 2% and 6% respectively for immunocompetent persons with diarrhea and 14% and 24% respectively in HIV-positive patients. Prevalences exceeding 50% are also known in the latter group. Among domesticated animals, particularly high prevalences are observed among young calves (often 20–100%).

Morphology and life cycle. *C. hominis* and *C. parvum* inhabit mainly the small intestine and produce oocysts 4–5 μm in diameter. Following peroral ingestion of infectious oocysts, each of which contains four sporozoites, the released sporozoites invade enterocytes where each stage resides within a parasitophorous vacuole just beneath the cell membrane in the microvillus region of the host cell. This localization is typical of cryptosporidia (Fig. 9.**15**). Following formation of type I meronts with eight merozoites, the latter can infect new cells. In the further course, type II meronts with four merozoites are produced that give rise to sexual forms (gamogony). The fertilized zygote encysts to produce about 80% thick-walled and 20% thin-walled oocysts. The oocysts sporulate while still intracellular in the intestine. Each sporulated oocyst contains four free sporozoites (i.e., not enclosed in a sporocyst). Thin-walled oocysts can burst within the host, releasing sporozoites that cause endogenous autoinfections. After a brief prepatent period (two to four, sometimes up to 12 days), thick-walled oocysts are shed with feces and can immediately infect new hosts. It is assumed that persistent infections in immunodeficient persons are due to endogenous autoinfections by sporozoites from thin-walled oocysts or by merozoites from type I meronts.

Epidemiology. *C. hominis* is transmitted within the human population. Humans may also acquire zoonotic infections with the bovine type of *C. parvum* (main source of infection: calves) or rarely with other species or genotypes of animal origin.

Transmission of the oocysts is by the direct fecal-oral route or in contaminated foods or drinking water. The oocysts of *C. parvum* remain viable in cool water for months. This explains the etiology of major epidemics due to fecal contamination and improper processing of drinking water such as occurred in Milwaukee in 1993 with 403 000 persons involved. Sewage contained up to 13 000 oocysts per liter, surface bodies of water up to 112 oocysts per liter. As few as 30–100 oocysts are sufficient to induce an infection in humans.

Clinical manifestations. Cryptosporidia inhabit mainly the small intestine, where they may cause destruction of microvilli, shortening, swelling, and fusion of the villi and cellular infiltration of the mucosa. The severity and course of an infection depends on the immune status of the infected person.

- **Immunocompetent persons.** Infections either take an inapparent course or result, after incubation periods of five to 28 days, in acute, self-limiting, in most cases mild illnesses lasting one to 26 days with diarrhea and various generalized symptoms.

- **Immunodeficient persons.** Chronic infections with severe diarrhea and long periods of oocyst excretion, e.g., in AIDS patients. The diarrhea is watery, voluminous, choleralike and often associated with other symptoms (abdominal pain, nausea, vomiting, mild fever, etc.). In HIV patients, cryptosporidia

***Cryptosporidium:* Life Cycle**

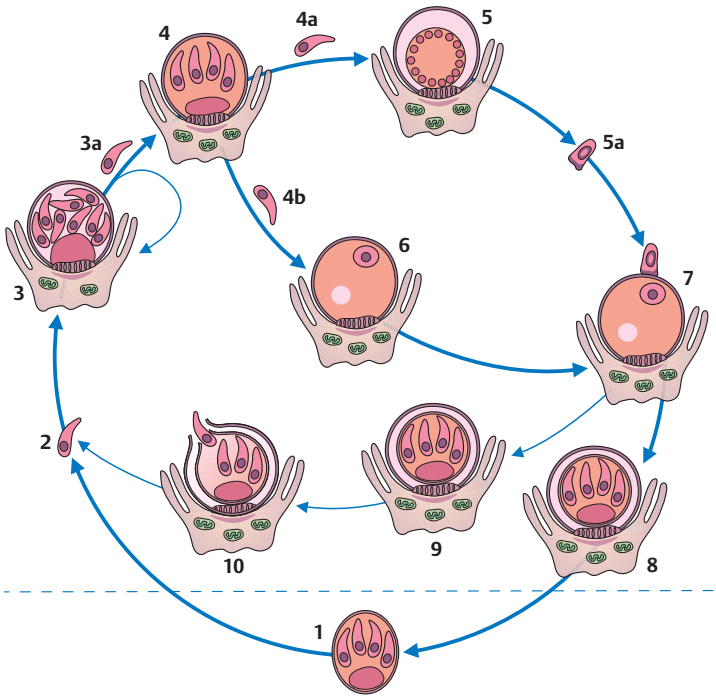


Fig. 9.**15** **1** Infective oocyst; **2** sporozoite before penetration into an enterocyte; **3** type I schizont with eight merozoites; **3a** free merozoite; **4** type II schizont with 4 merozoites; **4a, b** free merozoites; **5** microgamont; **5a** microgamete; **6** macrogamont; **7** macrogamete being fertilized by a microgamete; **8** thick-walled oocyst (shed with feces); **9, 10** thin-walled oocyst from which sporozoites are released in the host intestine (autoinfection).

are also found in other localizations (gallbladder, bile, and pancreatic ducts, esophagus, stomach, large intestine, respiratory tract).

Diagnosis, therapy, and prevention. *Cryptosporidium* oocysts can be diagnosed in stool smears after staining (e.g., modified Ziehl-Neelsen stain) (Fig. 9.**11i**, p. 504, Fig. 9.**14c**, p. 516), or visualization by immunofluorescence using monoclonal antibodies. In addition, coproantigens are detectable by ELISA. The only drug with efficacy against *Cryptosporidium* is nitazoxanide (see also *Giardia*).

Recommendations to avoid infection: hygienic precautions when handling oocysts excreters (humans, animals) and diagnostic specimens, improvement of community drinking water processing in some areas. The oocysts are resistant to the standard concentrations of chlorine or ozone in drinking water, but can be killed by heat (>70 °C) in a few minutes.

Plasmodium

Causative agent of malaria

■ Malaria, the most frequent tropical parasitosis, is also of medical significance in central Europe and other regions as a travelers' disease. The infection is caused by plasmodia (*Plasmodium vivax*, *P. ovale*, *P. malariae*, *P. falciparum*) transmitted by the bite of *Anopheles* mosquitoes. An infection initially presents in nonspecific symptoms (headache, fatigue, nausea, fever). Untreated malaria tropica (caused by *P. falciparum*) can quickly develop to a lethal outcome. Therefore, it is important to obtain an etiological diagnosis as quickly as possible by microscopic detection of the parasites in the blood, and to initiate effective treatment. Prophylactic measures are essential for travelers to regions where malaria is endemic (prevention of mosquito bites, chemoprophylaxis). ■

Occurrence. Malaria is one of the most significant infectious diseases of humans. According to the WHO (2000, 2004), the disease is currently endemic in more than 100 countries or territories, mainly in sub-Saharan Africa, Asia, Oceania, Central and South America, and in the Caribbean. About 2.4 billion people (40% of the world's population) live in malarious regions. Fig. 9.**16** shows the geographic distribution of malaria (WHO, 2000). The annual incidence of malaria worldwide is estimated to be 300–500 million clinical cases, with about 90% of these occurring in sub-Saharan Africa (mostly caused by *P. falciparum*). Malaria alone or in combination with other diseases kills approximately 1.1–2.7 million people each year, including 1 million children under the age of five years in tropical Africa. About 7000 cases of imported malaria were reported in Europe in the period from 1985 to 1995, whereby the data are incomplete.

Parasites. Four *Plasmodium* species infect humans and cause different types of malaria:

- *Plasmodium vivax*: tertian malaria (*malaria tertiana*),
- *Plasmodium ovale*: tertian malaria (*malaria tertiana*),

Distribution of Malaria

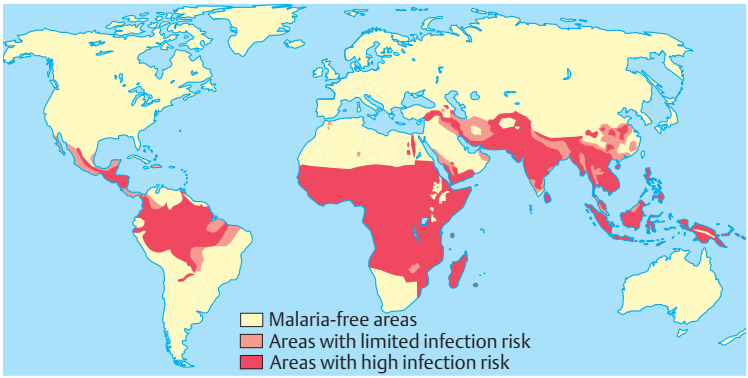


Fig. 9.**16** Status: 1999. (From: *International Travel and Health*, Geneva. World Health Organization, 2000.)

- *Plasmodium malariae*: quartan malaria (*malaria quartana*),
- *Plasmodium falciparum*: malignant tertian malaria (*malaria tropica*).

These *Plasmodium* species can be identified and differentiated from each other by light microscopy in stained blood smears during the erythrocytic phase of the infection in humans (Fig. 9.**18**, p. 524). A reduced apical complex and other characteristics of apicomplexan protozoa are recognizable in various stages of the organism (sporozoite, merozoite, ookinete) on the electron microscopic level (see *Toxoplasma*, p. 509).

Life cycle. The life cycle of malaria plasmodia includes phases of asexual multiplication in the human host and sexual reproduction and formation of sporozoites in the vector, a female *Anopheles* mosquito (Fig. 9.**17**). The developmental cycle within the human host is as follows:

- **Infection and exoerythrocytic development.** Humans are infected through the bite of an infected female *Anopheles* mosquito that inoculates spindleshaped sporozoites (see below) into the bloodstream or deep corium. Only a small number of sporozoites are needed to cause an infection in humans (about 10 *P. falciparum*). Within about 15–45 minutes of inoculation, the sporozoites of all *Plasmodium* species reach the liver in the bloodstream and infect hepatocytes, in which asexual multiplication takes place. In this process, the sporozoite develops into a multinuclear, large (30–70 µm) schizont (meront) described as a tissue schizont. Following cytoplasmic divi-

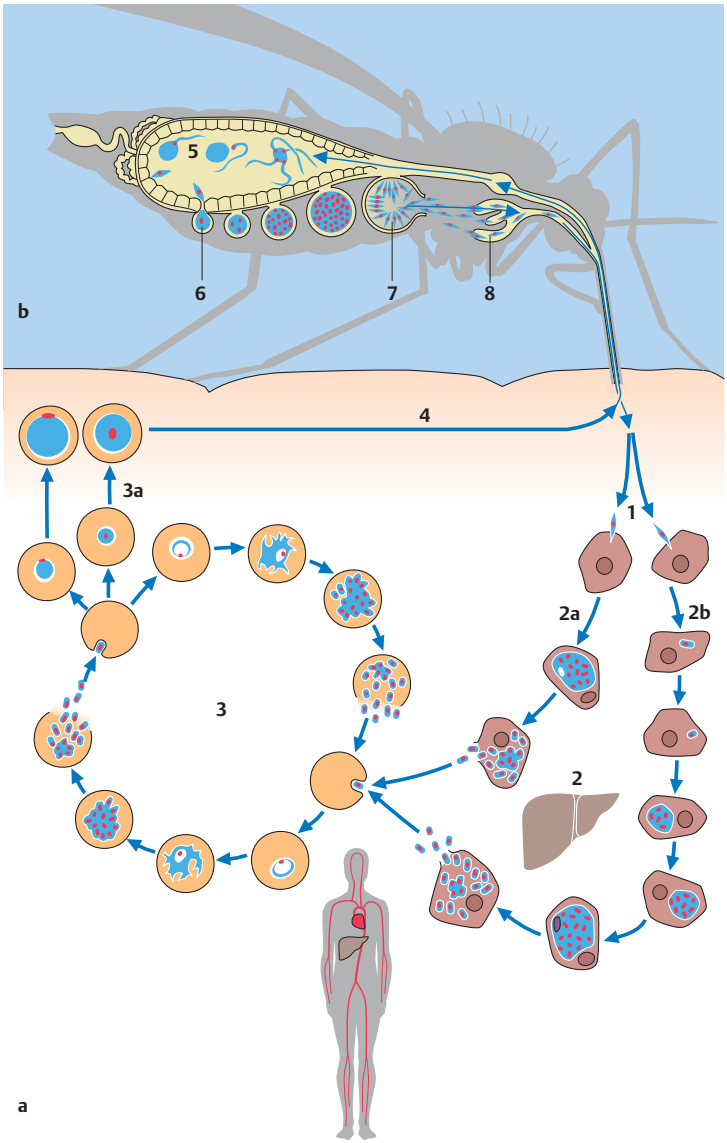
sion 2000 (*P. malariae*) to 30 000 (*P. falciparum*) merozoites are produced. This development takes six (*P. falciparum*) to 15 (*P. malariae*) days. Shortly thereafter, the tissue schizonts release the merozoites, which then infect erythrocytes (see below). In infections with *P. vivax* and *P. ovale*, sporozoites develop into tissue schizonts as described above, but some remain dormant as so-called hypnozoites, which may develop into schizonts following activation after months or years. Merozoites released from these schizonts then infect erythrocytes, causing relapses of the disease (see p. 527).

Erythrocytic development. The merozoites produced in the liver are released into the bloodstream where they infect erythrocytes, in which they reproduce asexually. The merozoites are small, ovoid forms about 1.5 µm in length that attach to receptor molecules on the erythrocyte surface. These receptors are species-specific, which explains why certain *Plasmodium* species prefer certain cell types: *P. malariae* infects mainly older erythrocytes, *P. vivax* and *P. ovale* prefer reticulocytes, and *P. falciparum* infects younger and older erythrocytes. Following receptor attachment, merozoites penetrate into the erythrocyte, where they are enclosed in a parasitophorous vacuole.

A *Plasmodium* that has recently infected an erythrocyte (<12 hours) appears ring-shaped with a thin cytoplasmic rim in a Giemsa-stained blood smear. Also visible are a central food vacuole and the dark-stained nucleus located at the periphery of the parasite. This stage is very similar in all four *Plasmodium* species (Fig. 9.**18**, p. 524). The ring forms develop into schizonts, which feed on glucose and hemoglobin. The latter is broken down to a brownish-black pigment (hemozoin)—after the amino acids used by the plasmodia are split off—and deposited in the parasite's food vacuole as "malaria pigment." The schizont undergoes multiple divisions to produce merozoites, in different numbers depending on the *Plasmodium* species (6–36). The merozoites enter

Fig. 9.**17** **a** In humans: 1 sporozoite from infected *Anopheles* mosquito; **2** development in the liver; **2a** primary tissue schizonts and schizogony in hepatocytes (all *Plasmodium* species); **2b** hypnozoites and delayed schizogony in hepatocytes (*P. vivax* and *P. ovale* only); **3** further schizogenic development in erythrocytes; **3a** development of sexually differentiated plasmodia (female macrogametocytes and male microgametocytes).
b in the *Anopheles mosquito*: **4** macrogametocytes and microgametocytes taken up by bloodsucking mosquito; **5** fertilization of macrogametes (round) by microgametes (long); **6** fertilized macrogamete (ookinete) in intestinal wall of mosquito; **7** oocyst with sporozoites in intestinal wall; **8** infective sporozoites in salivary gland (according to Peters W. *Chemotherapy and Drug Resistance in Malaria*. Vol. 1, London: Academic Press; 1987:16). ▶

Malarial Plasmodia: Life Cycle



Malarial Plasmodia: Differential Diagnosis in Blood Smears

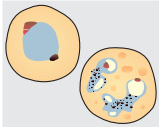
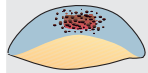
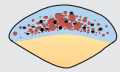
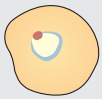
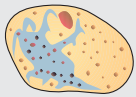
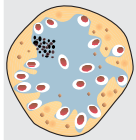
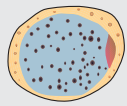
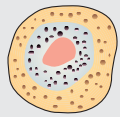
A: Young trophozoite	B: Older trophozoite	C: Schizont	D: Macro-gametocyte	E: Micro-gametocyte
Plasmodium falciparum Infected erythrocyte: size and form normal, multiple infection more frequent than with other *Plasmodium species*, rarely: Maurer's clefts				
				
Small rings; 1/3 to 1/5 of EDM, binuclear form frequent, narrow plasmic fringe, vacuole small	Vacuoles small or lacking, pigment dispersed or in clumps	8–24 merozoites, sometimes more, pigment usually peripheral	Sickle-shaped, nucleus compact and central, pigment arranged around nucleus	Sickle-shaped, plumper than D, nucleus larger and less compact
Plasmodium vivax Infected erythrocyte beginning at stage B: often larger than normal, often with red Schüffner's dots				
				
Rings 1/3 to 1/2 EDM, vacuole large, plasmic fringe narrow	Large rings or irregularly cleft form with diffuse pigment dispersal	12–24 merozoites, 1 to 2 pigment clumps, peripheral or central	Rounded, larger than EDM, nucleus small and excentric, with diffuse pigment dispersal	Rounded, nucleus larger than D, central or excentric, pigment finer than D and dispersed diffusely

Fig. 9.**18** EDM = erythrocyte diameter (according to Geigy R, Herbig A. *Erreger und Überträger tropischer Krankheiten*. Basel: Verlag für Recht und Gesellschaft; 1995).

the blood plasma when the erythrocyte is destroyed, they infect other erythrocytes and begin a new asexual cycle. After a short initial phase, the schizogonic cycles recur at regular intervals. A cycle takes 48 hours with *P. vivax*, *P. ovale*, and *P. falciparum* and 72 hours with *P. malariae*. Fever is induced when the schizonts burst and when many red blood cells are destroyed at once, causing the typical, intermittent fever attacks ("malarial paroxysm").

Malarial Plasmodia: Differential Diagnosis in Blood Smears

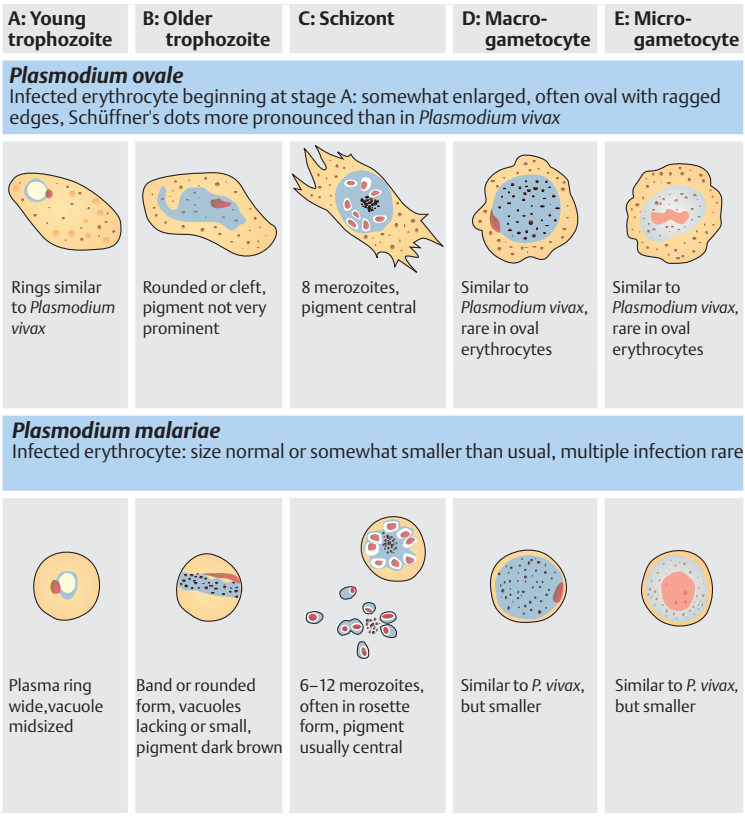


Fig. 9.**18** *Continued*

9

After one or more schizogonic generations, some of the plasmodia in each generation develop into sexual forms, the male microgamonts (microgametocytes), and female macrogamonts (macrogametocytes). These sexual forms (gametocytes) persist for a certain period in the blood (*P. vivax* one day, *P. falciparum* up to 22 days), after which those not taken up by bloodsucking *Anopheles* females die.

Development in the Mosquito (Sexual Development and Sporogony)

This developmental stage is shown in detail in Fig. 9.**17b** and will only be described briefly here. In the mosquito midgut, each microgamont develops into (in most cases) eight uninucleate, flagellate microgametes and the macrogamont is transformed into a macrogamete → fusion of a microgamete and macrogamete to form a motile zygote (ookinete) → the ookinetes occupy the space between the epithelial layer and basal membrane of the midgut → morphological transformation into oocysts (40–60 µm) → in oocyst nuclear proliferation and production of thousands of sporozoites → sporozoites emerge into the hemolymph and migrate through the body cavity to the salivary glands, from where they can be transmitted to a new host. The duration of the cycle in the mosquito depends on the plasmodial species and the ambient temperature; at 20–28 °C, it takes eight to 14 days.

Clinical manifestations

Incubation periods. The clinical manifestations of malaria are caused by the asexual erythrocytic stages of the plasmodia and therefore commence shortly after parasitemia at the earliest. The incubation periods vary, depending on the *Plasmodium* species involved, from seven to 35 days after infection. These periods can, however, be extended by weeks or even months, particularly if the infection is suppressed by prophylactic medication.

Clinical manifestations. The clinical manifestations of malaria depend on a number of different factors, above all the *Plasmodium* species and immune status of the patient. The *Plasmodium* species with the most pronounced pathogenicity is *Plasmodium falciparum*, which causes "malignant tertian malaria" (malaria tropica), whereas the other *Plasmodium* species cause milder forms ("benign malaria"). Children and nonimmune adults from nonmalarious areas (e.g., European and US tourists), as well as children in endemic regions aged six months to three years, are most susceptible to infection.

Onset symptoms. Malaria begins with nonspecific initial symptoms that last several days, including for instance headache, pain in limbs, general fatigue, chills, and occasionally nausea as well as intermittent fever, either continuous or at irregular intervals. These symptoms can easily be mistaken for signs of influenza!

Febrile patterns. Several days to a week after onset of parasitemia, the schizogonic cycle synchronizes: in infections with *P. vivax*, *P. ovale*, and *P. falciparum*, a cycle is completed within 48 hours, in infections with *P. malariae* within 72 hours. Bouts of fever occur at the same intervals, i.e., on day 1, then 48 hours later on day 3 (hence "malaria tertiana") or on day 1 and then again after 72 hours on day 4 (hence "malaria quartana"). It is important to note

that the malignant tertian malaria (malaria tropica) often does not show this typical periodicity.

■ **Classic malarial paroxysm.** After an initial rise in temperature to about 39 °C, peripheral vasoconstriction causes a period of chills (lasting for about 10 minutes to one hour), then the temperature once again rises to 40–41 °C (febrile stage two to six hours), whereupon peripheral vasodilatation and an outbreak of sweating follow. These bouts occur mainly in the afternoon and evening hours. Once the paroxysm has abated and the fever has fallen, the patient feels well again until the next one begins. In severe malaria tropica, however, circulatory disturbances, collapse, or delirium may occur without fever (algid malaria).

■ **Course of infection and recurrence.** The malarial paroxysms are repeated at intervals until parasite multiplication in the erythrocytes is suppressed by chemotherapy or the host immune response. Parasites that persist in the host can cause relapses for months or even years after the initial infection. Recurrence results either from persistence of erythrocytic forms (recrudescence) or reactivation of hypnozoites (p. 522) (relapse).

Types of malaria

■ **Tertian malaria** (*malaria tertiana*), caused by *P. vivax* or *P. ovale*:

Incubation period:	nine to 20 days, also several weeks or months.
Parasitemia:	generally low level, up to a maximum of 1–2%.
Course:	usually benign ("benign malaria"). Febrile stage three to four hours, again 48 hours later. If untreated, disease lasts three to eight weeks or longer.
Recurrence:	frequent relapses, after months and for up to five years; important: misdiagnosis is frequent!
Special characteristics:	"tertiana quotidiana" is characterized by daily bouts of fever and results when two parasite populations overlap.

■ **Quartan malaria** (*malaria quartana*), caused by *P. malariae*:

Incubation period:	15–40 days (usually longer than with other species).
Parasitemia:	generally low level, up to a maximum of 1%.
Course:	usually benign. Febrile stage four to five hours, again 72 hours later. If untreated, disease lasts three to 24 weeks or longer.
Recurrence:	frequent recrudescences, after months and even decades (30 years). Important: misdiagnosis is frequent!
Special characteristics:	nephrotic syndrome, especially in African children.

■ **Malignant tertian malaria** (*malaria tropica*), caused by *P. falciparum*:

Incubation period:	seven to 15 days or longer.
Parasitemia:	often at very high level, up to 20% or more!
Course:	initial symptoms often more pronounced than in other types. Rapid, severe course in nonimmune persons. High lethality rate if untreated (50–60% in persons from central Europe). After short initial phase fever high, continuous or with <48 hour rhythm. If untreated, disease lasts two to three weeks.
Recurrence:	recrudescence is rare, usually within one year.
Special characteristics:	**severe complications are possible**, especially cerebral malaria (e.g., with convulsions, disturbed vision and coordination, altered states of consciousness, coma); severe normocytic anemia; pulmonary edema and respiratory insufficiency; renal insufficiency; gastrointestinal disturbances; circulatory collapse; hypoglycemia; liquid/electrolyte unbalance, spontaneous hemorrhaging; disseminated intravasal coagulation; hyperpyrexia (39.5–42 °C); hemoglobinuria ("blackwater fever"); hyperparasitemia.

■ **Mixed infections**

Mixed infections with two *Plasmodium* species are observed in about 3–4% of all cases and may alter the course of the disease.

Pathogenesis and pathology. The clinical manifestations of malaria are caused by the erythrocytic stages ("blood stages") of the plasmodia and reflect multifactorial pathogenic process affecting many different organs. Only an outline of these processes can be drawn here, especially with regard to *falciparum* (tropical) malaria.

■ **The role of cytokines.** As a result of erythrocytic schizogony and the attendant rupture of erythrocytes (red blood cells = RBCs), malarial antigens (phospholipids and glycolipids) are released that stimulate macrophages and monocytes to produce tumor necrosis factor alpha (TNFα) and other cytokines (IL-1, IL-6, IL-8, etc.). Also associated with this process are bouts of fever, to which hemozoin presumably contributes as well. Cytokine production is also initiated by IFNγ produced in the immunological TH1 response. TNFα plays a special role in pathogenicity, since the concentration of this cytokine in the blood correlates with the severity of a *P. falciparum* infection. This substance also, at higher concentrations, induces fever, inhibits erythropoiesis, stimulates erythrophagocytosis, and causes various nonspecific

symptoms such as nausea, vomiting, and diarrhea. At lower concentrations, TNFα can contribute to the killing of the intracellular parasites. Various other cytokines (see above) either synergize with TNFα or induce different reactions.

Anemia. An important factor in malarial pathogenesis, especially in malaria tropica, is anemia, caused by destruction of RBCs in schizogony, increased elimination of both infected and noninfected RBCs in the spleen, inhibition of erythropoiesis by TNFα, and other factors.

Cytoadherence and rosette formation. RBCs infected with maturing *P. falciparum* schizonts adhere to the endothelium of blood vessels in various organs, especially in postcapillary venules. This phenomenon is due to an interaction between strain-specific ligands of the parasite with host receptors. During the development of *P. falciparum* from the ring form to the maturing schizont, buttonlike protrusions of the erythrocytic membrane develop, under which high-molecular (200–300 kDa) proteins are enriched, then presented at the cell surface. These so-called *P. falciparum* erythrocyte membrane proteins (PfEMP) bind to a variety of endothelial receptors, for instance to the intercellular adhesion molecule (ICAM), thrombospondin, E-selectin (ELAM), and the CD36 molecule. ICAM-1 and ELAM-1 are thought to be mainly responsible for cytoadherence in the brain. These substances are produced in significant amounts there and are inducible by TNFα and other cytokines. Outside of the brain the receptor CD36 is apparently the most important recognition protein. The PfEMP antigens, coded for by about 150 genes, are variable and play a role in parasite immunoevasion. The advantage of cytoadherence for the plasmodia is that part of their population thus avoids elimination in the spleen. For the host, however, cytoadherence has pathological consequences: it hinders local microcirculation as well as gas and substance exchange processes, the resulting anemia exacerbates tissue hypoxia and, finally, it causes cell and organ damage with grave sequelae in the brain in particular. Rosette formation refers to clumping of RBCs infected by *P. falciparum* with other noninfected ones caused by mechanisms similar to cytoadherence.

Other processes (a selection). Due to the destruction of RBCs and parasites and resulting production of TNFα, phagocytosing cells of the reticuloendothelial system are activated. Signs of this include splenic swelling in the course of the infection and increased elimination of erythrocytes in the spleen (see anemia). Renal damage in acute malaria tropica is caused by capillary cytoadherence and tubular necrosis. In malaria quartana, such damage is due to deposition of immune complexes in the renal capillaries.

Pathological changes. Such changes are known from cases of malaria tropica in particular. Brain capillaries are clogged with infected RBCs (the pig-

ment in the plasmodia is especially noticeable), hemorrhages, necrotic foci on obturated vessels surrounded by inflammatory reactions (Dürck granulomas). Further changes can be found in the spleen and liver (for instance swelling, hyperplasia of phagocytosing cells containing plasmodia and pigment), heart, lungs, kidneys, and other organs.

Resistance and immunity. Certain properties of blood are responsible for increased natural resistance to malarial infection. For instance, the intraerythrocytic development of *P. falciparum* is inhibited in persons with various hemoglobinopathies (HbS, HbE, HbF, HbC), in glucose-6-phosphate dehydrogenase deficiency (G6PDD) and β-thalassemia. On the other hand, persons with G6PDD are more sensitive to certain antimalarials (quinine, 8-aminoquinoline). Persons lacking the Duffy blood group antigen are resistant to *P. vivax*, but susceptible to *P. ovale*. A milk diet partially inhibits the development of malarial parasites in the RBCs because of a resulting reduced supply of *p*-aminobenzoic acid (vitamin H_1). This results in a milder malarial course, e.g., in infants.

In the course of a malaria infection, a host immune response develops, which, however, does not confer complete protection, but rather merely raises the level of resistance to future infections. Accordingly, the course of malaria infections is less dramatic in populations of endemic areas than in persons exposed to the parasites less frequently or for the first time. In these malarious areas, children are the main victims of the disease, which is less frequent and takes a milder course in older persons. Infants of mothers who have overcome malaria usually do not become ill in the first months of life due to diaplacental antibody transmission and a certain level of protection from the milk diet. On the other hand, children without maternal antibodies can become severely ill if they contract malaria, since their own immune defenses are developing gradually. Nonimmune travelers from nonmalarious regions are at special risk of infection.

The immunity conferred in humans by exposure to plasmodia develops gradually and is specific to the strains and stages that are capable of antigen variation. A particularly important part of the generalized immune response appears to be the component induced by asexual blood forms, which confers a protective effect against new infections. The specialist literature should be consulted for more details on this aspect. Despite many years of intensive effort, a decisive breakthrough in the development of malaria vaccines has not yet been achieved.

Epidemiology. Constant minimum temperatures of 16–18 °C (optimum: 20–30 °C) and high humidity for several weeks are preconditions for vectoral transmission of malaria. Further requirements for the plasmodial cycle are an epidemiologically relevant parasite reservoir in the population and the presence of suitable vectors.

Malarial parasites can be transmitted by female mosquitoes of about 80 species of the genus *Anopheles* (*Anopheles gambiae* complex, etc.). The larval and pupal stages of these mosquitoes develop in standing bodies of water, often near human dwellings. Anopheline mosquitoes are active from dusk to dawn. The females bite both in the outside and within buildings. Malaria often accompanies the rainy season, which provides the bodies of water the mosquitoes need. Occurrence is usually endemic, but epidemics do sometimes develop. The incidence of infections varies widely and the immune status of the population is a major factor (see immunity p. 530).

Alternative transmission routes for malarial plasmodia include diaplacental infection, blood transfusions (plasmodia survive in stored blood for five days, rarely longer), and contaminated needles used by drug addicts.

Diagnosis. Etiological confirmation of a clinical diagnosis is obtained by detecting malarial parasites in the blood (Fig. 9.**18**). Capillary blood is sampled before chemotherapy is started, if possible before the onset of fever, and examined microscopically in both thick and thin blood smears following Giemsa staining (p. 622). Stages of *P. falciparum*, *P. vivax*, and *P. ovale* can be found in blood five to eight days after the infection at the earliest, *P. malariae* not until after 13–16 days. The QBC (quantitative buffy coat) method can be used to concentrate the plasmodia. Rapid tests (ParaSight, MalaQuick) have also been available for some years to diagnose *P. falciparum* infections. Using a monoclonal antibody, these tests can detect a specific *Plasmodium* antigen (HRP2) in whole blood with a very high level of sensitivity and specificity. Another rapid test (OptiMAL) for diagnosis of all *Plasmodium* species is based on detection of specific lactate dehydrogenase.

Detection of specific antibodies in the serum of persons infected with plasmodia for the first time is not possible until six to 10 days after inoculation (Table 11.**5**, p. 625). In such cases, a serological antibody assay is not a suitable tool to confirm a diagnosis in an acute attack of malaria, although this method does provide valuable help in confirming older infections and screening out blood donors infected with plasmodia. DNA detection by means of PCR can be used to identify the different *Plasmodium* species for research purposes.

Therapy. Patients infected for the first time (e.g., travelers from the northern hemisphere returning from a stay in the tropics) may suffer highly acute and severe courses of malaria. Therapy and intensive clinical monitoring must therefore begin immediately, especially in acute malignant tertian malaria (malaria tropica) (medical emergency!). Table 9.**6** summarizes a number of antimalarials and their spectra of action. The best that can be offered here by way of a description of the highly complex field of malaria treatment is a brief sketch of the main principles involved.

Table 9.**6** Antimalarial Agents (a selection)

Chemical group and drug (P): used for prophylaxis	**Spectrum of efficacy**			
	Asexual blood stages	**Game-tocytes**	**Liver schizonts**	**Hypnozoites of *P.vivax*, *P. ovale***
Arylaminoalcohls				
Quinine	+	VOM	–	–
Lumefantrine	+	VOM	–	–
Mefloquine (P)	+	VOM	–	–
4-Aminoquinolines	+	VOM	–	–
Chloroquine (P)	+	VOM	–	–
Amodiaquine	+	VOM	–	–
8-Aminoquinolines				
Primaquine	+/–	+	+	+
Naphtoquinones				
Atovaquone	+	VOM	+	–
Phenanthrene methanoles				
Halofantrine	+	–	–	–
Sesquiterpene lactones				
Artemisinin	+	+	–	–
Artemether	+	ni	ni	ni
Artesunates	+	ni	ni	ni
Sulfones/Sulfonamides				
Dapsone	+	–	F	–
Sulfadoxine (P)	F	–	F	–
Biguanides				
Proguanil (P)	+/–	?	+	–
Diaminopyrimidines				
Pyrimethamine (P)	+	–	–	v
Antibiotics (Tetracyclines)				
Doxycycline (P)	+	–	F	–

Table 9.**6** *Continued: Antimalarial Agents (a selection)*

Chemical group and drug (P): used for prophylaxis	Spectrum of efficacy			
	Asexual blood stages	Gametocytes	Liver schizonts	Hypnozoites of *P.vivax*, *P. ovale*
Drug combinations				
Atovaquone + proguanil (P)	+	VOM	+	–
Artemether + lumefantrine	+	+	ni	–
Chloroquine + proguanil (P)	+	VOM	F	–
Sulfadoxine[2] + pyrimethamine[3]	+	VOM	–	–
Sulfadoxine[2] + pyrimethamine[3] + mefloquine	+	VOM	–	–

[1] Effectiveness: +: effective; +/–: moderately effective; ?: questionably effective; –: ineffective.

F: effective against *P. falciparum*; VOM: effective against *P. vivax*, *P. ovale*, *P. malariae*; ni: no information

[2] Dihydropteroate synthetase inhibitors (= sulfonamides and sulfones)

[3] Dihydrofolate reductase inhibitors (= antifolates)

Treatment of acute disease. The clinical symptoms of malaria are caused by the asexual forms in the erythrocytic schizogonic cycle. A clinical cure is thus achieved by eliminating these forms or stages with so-called schizonticides (Table 9.**6**). The antimalarials preferred in this indication are fast-acting schizonticides such as quinine, mefloquine, and halofantrine (in some countries artemisinin derivatives as well) as well as quinine combined with doxycycline (especially in complicated tropical malaria) and various combined preparations (Table 9.**6**). Some of the above substances are also effective against chloroquine-resistant and multiresistant *Plasmodium* strains. Chloroquine, a former mainstay of malaria therapy, has now lost some of its importance due to widespread drug resistance of plasmodia.

Prevention of relapses (radical cure). Agents effective against blood schizonts do not eliminate the latent tissue forms (hypnozoites) of *Plasmodium vivax* and *Plasmodium ovale* in the liver. To prevent relapses, tissue forms can be eliminated with primaquine after the acute therapy is completed (Table 9.**6**). This therapy is not required for infections by *P. falciparum* and *P. malariae* since they do not produce hypnozoites.

Drug resistance. The resistance of malaria plasmodia to certain antimalarial drugs is a growing problem. Resistance is classified from RI (low grade) to RIII (high grade) and applies particularly to malaria tropica. Table 9.**7** and Fig. 9.**19** provide information on regions in which resistant *P. falciparum* strains have developed. Selection of drugs and their dosage in therapy and prevention must take this problem into account. In-vitro methods are available for resistance testing.

Prevention. Travelers to malarious areas should be informed well ahead of time concerning the risk of infection at their destination and the necessary prophylactic measures. This information is available from specialists and institutions in the field of tropical medicine, health offices, etc., as well as on the internet (WHO: www.who.int; Austria: www.reisemed.at; Germany: www.dtg.mwn.de; Switzerland: www.safetravel.ch). **It is important to remember that updated information is required because recommended malaria prevention measures vary from country to country and are subject to sudden changes.**

Prophylactic measures are necessary for travelers to malarious areas in **Africa**, **Central** and **South America**, and **Asia**. **Sub-Saharan Africa** in particular must be considered a high-risk area. Within a malarious area, the risk of infection may vary widely depending on the season, locality, and length of stay. Prophylactic measures must take this variation into consideration.

The following methods can be used to **prevent a malaria infection**:
- mosquito bite prevention,
- chemoprophylaxis,
- emergency stand-by therapy.

Malaria Prophylaxis by Areas

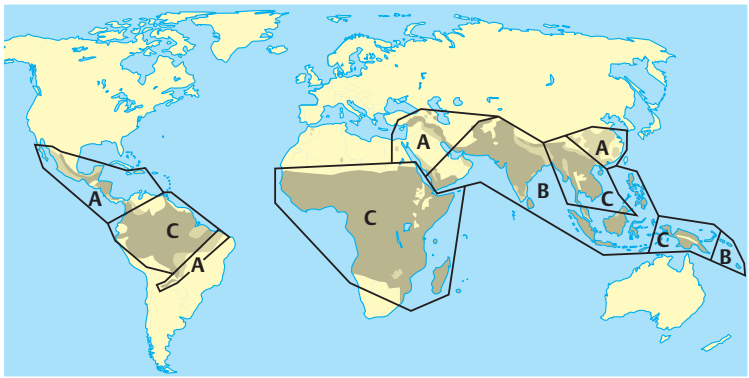


Fig. 9.**19** See Table 9.**7** for explanation (according to: *International Travel and Health*. Geneva: World Health Organization; 2000).

Table 9.7 Examples of Chemoprophylactic Regimens and Standby Medications by Areas[1]

Area	Characteristics of areas[2]	Prophylactic drugs	Standby drugs
A	Areas without chloroquine resistance or without *P. falciparum*	Chloroquine	None
		None	Chloroquine
B	Areas with chloroquine resistance	Chloroquine + proguanil or mefloquine	None
		None	Mefloquine or Atovaquone + proguanil
C	Areas with high chloroquine resistance or multiresistance	Mefloquine (doxycycline)[3]	None
		Doxycycline	Mefloquine or atovaquone + proguanil
		Chloroquine + proguanil	Mefloquine or atovaquone + proguanil

[1] Modified and supplemented according to: *International Travel and Health*. Geneva: World Health Organization; 2000 and other sources.
Note: Actual updates with detailed information on infection risk by country, region, and season can be obtained from the internet, for example: www.dtg.mwn.de.
[2]The data on resistance do not indicate the actual infection risk.
[3]In certain parts of Southeast Asia (border region Cambodia, Myanmar, Thailand).

The main aim of these measures is prevention of the life-threatening malignant tertian malaria (*malaria tropica*) caused by *P. falciparum*.

■ **Mosquito bite prevention (prevention of exposure):** in view of widespread drug resistance in plasmodia, it is very important to prevent mosquito bites in addition to chemoprophylactic measures. Remember, ***Anopheles* mosquitoes are active from dusk to dawn** and bites are possible both outside and inside buildings (although this is unusual in air-conditioned rooms). In general, the risk of being bitten by an *Anopheles* mosquito is lower in urban

areas than in rural areas and may even be negligible in a city (exception: certain cities in tropical Africa and India). The following protective measures are recommended:

- Always wear **clothing** in the dusk and at night (long sleeves, long trousers) that prevents mosquito bites as far as possible. Spray clothing with a fast-acting insecticide (pyrethrines).
- Apply an **insect repellent** to uncovered skin (spray or spread by hand) (products with 20% diethyl-m-toluamide are protective for three to five hours).
- **Screen off** rooms to keep mosquitoes out (close doors and windows, fit fine-meshed screens on doors and windows).
- Spray mosquito resting places in room with **insecticide**. Use insecticide dispenser with renewable insecticide pellet or pyrethroid smoke coils.
- Screen off beds with mosquito nets (very important to protect infants and small children!).
- Impregnating bed nets with an insecticide (pyrethroids: permethrin, deltamethrin) increases their effectiveness.

Chemoprophylaxis and emergency treatment. Chemoprophylaxis comprises regular intake of antimalarial drugs before, during, and for a defined period after a stay in a malarious area. Depending on the target a distinction between suppressive and causal prophylaxis can be made: suppressive drugs prevent clinical symptoms by affecting the asexual stages in the erythrocytes, whereas causal drugs act against the tissue schizonts of *P. falciparum* in the liver, thus preventing the erythrocytic cycle. Most of the agents currently in use have a suppressive effect (Table 9.**6**). For short stays in low-risk areas, it may under certain circumstances make sense to refrain from chemoprophylaxis and take along an **emergency stand-by drug.** Self-treatment can be initiated in response to malarious symptoms if a physician cannot be reached within 12 hours. Taking along a stand-by drug is also worth considering if there is a high risk of infection with *P. falciparum* (especially multiresistant strains) and it is unclear whether the planned chemoprophylaxis will provide sufficient protection. Always remember the following principles:

- There is at present no chemoprophylactic regimen that can guarantee 100% efficacy. Therefore, a physician must be consulted immediately if fever occurs during or after the chemoprophylactic regimen.
- Specific antimalarials recommended by specialists must be used for chemoprophylaxis and emergency treatment. These substances may cause side effects.
- Specific advisement of travelers adapted to their individual situation (general health status, pregnancy, age, small children, allergies, etc.) and the specific situation at their destination is very important.

- Begin with chemoprophylaxis at the latest *one to two weeks before traveling* to a malarious area. During this period, potential side effects can be recognized and countermeasures can be taken or the medication changed as necessary.
- Duration of chemoprophylaxis: *during and four weeks after the traveler's stay* in the malarious area (with atovaquone/proguanil only one week). This measure is intended to prevent malaria tropica and does not affect hypnozoites of *P. vivax* and *P. ovale* (treatment with 8-aminoquinolines as required to prevent relapse, see above).
- The drugs are swallowed with liquid after meals. The dosages, intervals between intake and any restrictions (e.g., for pregnant women) must be strictly complied with.

Examples of chemoprophylaxis and use of emergency stand-by drugs. The modified and supplemented WHO recommendations are used as examples here (Table 9.**7**). NB: recommendations in some countries may differ considerably from the information in the table! The necessary measures differ in the different risk zones (Fig. 9.**19**) and apply to brief stays in malarious areas of up to three months for nonimmune persons. For longer stays (more than three months), the prophylaxis should be started as for a shorter stay, then a physician in the endemic area should be consulted concerning long-term measures.

Disease control. The main methods applied are *Anopheles* control by spraying houses and stables with insecticides (indoor spraying), environmental sanitation measures to eliminate mosquito-breeding places, and the usage of insecicide-impregnated bed nets to reduce vector-human contacts. Further measures in endemic areas are early diagnosis and treatment of malaria cases as well as chemoprophylaxis in selected population groups. Antimalaria vaccines are not available yet.

Babesia

Causative agent of babesiosis

Babesia species are apicomplexan blood parasites of the order *Piroplasmida* that occur quite frequently in domestic and wild animals in countries on all continents and are transmitted by hard tick species. In vertebrate hosts, they parasitize in erythrocytes and are detectable in stained blood smears, usually in the form of small rings and single or double pearshaped organisms (about 2–2.5 µm long). In contrast to plasmodia they do not contain pigment (hemozoin). *Babesia* infections are infrequently observed in humans, primarily affecting splenectomized, elderly, and immunocompromised patients. The causative agents were identified as *Babesia microti* from rodents, *B. divergens* from cattle, and some previously unknown *Babesia* species or strains. Such infections can cause severe malarialike symptoms.

Microspora

Causative agents of microsporosis

■ The clinical significance of the microspora is based mainly on their role as "opportunistic parasites" in HIV patients. The most important species are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. Transmission is by characteristic spores. Little is known about the epidemiology of these organisms that are closely related to the fungi. ■

Parasites. The phylum Microspora includes about 140 genera and 1300 species. They are parasites with intracellular development and spore formation. The host spectrum ranges from numerous invertebrates (e.g., protozoa, insects) to many species in all classes of vertebrates. The lack of mitochondria, peroxisomes, and typical Golgi membranes as well as their prokaryotelike ribosomes were previously regarded as characteristics of most primitive eukaryotes. Recently, analyzes of a variety of genes and proteins have revealed a close relationship to fungi. Therefore, some authorities now consider the Microspora to be highly specialized fungi rather than primitive protozoa and place them as a superclass into the subphylum fungi. A notable characteristic of the microspora is the unique morphology of their spores (see below).

Microspora, known since the middle of the last century, have attained attention as human pathogens and opportunistic parasites in the course of the AIDS epidemic. Several genera and species have been identified in humans to date (Table 9.**1**, p. 477).

Morphology and life cyle. Microspora reproduce intracellularly by means of repeated, asexual binary or multiple fission (merogony), then form spores in a subsequent phase (sporogony) (and sexual stages as well in *Thelohania*). The developmental stages are located freely in the host cell cytoplasm (*Enterocytozoon*, *Nosema*) or they inhabit a parasitophorous vacuole (*Encephalitozoon*); in other genera (*Pleistophora*, *Trachipleistophora*) the intracellular stages are separated from the cytoplasm by an amorphous layer (pansporoblastic membrane). Sporogony begins with formation of sporonts, which are derived from merogonic cells and possess a thicker cell wall. The sporonts divide to form sporoblasts, followed by morphological differentiation into spores.

The fine structure of these spores is typical of Microspora (Fig. 9.**20a, b**). The two-layered spore wall (exospore and endospore) encloses the uninucleate (rarely: binucleate) infective parasite stage called a sporoplasm or "ameboid organism" and a complex expulsion apparatus consisting of a coiled polar tubule and the polaroplast, a membranous anchoring component. The size of the spores of Microspora species infecting humans varies between about 1 and 4 µm. The number and position of the polar tubule windings as seen on the electron microscopical level (Fig. 9.**20a, b**) are of diagnostic importance.

The spores are eliminated in feces, urine, or sputum and can remain viable for several weeks outside of the host. Following peroral ingestion by a suitable host, the polaroplast swells up, the internal pressure in the spore in-

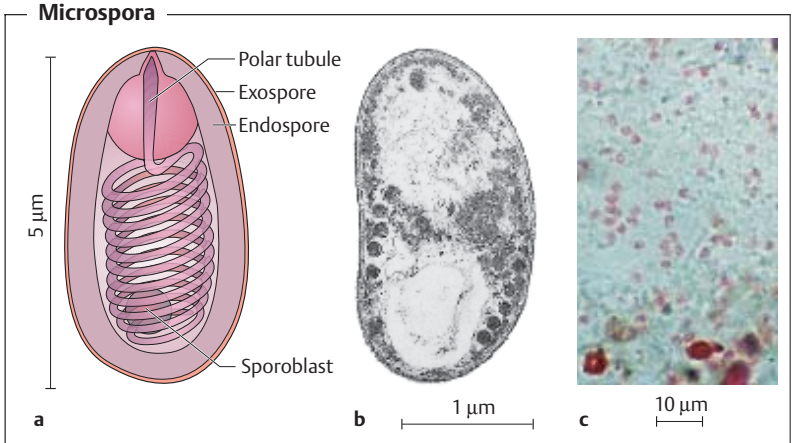


Fig. 9.**20** **a** Spore (modified from Binford CH, Connor D, eds. *Pathology of Tropical and Extraordinary Diseases*. Vol. 1. Washington: Armed Forces Institute of Pathology; 1987: 336); **b** immature spore of *Encephalitozoon hellem* (TEM); **c** spores of *Enterocytozoon bieneusi* in stool smear, chromotropic stain according to Weber.

creases and the polar tubule, which is up to 100 μm long, is extruded rapidly. If the tip of the polar tubule penetrates the wall of an enterocyte, the sporoplasm migrates through the hollow tubule into the host cell. The Microspora then reproduce locally in intestinal cells or invade other organs from this site. Aerogenic infections appear probable in some genera. In animals, diaplacental transmission of *Encephalitozoon* has been confirmed.

It is not entirely clear by what mechanisms the Microspora are disseminated in the body. In cell cultures, the parasites are able to infect neighboring tissue cells by extruding their polar tubule and injecting the sporoplasm into them. In vitro, Microspora are phagocytosed by macrophages and other host cells (so-called nonprofessional phagocytes: epithelial and endothelial cells, mesenchymal cells). It is assumed that they may be transported within the body inside such cells.

Clinical manifestations. Microspora attain clinical significance almost exclusively in immunodeficient persons, in particular AIDS patients. The following list summarizes the diseases caused by the individual species together with some diagnostic information.

■ ***Enterocytozoon bieneusi***

Occurrence:

Probably worldwide, found in 2–50% of HIV patients with chronic diarrhea, with prevalence showing a downward trend since the new type of antiretroviral therapy was introduced. Rarely diagnosed in immunocompetent persons. *E. bieneusi* was also found in the biliary epithelium of monkeys (macaques) and in fecal samples of animals, including pigs, cattle, dogs, and cats. The species *E. bieneusi* consists of number of various genotypes. Current knowledge suggests that humans acquire the infection predominantly from infected persons, whereas transmission of genotypes from animals to man—if it occurs at all—is a rare event.

Localization:

Mainly in the small intestine, in enterocytes at the tips of villi, less frequently in the colon as well, in the bile ducts and gallbladder. Intracellular localization in plasma without parasitophorous vacuole. Symptoms: chronic diarrhea, also with cholangiopathy; asymptomatic infections are known to occur.

Diagnosis:

Detection of tiny spores (1.1–1.6 × 0.7–0.9 μm) in stained stool smears. The spores have four to seven polar tubule windings in a double row (in other species: single row!).

■ ***Encephalitozoon intestinalis*** (formerly *Septata intestinalis*).

Occurrence:

In HIV patients, but less frequent than *Enterocytozoon bieneusi*; (in a German study this pathogen was found in 2% of 97 patients). There is unconfirmed evidence of animal reservoirs.

Localization:

Mainly in the small intestine, in enterocytes, lamina propria, fibroblasts, macrophages, and endothelial cells, also found disseminated, for instance in bile ducts, airways, and the kidneys. Within host cell located in "chambers," separated off by septa (hence the earlier name *Septata*).

Symptoms:

Chronic diarrhea as with *E. bieneusi*, other symptoms as per organ localization. Diagnosis: spore detection in urine or stool, spores somewhat larger than in *E. bieneusi* (1.5–2.0 × 1.0–1.2 µm); four to seven polar tubule windings.

Encephalitozoon cuniculi

Occurrence:

Worldwide; occur frequently in domestic and wild rabbits, also described in many other animal species (rodents, dogs, cats, foxes, monkeys); rarely found in HIV patients. Of the three known pathogenic strains, two (rabbit and dog strain) have also been found in humans (= zoonosis).

Localization and symptoms:

Intracellular development in parasitophorous vacuoles. In rabbits mainly in renal tubuli and CNS. In HIV patients with disseminated infection causing hepatitis, peritonitis, nephritis, pneumonia, sinusitis, and encephalitis.

Diagnosis:

Spore detection in urine and organ specimens. Spores 2.5–3.2 × 1.2–1.6 µm with four to six polar tubule windings, morphologically indistinguishable from *E. hellem* spores (see *E. hellem*).

Encephalitozoon hellem

Occurrence:

Rare, in HIV patients.

Localization and symptoms:

Keratoconjunctivitis, sinusitis, bronchitis, pneumonia, nephritis, urinary tract infection, disseminated infection.

Diagnosis:

Morphologically identical to *E. cuniculi*, differentiation possible based on immunology and molecular biology.

Other species infecting humans

Brachiola (formerly *Nosema*) *connori* (disseminated in internal organs), *Nosema ocularum* (cornea), *Microsporidium africanum*, *M. ceylonensis* (cornea), *Vittaforma corneae* (formerly *Nosema corneum*) (cornea), *Pleistophora* sp. (skeletal muscle), *Trachipleistophora hominis* (skeletal muscle, nasal mucosa), and *Trachipleistophora anthropophthera* (cardiac and skeletal muscle, liver, brain).

Epidemiology. Little is known about the epidemiology of the Microspora. Their spores can remain viable outside of a host for several weeks, are relatively heat-resistant, and are killed by 70% ethanol in 10 minutes. *E. cuniculi* has a reservoir in animals; isolates of this species from rabbits and humans are morphologically, immunologically, and genetically identical. Pigs, dogs, and cats can function as carriers and excreters of *E. bieneusi*, but the genotypes of animal origin are of little—if any—significance for humans.

Diagnosis. Direct detection of the Microspora and identification taking into account species-specific characteristics (see Figs. 9.**11g**, 9.**20c**). *Encephalitozoon* and *Nosema* species can be grown and concentrated in cultures in various cell types. Material obtained in this way can then be used to identify species or strains using antigen or DNA analysis. In vitro culturing of *Enterocytozoon* has not succeeded yet. Serological antibody assay methods are still being evaluated and do not currently play a significant role in diagnostic practice.

Therapy and prevention. According to case reports, treatment with albendazole is clinically and parasitologically beneficial in enteral and systemic infections with *Encephalitozoon* species; the substance is, however, less effective against *Enterocytozoon bieneusi*. Nitazoxanide was reported to be effective in single cases against this latter species.

Balantidium coli

Causative agent of balantidiosis

Balantidium coli is a worldwide distributed ciliate of highly variable size (30–150 µm long). It is frequently found as an inhabitant of the large intestine of monkeys, rats, and in particular pigs. It is also found, more rarely, in humans, in whom it occasionally causes intestinal necrosis and inflammation with ulceration. The disease is transmitted through spherical cysts (40–60 µm) from host to host on the fecal-oral route. Diagnosis involves detection of cysts or vegetative forms in fecal samples. Drugs recommended for treatment are tetracyclines and metronidazole.