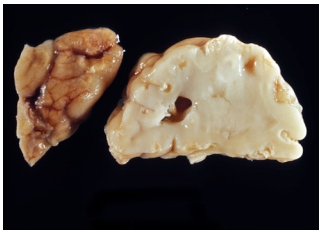

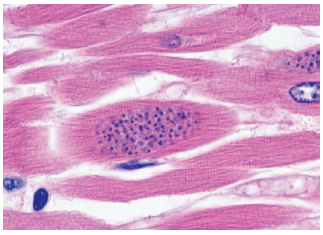

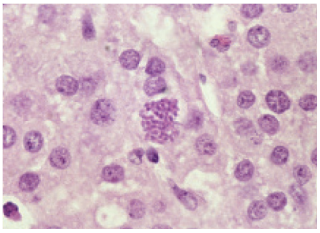

12

Toxoplasmosis

Ronald C. Neafie, Mary K. Klassen-Fischer, and Wayne M. Meyers

Introduction

Definition

Toxoplasmosis is infection by *Toxoplasma gondii*, a coccidian protozoan parasite of birds, cats, humans, and other mammals. In humans, infection is usually asymptomatic. Clinical symptoms arise in some congenitally infected infants and in adults whose immune systems have been compromised by, for example, corticosteroids, cytostatic agents, or AIDS.

General Considerations

The generic name *Toxoplasma* comes from the Greek word "toxon," meaning bow or arc, and refers to the crescent shape of the parasite. The specific name is derived from the gondi, a local rodent used at the Pasteur Institute in Tunisia, in which Nicolle and Manceaux discovered *Toxoplasma* in 1908.[1] In the same year, Splendore identified *Toxoplasma* in a laboratory rabbit in Brazil.[2] In 1923, the organism was recognized in Czechoslovakia in histologic sections of a child's eye.[3] In 1937, Wolf et al suggested placental transmission after finding the parasite in the brains of several babies dying of neonatal encephalitis.[4] A serologic test developed by Sabin and Feldman in 1948 revealed widespread subclinical infection worldwide.[5] Wilder, at the Armed Forces Institute of Pathology (AFIP), identified *Toxoplasma* in eyes previously considered tuberculous or syphilitic.[6] In the 1950s, Jacobs et al at the National Institutes of Health (USA) confirmed that *Toxoplasma* could be transmitted by raw or undercooked meat.[7,8] A coccidian type of sexual development was described in cats in 1970, adding oocysts from cat feces and contaminated sand or soil to the known sources of infection.[9] Lehmann et al characterized 3 subgroups of *T. gondii* by molecular biology for phylogenetic analysis.[10] Subgroup types vary in virulence and geographic distribution, for example, type II predominates in ocular disease in France.[11]

Epidemiology

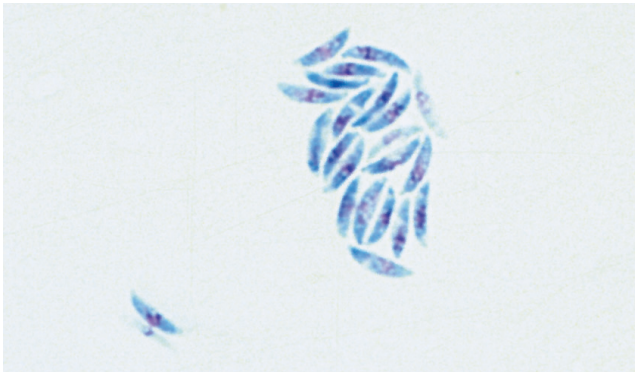

Figure 12.1
Toxoplasma tachyzoites in smear of cytospin specimen from HIV-positive patient. Each parasite is crescentic and has a prominent nucleus. Giemsa x1250

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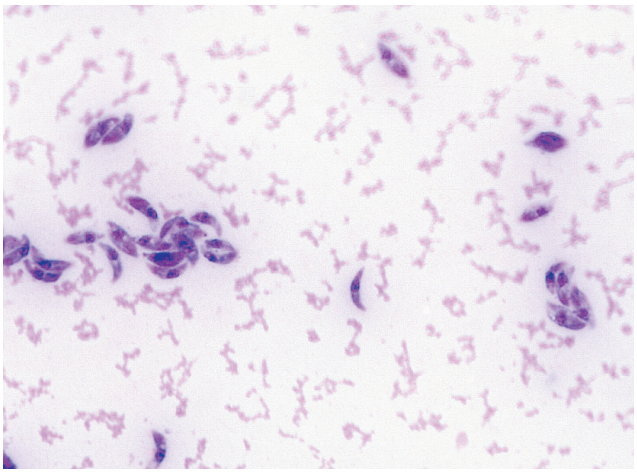

Figure 12.2
Toxoplasma tachyzoites in smear showing variation in shape and size. Giemsa x1130

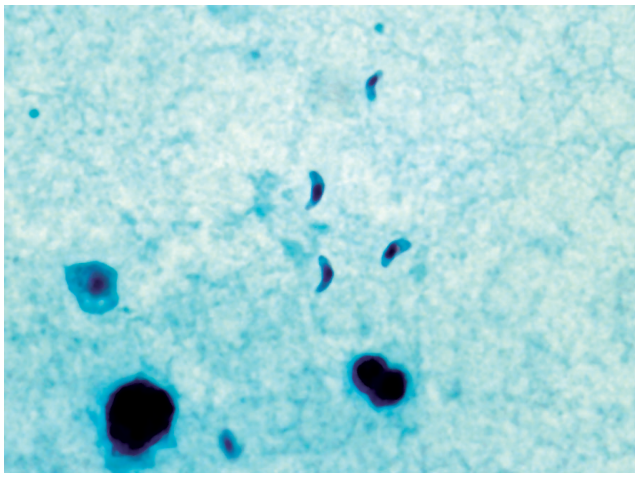

Figure 12.3
Toxoplasma tachyzoites in Pap smear. Note prominent reddish nucleus in each parasite. Papanicolaou x820

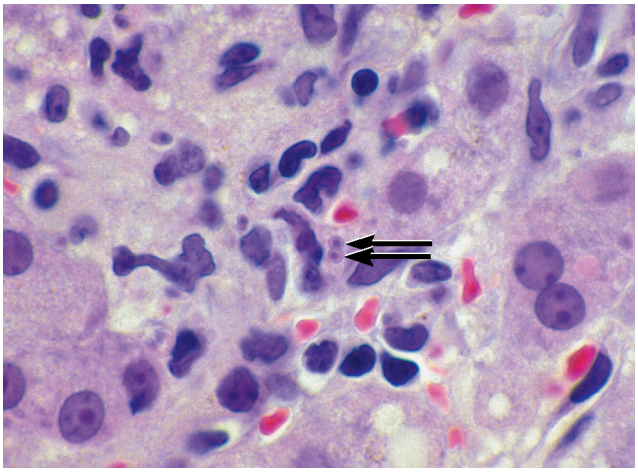

Figure 12.4
Toxoplasma tachyzoites in biopsy of liver in HIV-positive patient. Note 2 spherical organisms (arrows), each with prominent nucleus. H&E x1460

Toxoplasmosis is one of the most common parasitic infections of humans.[12] Animals and humans on 5 continents show serologic evidence of infection with *Toxoplasma*. Prevalence is highest in warm, humid regions. In the lowlands of Central America, where cats are numerous and shade and moisture favor survival of oocysts in soil, almost all adults have antibodies to *Toxoplasma*. In urban and rural areas of Costa Rica and Panama, where transmission to humans is almost exclusively by oocysts from cats, 25% to 50% of schoolchildren are serologically positive.[12-16] In rain forest areas, where human and feline habitats are less likely to overlap, transmission to humans is irregular.[16] In the United States, infection is most commonly acquired by young adults who have eaten undercooked meat. Viable *T. gondii* can also persist in commercially cured meats, which may be another source of transmission.[17] Pigs raised on small farms in close proximity to cats, rodents, and birds are more likely to be infected with *Toxoplasma* than industrially raised pigs.[18] Sheep are rarely infected on the range, but are likely to be infected when brought to farms where cats are present.[19] Contaminated meat seems to remain the primary source of infection but environmental sources are common. [20,21]

Infectious Agent

Morphologic Description

Two stages of *T. gondii* occur in human tissues: tachyzoites, the rapidly multiplying form found in acute infection, and bradyzoites, the slowly multiplying form found in chronic infection. Interconversion between rapidly growing tachyzoites and latent encysted bradyzoites is accompanied by numerous morphologic and metabolic adaptations.[22]

Tachyzoites infect many types of cells and multiply asexually by repeated endodyogeny. Daughter cells form within the mother cell until the mother cell ruptures, releasing free tachyzoites that invade new tissue cells.

In fresh preparations and impression films, tachyzoites are crescent-shaped and up to 7µm long and 1µm to 3µm wide, with a well-defined, usually centrally located nucleus (Figs 12.1 to 12.3). They stain well with Giemsa, Wright's, Dif-Quick, and Papanicolaou's stains. In tissue sections prepared from biopsy or autopsy specimens, tachyzoites are best observed in hematoxylin and eosin (H&E) stained sections (Figs 12.4 & 12.5). They are usually round to oval and 2µm to 3µm in greatest dimension, but may be crescentic and 5µm long (Fig 12.6). Tachyzoites sometimes divide by binary fission and occasionally have multiple nuclei (Fig 12.7). Organisms lie free in tissue, unbound by a cyst wall (Figs 12.4 to 12.7), but may aggregate in clusters referred to as groups (Fig 12.8). Hematoxylin and eosin is the preferred stain for identifying tachyzoites in tissue sections, but some special stains may be useful. Tachyzoites are gram-negative by the Brown-Hopps (B&H) modified Gram stain (Fig

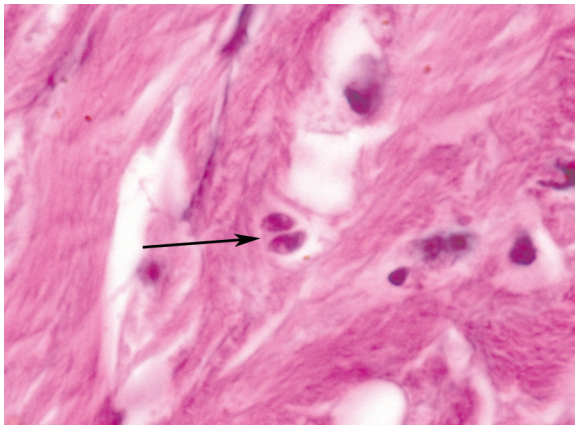

Figure 12.5
Toxoplasma tachyzoites (arrow) in choroid of enucleated eye of HIV-positive patient. Organisms are oval and each has a prominent nucleus. H&E x1350

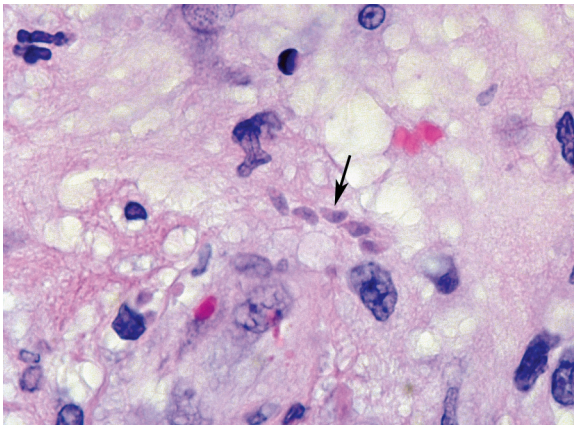

Figure 12.6
Toxoplasma tachyzoites (arrow) in brain of patient who died of AIDS. Note prominent nucleus within each crescent-shaped organism. H&E x815

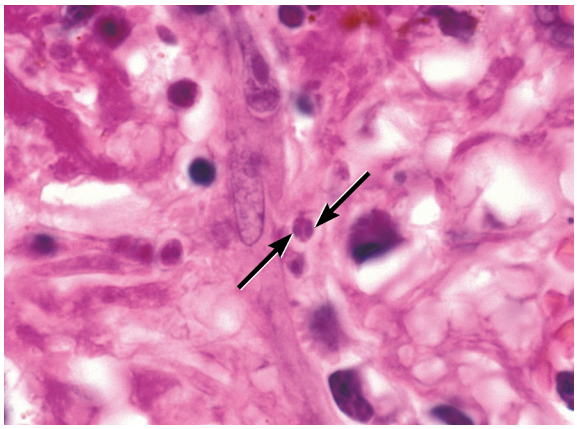

Figure 12.7
Toxoplasma tachyzoite with 2 nuclei (arrow) undergoing binary fission in choroid of enucleated eye of HIV-positive patient. H&E x1000

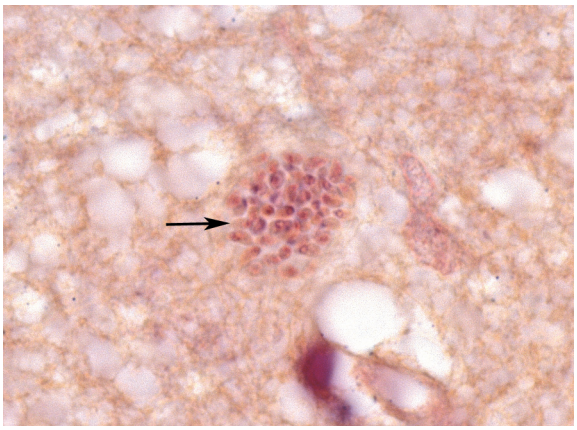

Figure 12.8
Group of *Toxoplasma* tachyzoites (arrow) in brain of immunodeficient patient. Note absence of cyst wall. B&H x1000

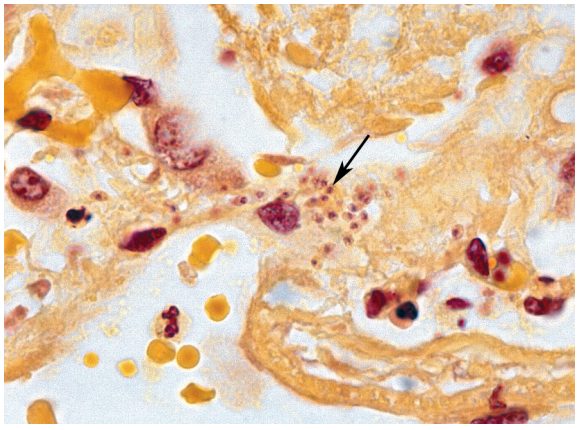

Figure 12.9
Section of lung showing gram-negative *Toxoplasma* tachyzoites (arrow), each with prominent nucleus. B&H x1500

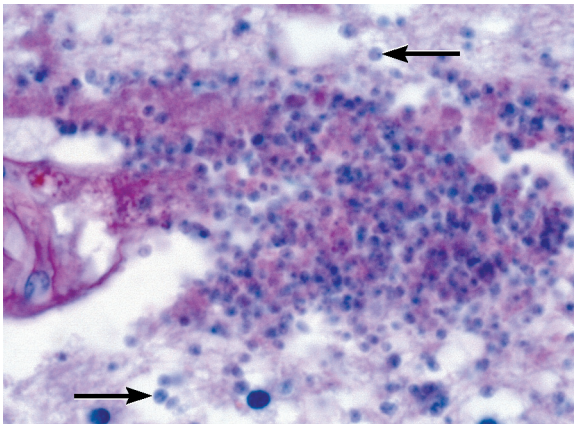

Figure 12.10
PAS-negative *Toxoplasma* tachyzoites (arrows) are nonetheless identifiable in this section of brain. PAS x770

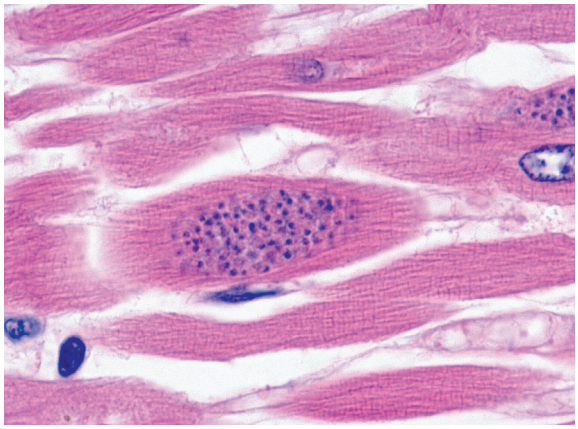

Figure 12.11a
Group of *Toxoplasma* tachyzoites in myocardium of HIV-positive patient. Note absence of cyst wall. H&E x860

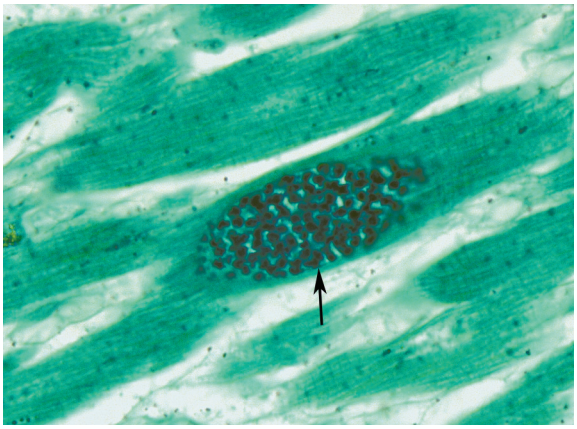

Figure 12.11b
Silvered tachyzoites in section (arrow) adjacent to that seen in Figure 12.11A. GMS x875

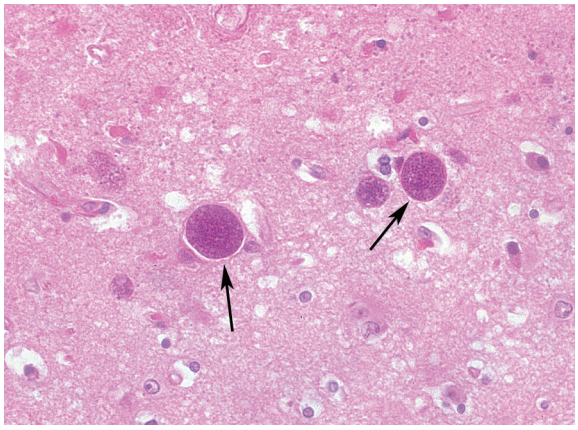

Figure 12.12
Toxoplasma bradyzoites (arrows) within cysts in brain of immunocompromised patient. Cysts stain well with H&E. H&E x260

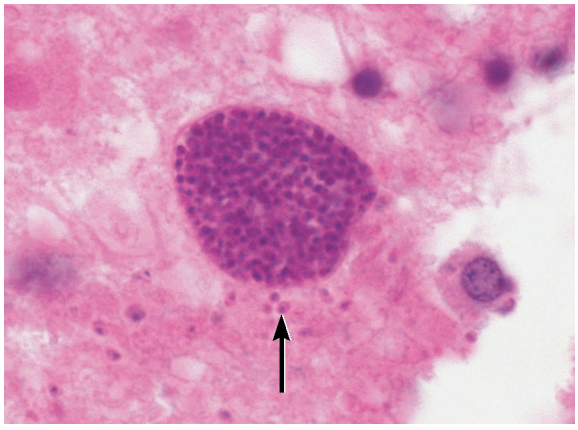

Figure 12.13
Single *Toxoplasma* cyst in brain. Note numerous bradyzoites and thin cyst wall, and tachyzoites (arrow) adjacent to cyst. H&E x960

12.9), and PAS-negative by the periodic acid-Schiff (PAS) technique (Fig 12.10). Gomori's methenamine silver (GMS) usually does not stain free tachyzoites, but may stain groups (Figs 12.11a & 12.11b).

Bradyzoites reproduce by both endodyogeny and endopolygeny. They are highly motile and can infect many types of cells. Cysts can proliferate without undergoing an intermediate tachyzoite stage through the process of fission, or by migration of free bradyzoites.[22] Morphologically, individual bradyzoites are nearly identical to tachyzoites; the difference is that bradyzoites are always encysted. Most cysts are less than 50 µm in diameter, but may be up to 100 µm in diameter and contain hundreds of bradyzoites. As with tachyzoites, H&E is the preferred stain for identifying cysts in tissue sections (Figs 12.12 & 12.13), but special stains may be useful, including B&H (Figs 12.14 & 12.15), GMS (Figs 12.16 & 12.17), and PAS (Figs 12.18 to 12.20). It must be emphasized that these special stains vary greatly in their ability to demonstrate *Toxoplasma*.

Life Cycle and Transmission

In a variety of mammals and birds that act as intermediate hosts, *T. gondii* multiplies asexually in an extraintestinal cycle (Fig 12.21). In domestic and wild cats, the definitive hosts, an enteroepithelial cycle also takes place which, after sexual recombination, leads ultimately to the formation of resistant oocysts eliminated in feces (Fig 12.22). When a cat ingests an animal containing bradyzoites in tissue cysts, the enteroepithelial cycle takes place in the cat's intestine and oocysts appear in feces in 3 to 10 days depending on the quantity of bradyzoites ingested. If a cat ingests sporozoites from oocysts, or an animal with only tachyzoites, a generalized infection with tachyzoites develops first, followed by the development of bradyzoites in tissue cysts, which initiate the enteroepithelial cycle.[23] Oocysts are shed in 21 to 40 days. Enteroepithelial stages of *Toxoplasma* in the intestines of cats include 5 types of multiplicative stages,

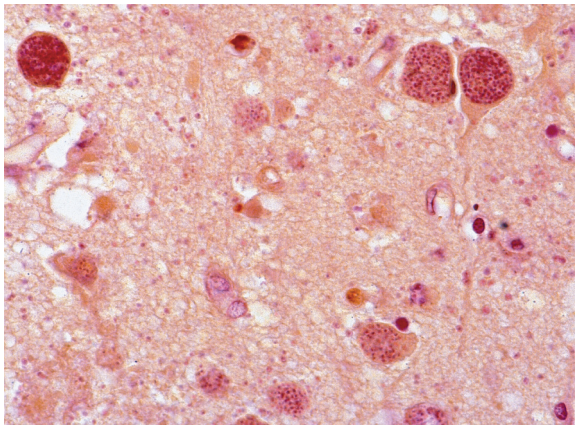

Figure 12.14
Numerous bradyzoites within 2 thin-walled cysts in brain. B&H x145

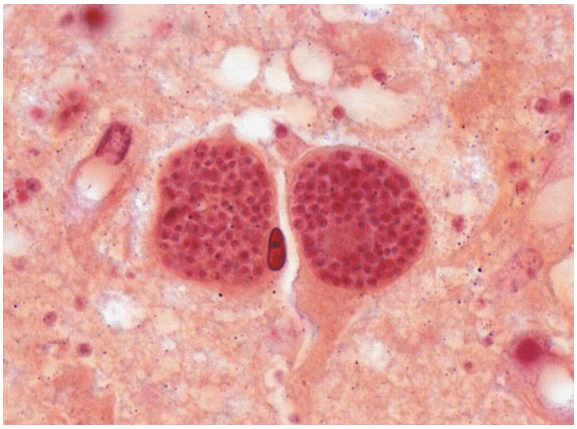

Figure 12.15
Several well-stained *Toxoplasma* cysts in brain. B&H x875

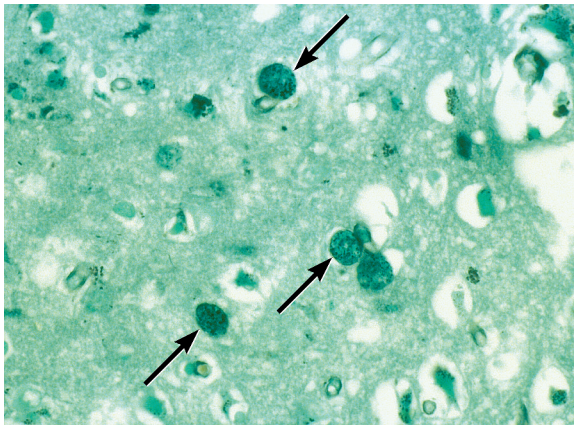

Figure 12.16
Several *Toxoplasma* cysts (arrows) in brain. GMS x350

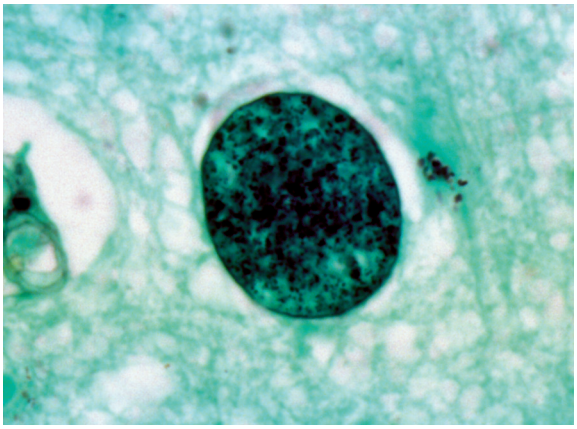

Figure 12.17
Single *Toxoplasma* cyst in brain. Note GMS-positive cyst wall and internal amylopectin granules. GMS x900

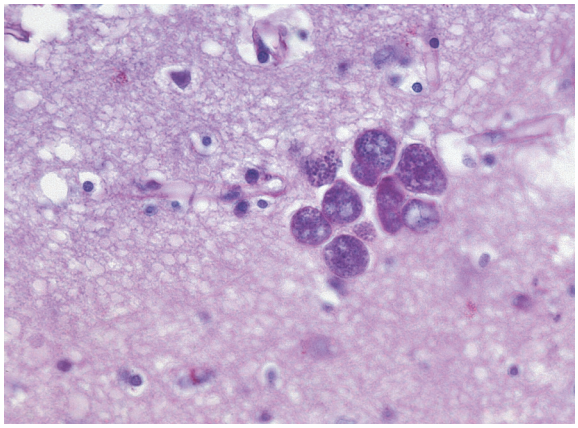

Figure 12.18
Several readily identifiable *Toxoplasma* cysts in brain. PAS x320

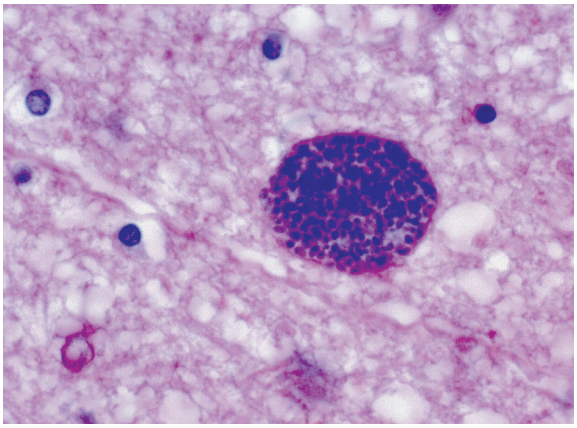

Figure 12.19
Single readily identifiable *Toxoplasma* cyst in brain. Cyst wall and amylopectin granules are PAS-negative. PAS x540

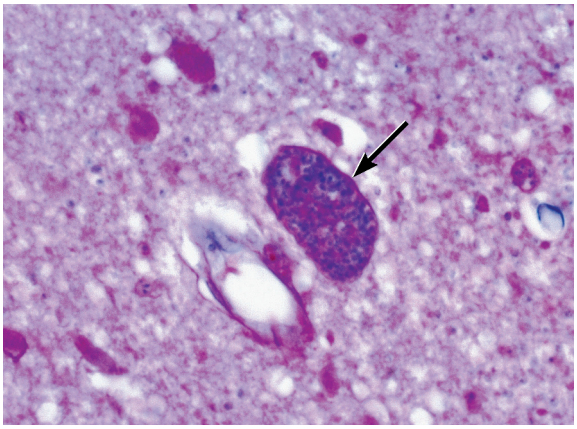

Figure 12.20
Single *Toxoplasma* cyst in brain of patient depicted in Figure 12.19. Cyst wall (arrow) and amylopectin granules are PAS-positive. PAS x665

gametocytes, and oocysts.[24]

Transmission to carnivores is mainly by tissue cysts contained in meat, and to herbivores by oocysts ingested with soil or feed contaminated by cat feces. Humans acquire infection by eating meat from chronically infected animals or by ingesting oocysts deposited in soil or sand by cats (Fig 12.21). Mechanical vectors include dogs, flies, cockroaches, and earthworms.[13] The possibility that dogs play a role in transmission through coprophagia and rolling in cat feces was suggested in the 1990s.[13]

Clinical Features and Pathogenesis

Although most *T. gondii* infections in humans are asymptomatic, there are several clinical patterns of toxoplasmosis: 1) Acute febrile illness, sometimes with pneumonia and myocarditis; 2) Lymphadenopathy, sometimes with or following acute febrile illness; 3) Asymptomatic primary maternal infection with transmission to the fetus; 4) Congenital infection with growth retardation, jaundice, or encephalitis; 5) Acute or chronic encephalitis in an immunosuppressed host; 6) Retinochoroiditis in children or adults, usually without other manifestations.

Acute *Toxoplasma* infection is usually followed by chronic disease. Both are asymptomatic in humans and animals that promptly acquire immunity to the organism. Mammals in Australia and Madagascar that evolved without contact with felines, and neotropical, arboreal primates that have little contact with terrestrial felines, often develop clinically apparent and sometimes fatal toxoplasmosis.[25-27] During acute infection, *Toxoplasma* tachyzoites multiply in many types of cells and tissues. Pathologic changes vary with the number of parasites that are destroying host

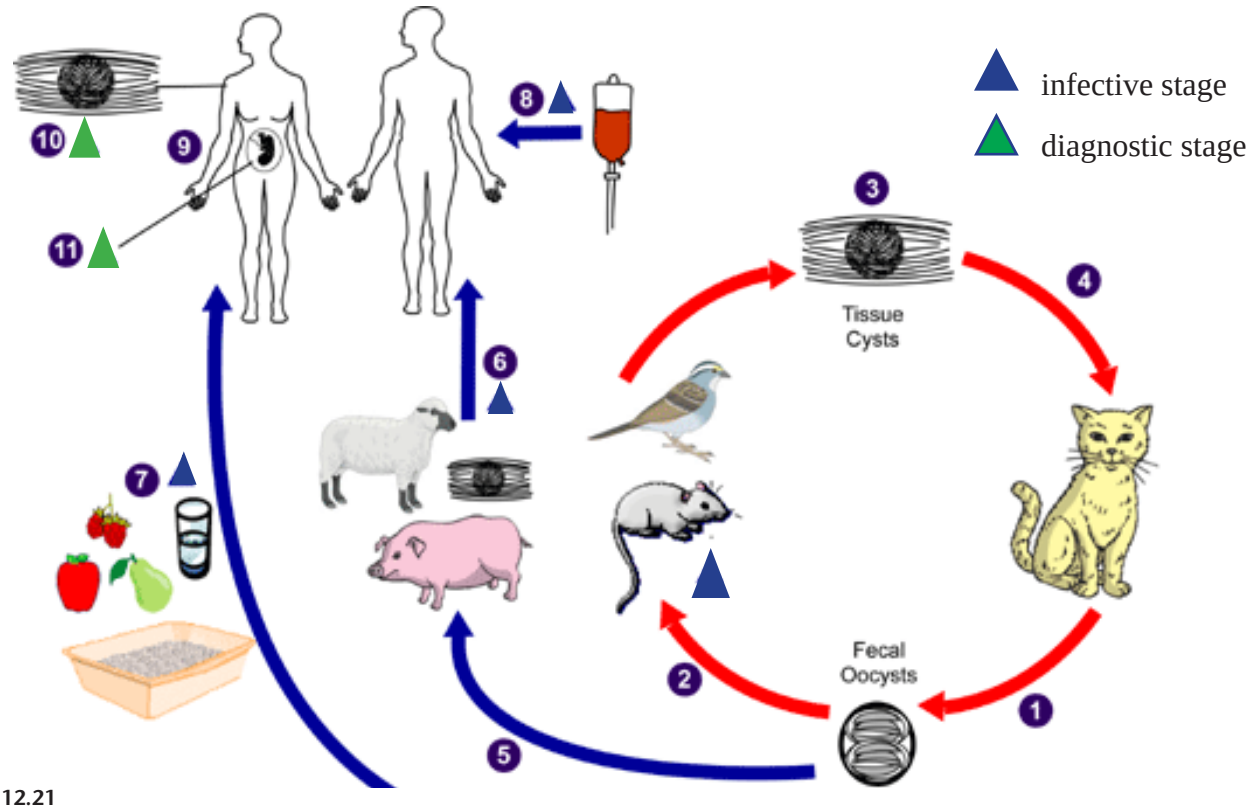

Figure 12.21
General *Toxoplasma gondii* life cycle: (1-4) cat to small animal to cat; (5-6) fecal oocysts are eaten by animals that become food sources; (7) fecal oocysts contaminate fruits, water or cat litter; (8) human to human via blood transfusion; and (9-11) risk to fetus.

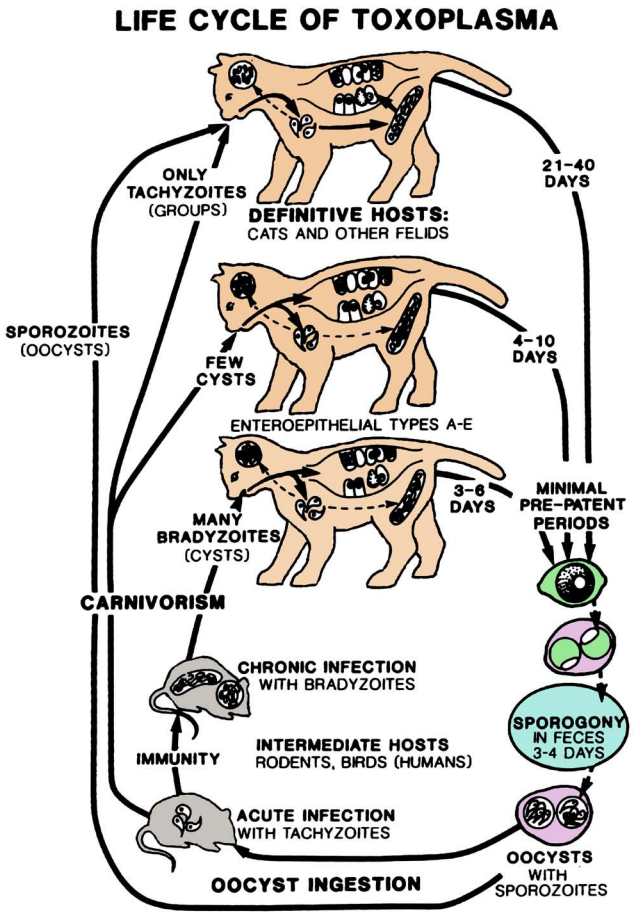

Figure 12.22
Life cycle—cat

cells. Tachyzoites enter a host's intestines and disseminate through blood and lymph. Lesions form as a result of cell destruction (Fig 12.23), usually in the lung but sometimes in the heart or other parts of the body. Immunity usually develops during acute infection. High antibody titers develop, but cell-mediated immunity is decisive. With immunity, the number of tachyzoites in the viscera decreases, but bradyzoites persist in many tissues, especially the brain, retina, and placenta. Approximately 30% to 40% of women who become infected during pregnancy transmit infection to the fetus.[28] Maternal infection and placentitis are usually asymptomatic.

While searching for infections predisposing to schizophrenia, several authors noted higher prevalence rates of antibody to *Toxoplasma* in patients with schizophrenia than in normal controls, as well as epidemiologic similarities between the two conditions, and poorer delayed and immediate memory in individuals with *Toxoplasma* antibody than in those without the antibody.[29] Other authors found in individuals who had caused an automobile accident to have more than twice the rate of antibody to *Toxoplasma* than in controls.[30,31] In a study from Istanbul, Turkey, patients with schizophrenia had similarly elevated *Toxoplasma* serologic rates and 59% of this group had contact with cats, compared to 7.5% in controls. Amongst individuals who had contact with cats there was no positive association of schizophrenia with *Toxoplasma* antibody, and of those without cat contact there was a significant negative correlation between schizophrenia and *Toxoplasma* antibody.[32] The effect of toxoplasmosis on risk for schizophrenia disappeared in a complex model analyzed with multivariate logistic regression. Clearly, these provocative findings need further study. In a sample of 20 European countries *T. gondii* infections were positively associated with suicide rates.[33]

Chronic infection is maintained by bradyzoites in tissue cysts, which are relatively nonpathogenic and can survive for long periods in neurons, myocardial and skeletal muscle, and other cells. In children and young adults believed to have been infected in utero, ocular lesions sometimes develop after many years of asymptomatic infection. In such patients optic nerve edema may accompany a concurrent distant active lesion.[34] Another common lesion is juxtapap-

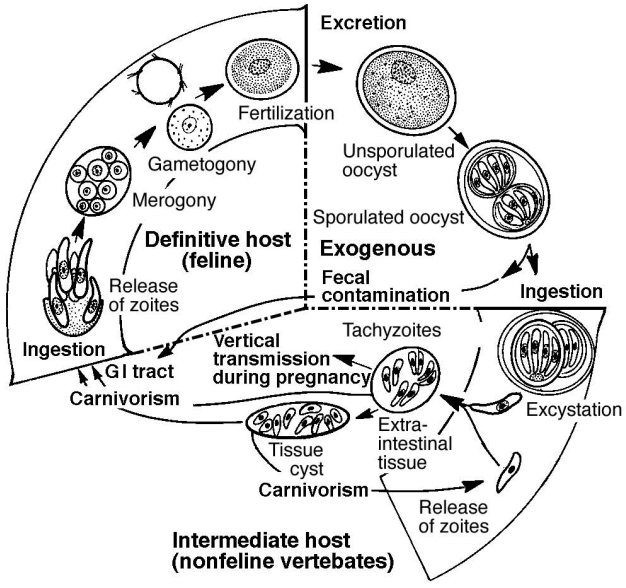

Figure 12.23
Diagram of *Toxoplasma gondii* development stages compared to stages in Figures 12.21 and 12.22 : upper left quadrant concerns the cat; upper right quadrant the maturation of the fecal oocyst in the ground or cat box; and the lower half in animals or humans.

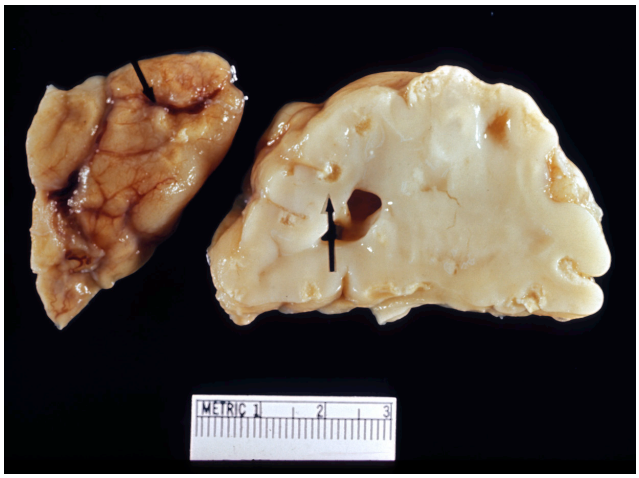

Figure 12.24
Congenital toxoplasmic encephalitis in 11-day-old infant with focal infarcts (arrows).

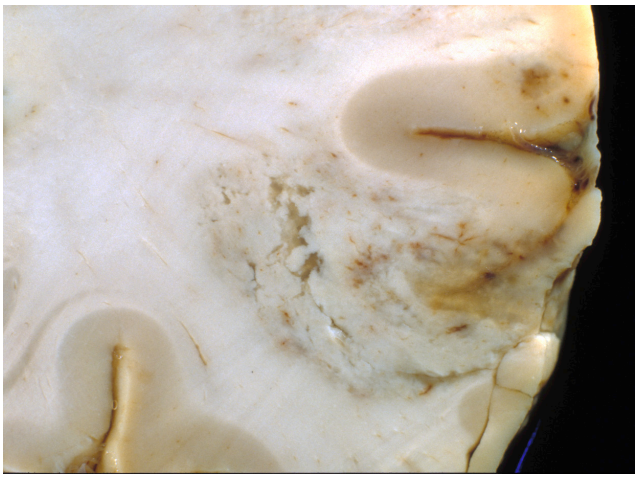

Figure 12.25
Focus of cortical necrosis caused by infarction in congenital toxoplasmic encephalitis.

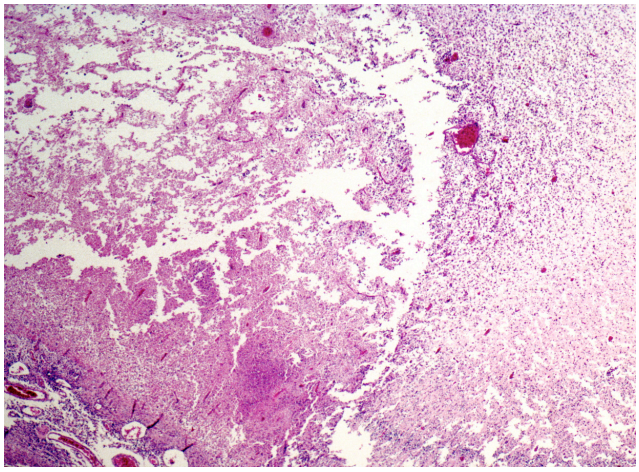

Figure 12.26
Section of specimen from patient described in Figure 12.24 showing interface of ischemic necrotic (left) and viable (right) brain tissue with vascular congestion. H&E x19

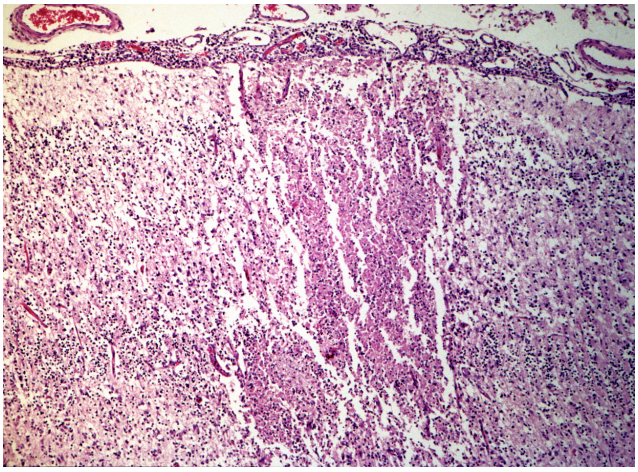

Figure 12.27
Meningeal mononuclear-cell infiltrate overlying area of ischemic necrosis in section of specimen from patient described in Figure 12.24. H&E x45

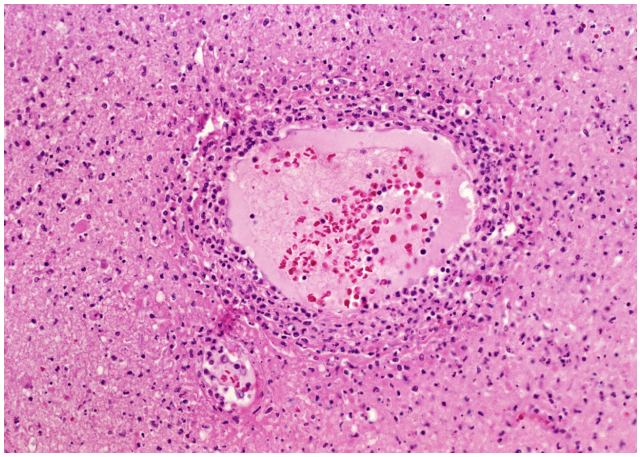

Figure 12.28
Primary vasculitis of brain in congenital toxoplasmosis. H&E x135

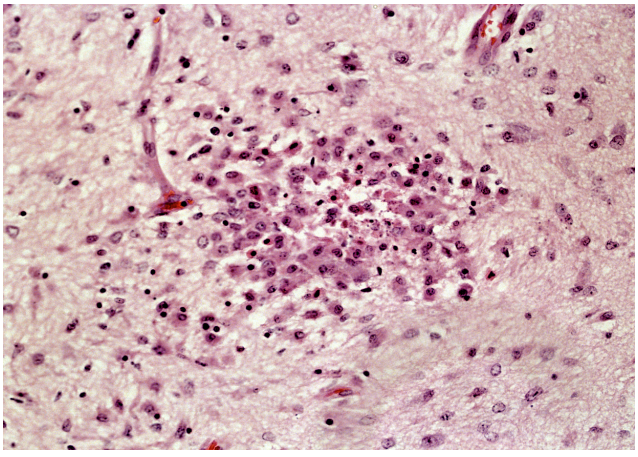

Figure 12.29
Glial nodule in patient with congenital toxoplasmosis. H&E x145

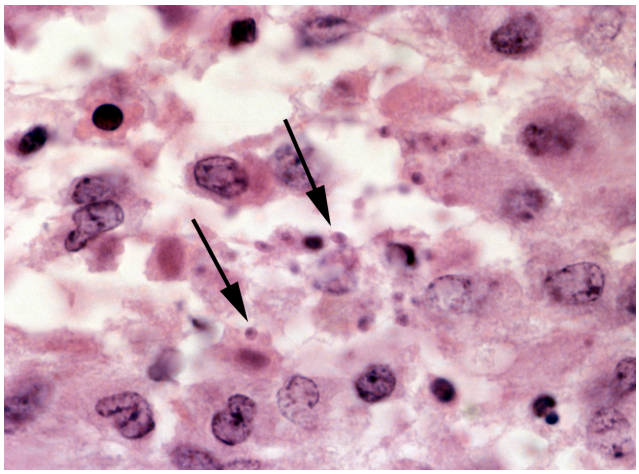

Figure 12.30
Tachyzoites (arrows) in higher magnification of glial nodule shown in Figure 12.29. H&E x 780.

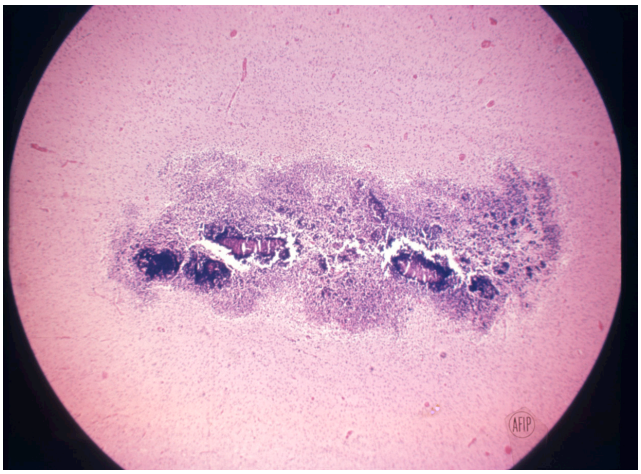

Figure 12.31
Calcification in brain of patient with congenital toxoplasmosis. H&E x340

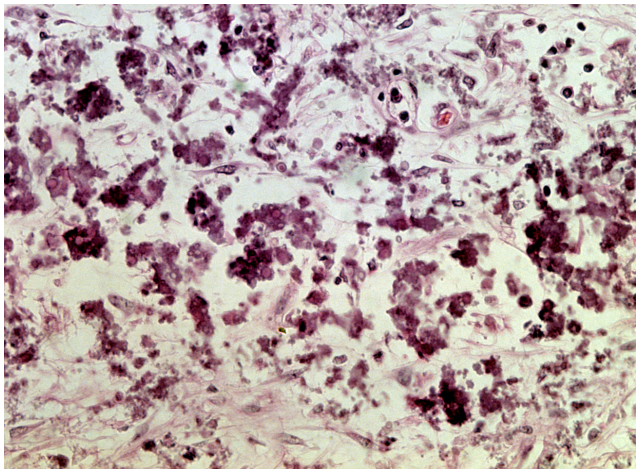

Figure 12.32
Calcification in brain of patient with congenital toxoplasmosis. H&E x220

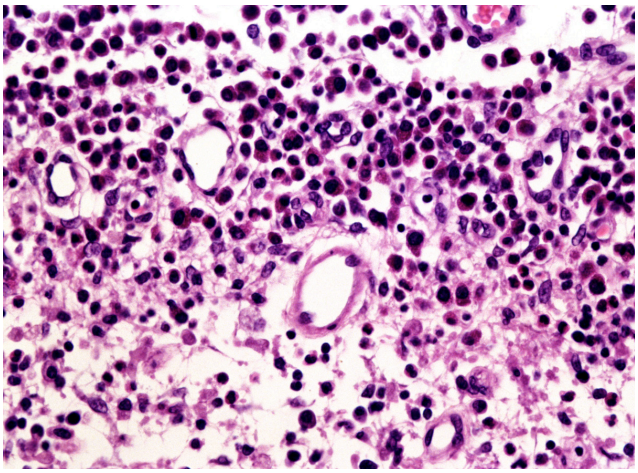

Figure 12.33
Prominent eosinophilia in meninges of patient with congenital toxoplasmosis. H&E x260

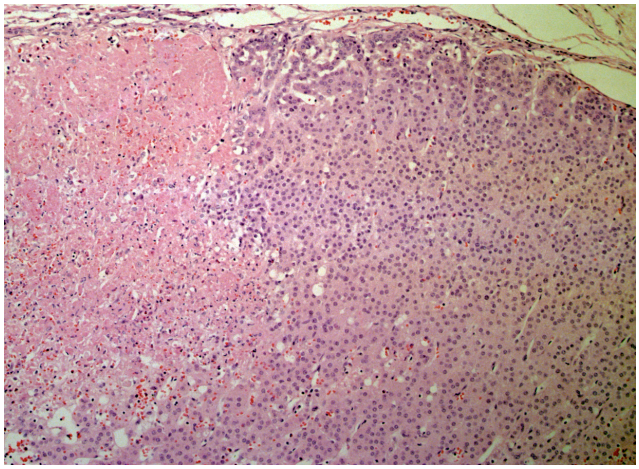

Figure 12.34
Necrosis in adrenal gland of patient with congenital toxoplasmosis. H&E x60

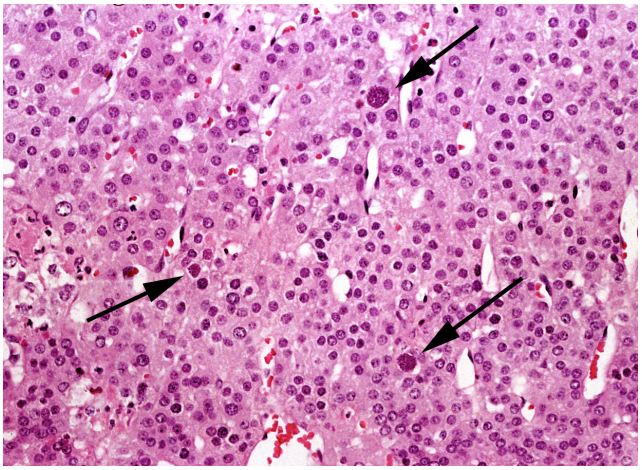

Figure 12.35
Several groups of tachyzoites (arrows) in viable adrenal gland of patient with congenital toxoplasmosis. H&E x150

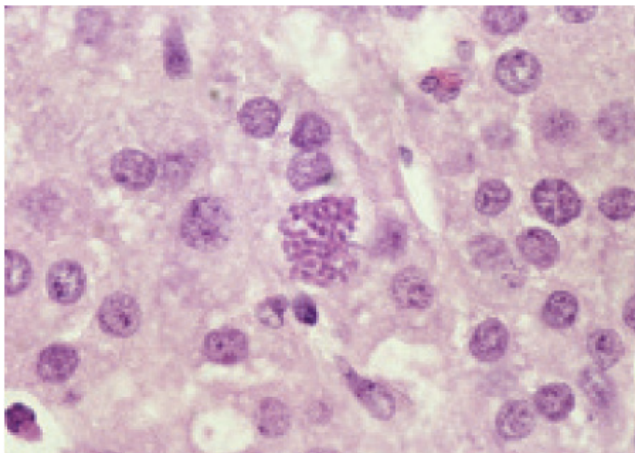

Figure 12.36
Group of tachyzoites in viable adrenal gland of patient with congenital toxoplasmosis. Note absence of cyst wall. H&E x590

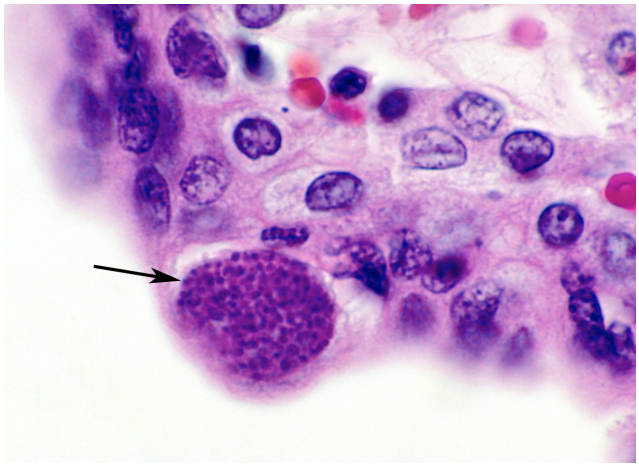

Figure 12.37
Toxoplasma cyst (arrow) with bradyzoites in viable placental villus. H&E x825

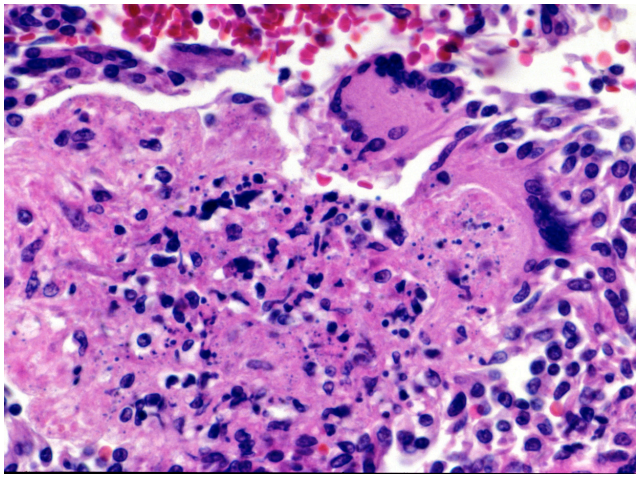

Figure 12.38
Toxoplasma gondii is presumptive cause of necrotizing granulomatous inflammation in placenta of patient with toxoplasmosis, though careful examination revealed no organisms in specimen. H&E x335

illary retinochoroiditis, which some researchers attribute to disintegration of cysts with resulting inflammatory reaction in a hypersensitive host.[35] Others believe that only proliferation of *Toxoplasma* causes ocular lesions.[36] However, generalized immunity remains effective, as suggested by the self-limiting nature of most untreated lesions. *Toxoplasma gondii* induces production of interleukin-12 by dendritic cells, resulting in a cell-mediated immune response that halts replication of tachyzoites, thus promoting host survival and parasite transmission.[37] Apoptosis is a crucial factor in promoting both a stable host-parasite interaction and persistent infection. Initially, *T. gondii* triggers apoptosis in T lymphocytes and other leukocytes, which suppresses immune response and allows unrestricted parasite replication. *Toxoplasma gondii* can also inhibit apoptosis. Inhibiting apoptosis in nearby uninfected cells modulates the local inflammatory response and facilitates intracellular parasite development.[38] Inflammatory reaction to cyst rupture, with maintenance of immunity, has also been observed in the brain.[39]

Recrudescent toxoplasmosis is increasingly identified in immunocompromised patients with chronic infection. Pregnancy can provoke or be accompanied by the recurrence of ocular toxoplasmosis in an infected patient.[40] Immunosuppressed pregnant women with chronic *Toxoplasma* infection sometimes pass the infection to their fetus.[41] An infected fetus sustains a generalized infection which may be moderated by maternal antibody. Immunity is acquired more slowly in the fetus and newborn than in the generally asymptomatic mother. Active infection of the newborn is liable to persist in the brain and eye and produce significant lesions. In patients treated with corticosteroids and patients with AIDS, lesions progress with proliferation of tachyzoites.[42,43] About 25% of AIDS patients with *Toxoplasma* antibody sustain recrudescent infection, mainly in the brain and retina, but only occasionally in the lungs, stomach, and other parts of the body.[44] Other tissues generally retain immunity. The initiating event is probably a disintegrating tissue cyst from which liberated, surviving bradyzoites develop into tachyzoites that migrate along arterioles and among cells, causing cell destruction.[42] Because some affected arterioles undergo thrombosis, infarcts without *Toxoplasma* can develop. Due to the increased risk of allograft-transmitted toxoplasmosis, serologic evaluation and prophylaxis are standard for donor and recipient in heart and heart-lung transplantation. Screening is not yet routine in transplantation of other solid organs.[45]

Pathologic Features

Congenital infection

In congenital toxoplasmic encephalitis, there may be gross evidence of infarction, such as focal swelling, necro-

sis, or hemorrhage (Figs 12.24 & 12.25). Histopathologic changes include periventricular ependymal ulcerations, swelling of vessel walls, perivascular inflammation, vascular thrombosis, and necrosis (Figs 12.26 & 12.27). These periventricular lesions, unique to toxoplasmosis, may obstruct the aqueduct and are characterized by vasculitis without major participation of tachyzoites (Fig 12.28).[46] There may be scattered glial nodules with or without tachyzoites (Figs 12.29 & 12.30), and calcium deposits in necrotic areas (Figs 12.31 & 12.32). A prominent tissue eosinophilia may occur in any organ (Fig 12.33). The adrenal gland may be involved, resulting in extensive necrosis and readily identified tachyzoites (Figs 12.34 to 12.36). The placenta, though grossly normal, may nonetheless be infected (Figs 12.37 & 12.38). Placental toxoplasmosis with necrotizing granulomatous villitis has been reported in a patient with acute toxoplasmosis. Granulomas, formed by maternal inflammatory cells, contained rare cysts.[47] Other organs that may be involved in congenital toxoplasmosis include heart, lung, spleen, bone marrow, and eyes (Figs 12.39 to 12.44).

Infection in Non-immunocompromised Patients

Lymph node

In acute toxoplasmic lymphadenopathy, although lymph node histologic architecture remains intact, there is prominent reactive follicular hyperplasia. Affected nodes contain clusters of epithelioid histiocytes, principally in perifollicular zones and occasionally within follicles.[48,49] These histiocytes do not form well-defined granulomas or develop multiple nuclei, and are not accompanied by necrosis (Fig 12.45). Monocytoid B cells commonly distend capsular and trabecular sinuses. There may be focal or diffuse infiltrates of plasma cells, but no eosinophilia, fibrosis, or periadenitis. The differential diagnosis includes Hodgkin disease, Whipple disease, infectious mononucleosis, granulomatous lymphadenitis,the lymphoepithelioid cell variant of T-cell (Lennert) lymphoma, smallpox vaccination reaction, HIV-related lymphadenopathy, and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease).[50] *Toxoplasma* cysts in histologic sections of lymph nodes have been found in less than 1% of cases submitted to the AFIP (Figs 12.46 & 12.47).

Infection in Immunocompromised Adults

Brain

In toxoplasmic encephalitis, tachyzoites multiply in neurons, glial and ependymal cells, and vessel walls (Figs 12.48 & 12.49). Tachyzoites tend to migrate along arteriolae, causing vasculitis, thrombosis, and infarction necrosis, mainly in gray matter (Figs 12.50 & 12.51).[42]

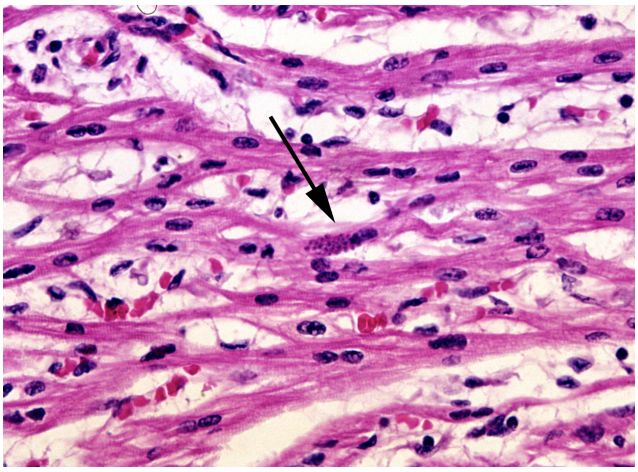

Figure 12.39
Group of *Toxoplasma* tachyzoites (arrow) in myocardium of patient with congenital toxoplasmosis. H&E x310

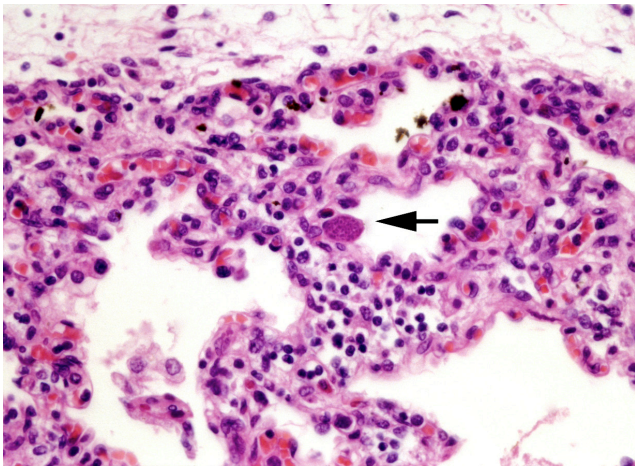

Figure 12.40
Toxoplasma cyst with bradyzoites (arrow) in lung of patient with congenital toxoplasmosis. H&E x280

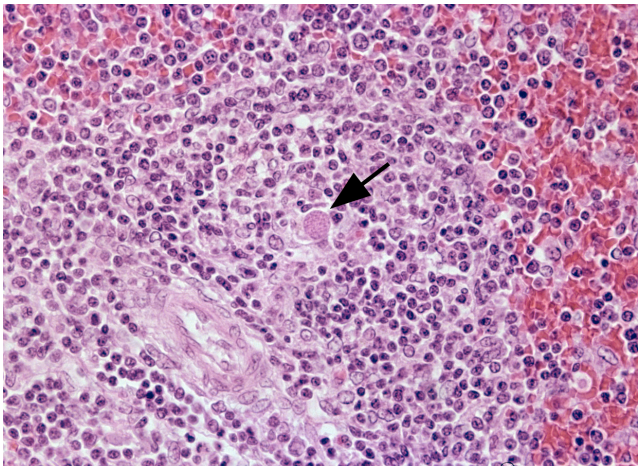

Figure 12.41
Toxoplasma cyst with bradyzoites (arrow) in white pulp of spleen of patient with congenital toxoplasmosis. H&E x260

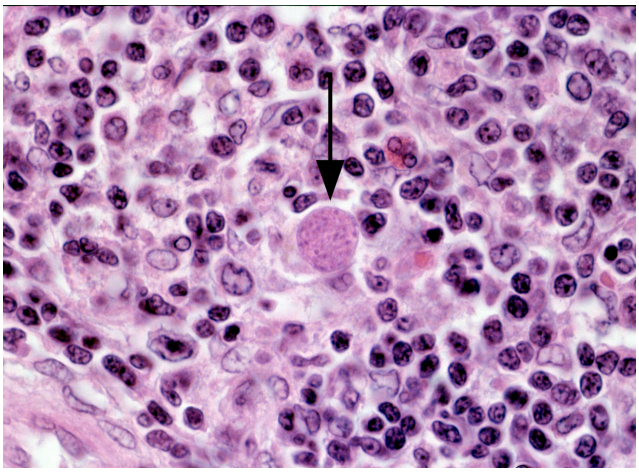

Figure 12.42
Higher magnification of *Toxoplasma* cyst in Figure 12.41. Note thin cyst wall (arrow). H&E x660

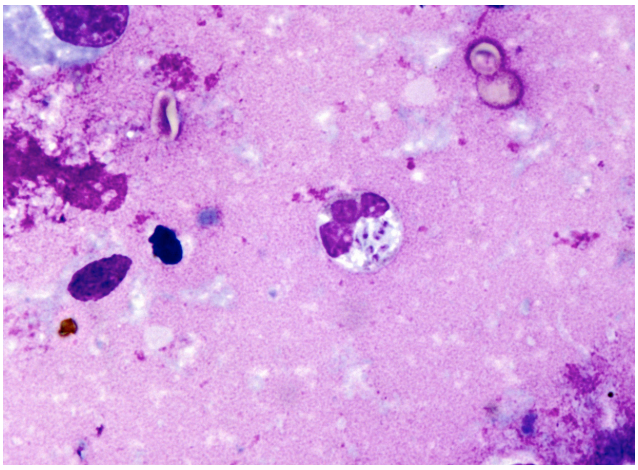

Figure 12.43
Smear of bone marrow of patient with congenital toxoplasmosis, demonstrating several *Toxoplasma gondii* organisms in macrophage. Giemsa x1265

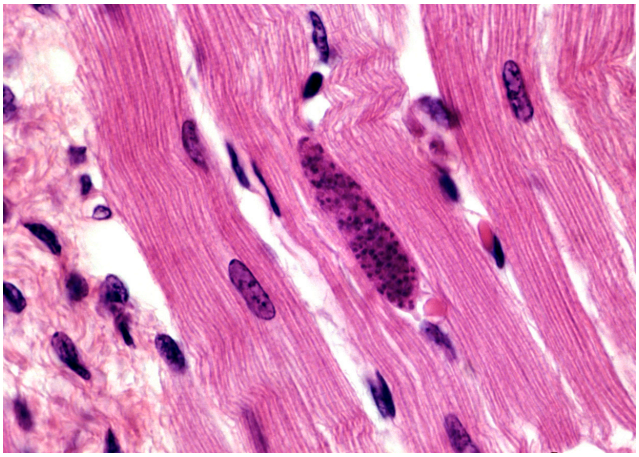

Figure 12.44
Toxoplasma cyst with bradyzoites in striated muscle of larynx of patient with congenital toxoplasmosis. H&E x660

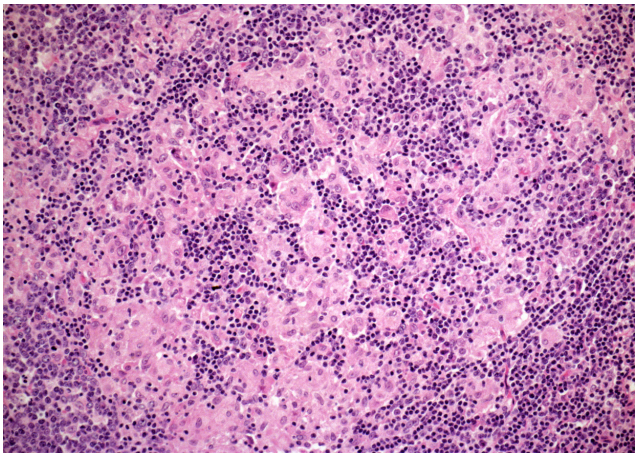

Figure 12.45
Toxoplasmic lymphadenitis with characteristic clusters of histiocytes that do not form well-defined granulomas. Note absence of necrosis. H&E x115

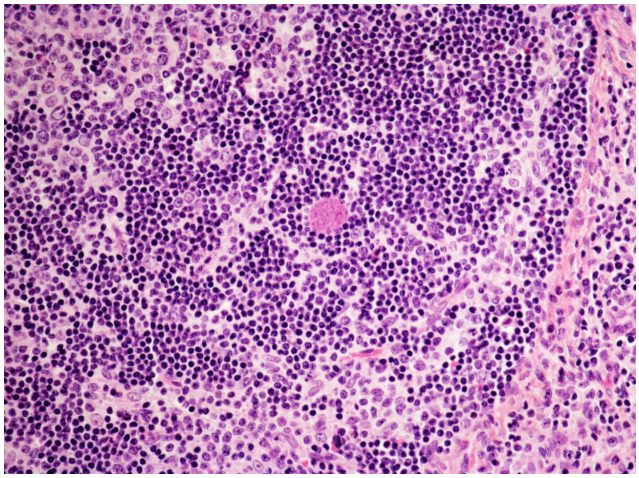

Figure 12.46
In lymph node, *Toxoplasma* cyst with bradyzoites is rare finding. H&E x175

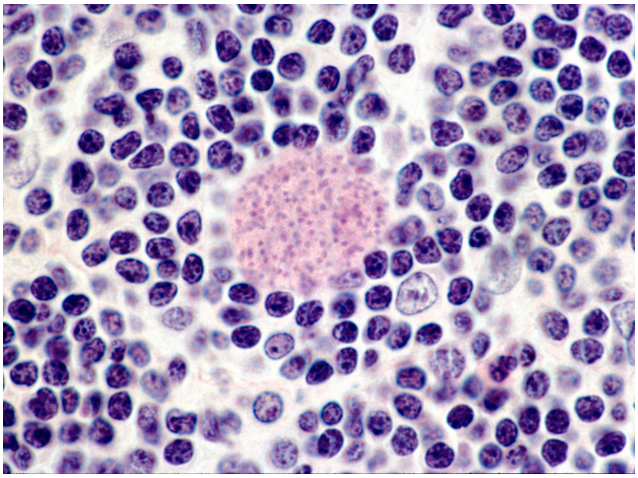

Figure 12.47
Higher magnification of bradyzoites within *Toxoplasma* cyst depicted in Figure 12.46. H&E x725

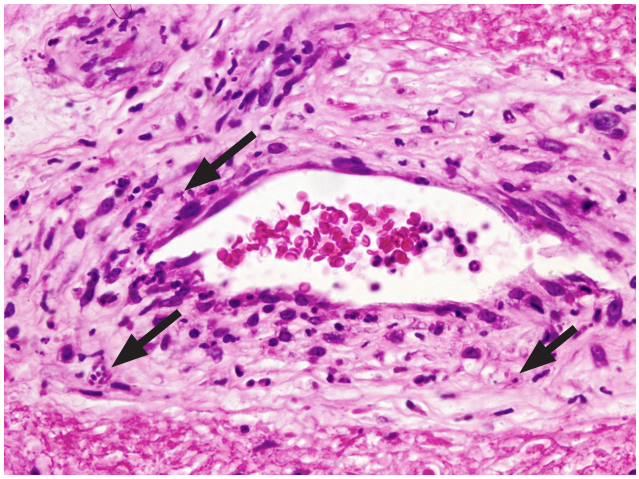

Figure 12.48
Toxoplasma tachyzoites within vessel wall (arrow) of biopsied brain of 71-year-old male who had been clinically diagnosed with glioma. H&E x235

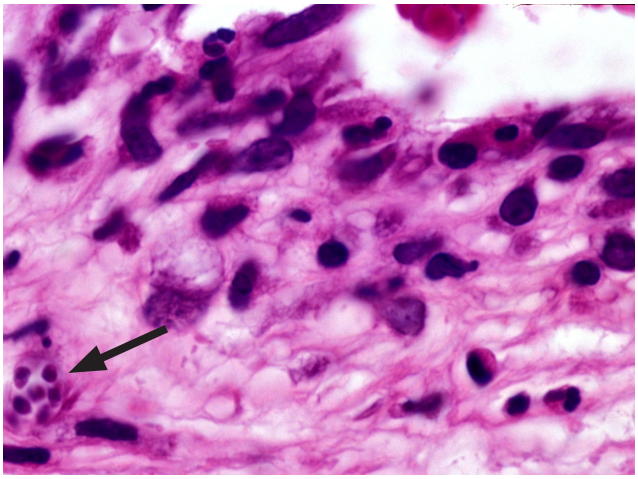

Figure 12.49
Higher magnification of vessel wall depicted in Figure 12.48. Note well-stained group of tachyzoites (arrow). H&E x745

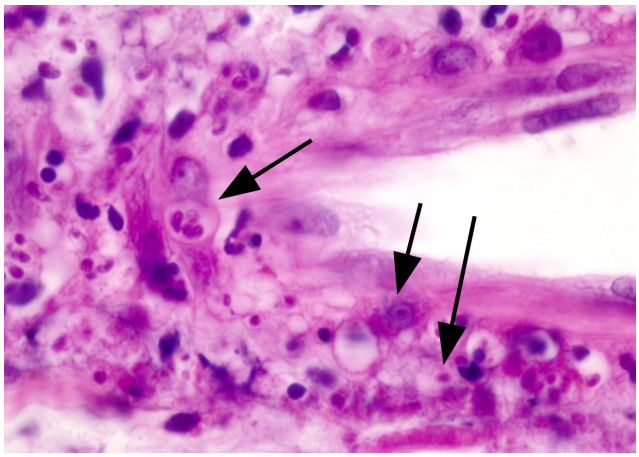

Figure 12.50
Primary vasculitis in brain of patient described in Figure 12.48. Vessel wall contains inflammatory cells and numerous tachyzoites (arrows). H&E x785

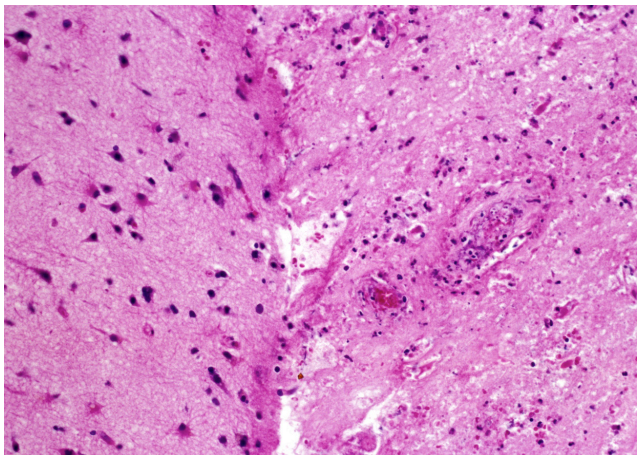

Figure 12.51
Interface of viable and necrotic tissue in biopsied brain of patient with toxoplasmosis. H&E x125

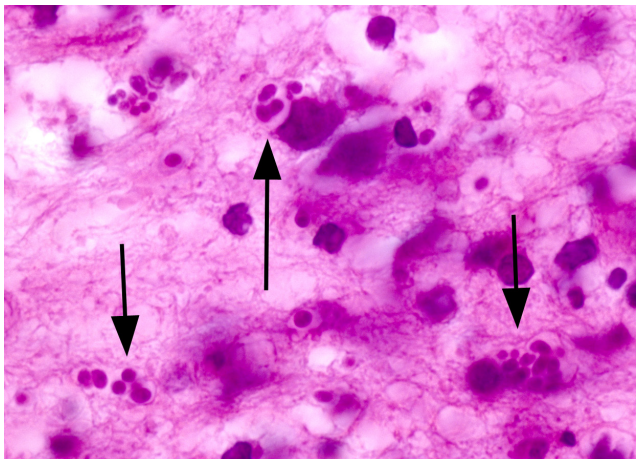

Figure 12.52
Clumps of *Toxoplasma* tachyzoites (arrrows) in biopsied brain. H&E x785

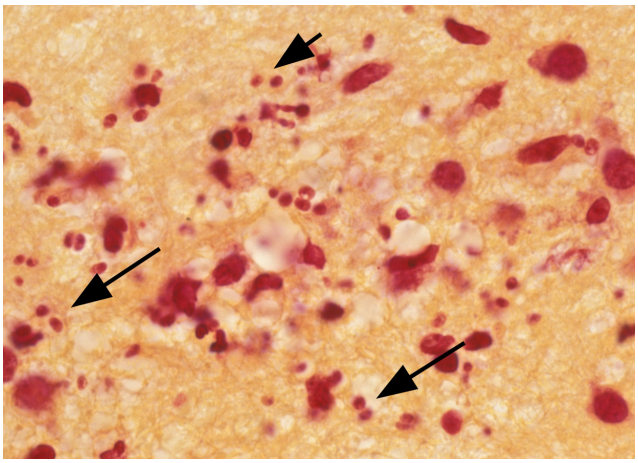

Figure 12.53
Many free *Toxoplasma* tachyzoites in biopsied brain. Each tachyzoite is round to oval with well-defined nucleus (arrows). B&H x770

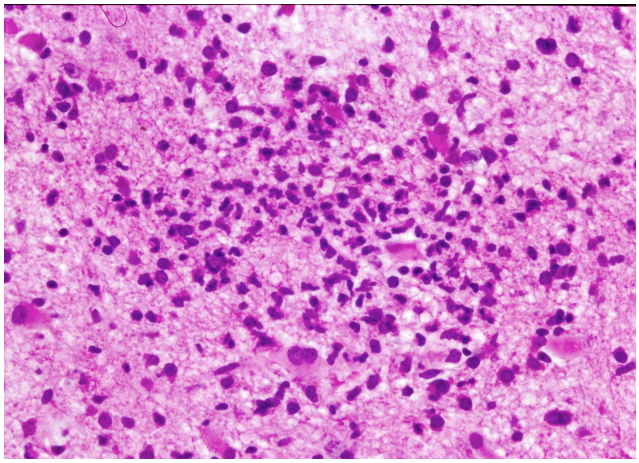

Figure 12.54
Focus of neutrophils in biopsied brain of patient with toxoplasmosis. H&E x765

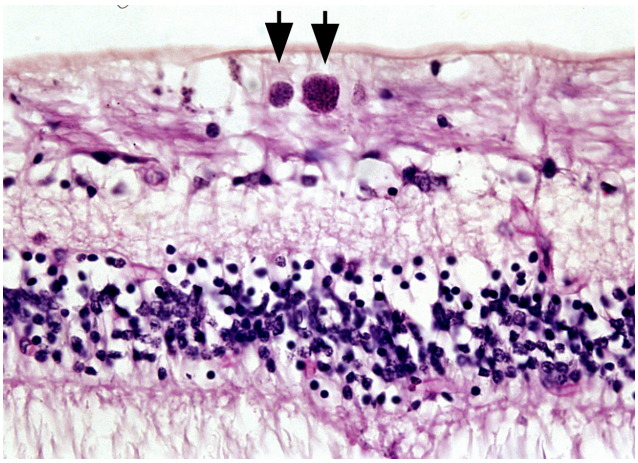

Figure 12.55
Two *Toxoplasma* cysts in nerve fiber layer of retina. PAS x260

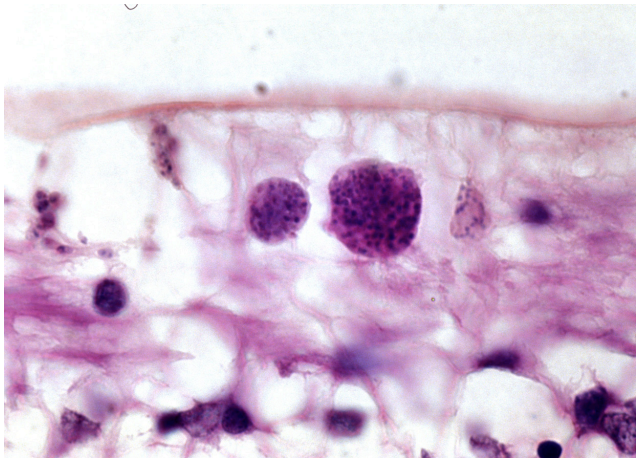

Figure 12.56
Higher magnification of *Toxoplasma* cysts in Figure 12.55. PAS x640

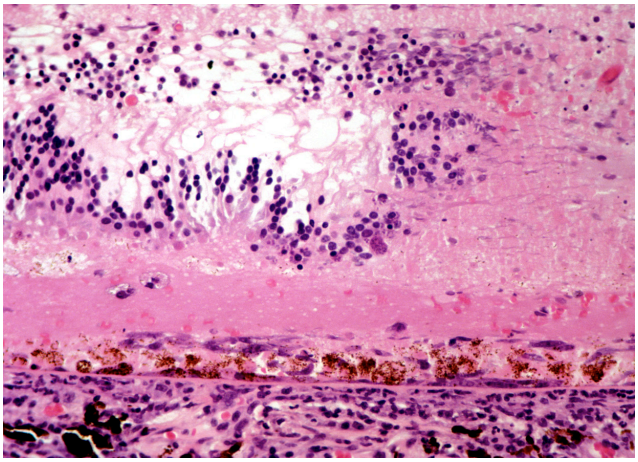

Figure 12.57
Acute retinal necrosis caused by toxoplasmosis. H&E x205

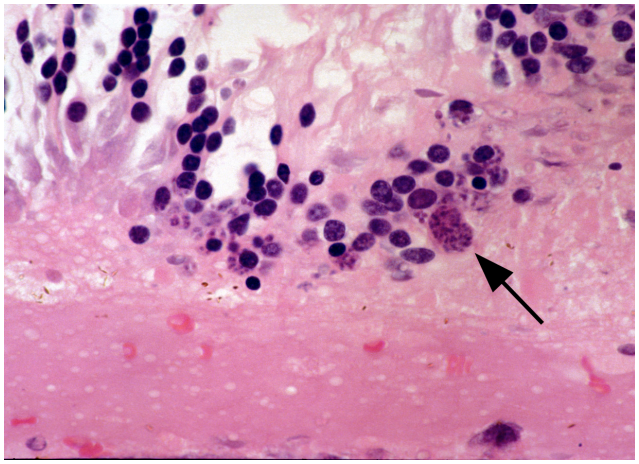

Figure 12.58
Higher magnification of retinal necrosis in Figure 12.57, depicting *Toxoplasma* cyst (arrow) and free tachyzoites. H&E x440

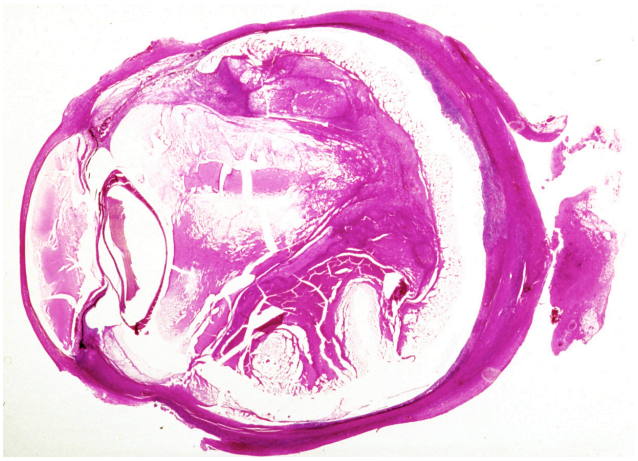

Figure 12.59
Enucleated eye from patient with AIDS-related toxoplasmosis, showing detached, necrotic retina and proteinaceous exudate between retina and choroid. H&E x2.8

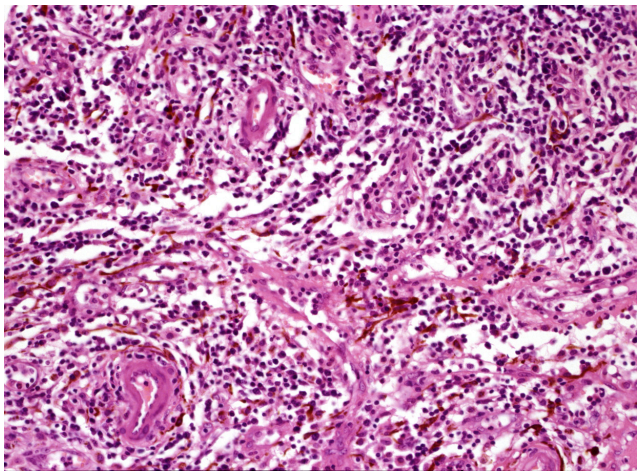

Figure 12.60
Chronic choroiditis in enucleated eye from patient described in Figure 12.59. H&E x130

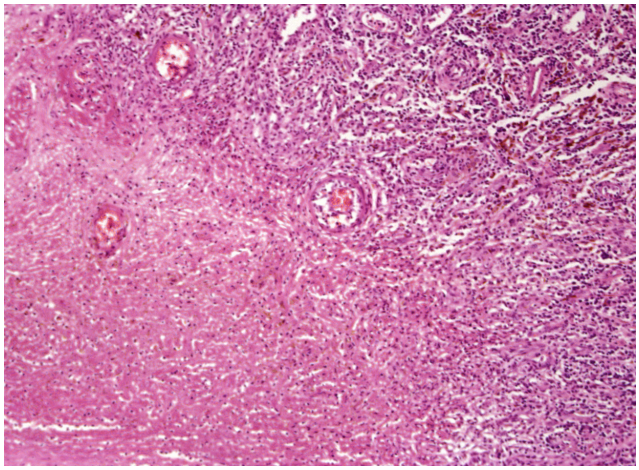

Figure 12.61
Interface of viable and necrotic choroid in enucleated eye from patient described in Figures 12.59 and 12.60. H&E x65

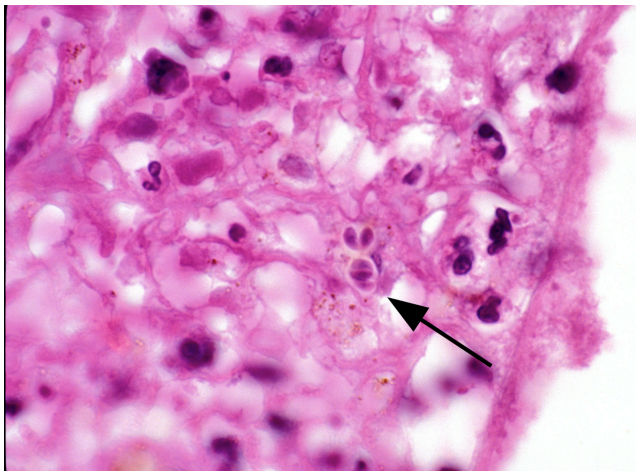

Figure 12.62
Several *Toxoplasma* tachyzoites in necrotic choroid (arrow) in enucleated eye from patient described in Figures 12.59 to 12.61. H&E x745

Tachyzoites may be numerous, especially at the periphery of necrotic foci (Figs 12.52 & 12.53), and cysts containing bradyzoites may also be seen (Fig 12.12). Free tachyzoites, disintegrating cysts, and infarction provoke an inflammatory response composed mainly of neutrophils (Fig 12.54). Intracellular tachyzoites and intact cysts do not provoke inflammation. Glial nodules, which are composed of pyknotic nuclei, necrosis, microglial cells, and other inflammatory cells, result from death of parasitized cells. Tachyzoites may be identified in or at the periphery of glial nodules.

Eye

Examination of enucleated eyes blinded by retinal destruction or glaucoma caused by toxoplasmosis may reveal cysts and/or tachyzoites in the retina (Figs 12.55 to 12.58). In some patients with sporadic retinochoroiditis caused by toxoplasmosis, cysts may persist in the retina for months or years.[51] The anti-inflammatory and immunosuppressive effects of corticosteroids may permit tachyzoites to multiply in the retina; however, liberated tachyzoites are usually inactivated by adequate immunity. Bradyzoites liberated from disintegrating cysts produce intense inflammation and scarring; when tachyzoites destroy parasitized cells, the retinal lesion is more diffuse and inflammation may extend to the vitreous and anterior chamber. The retina is largely necrotic, with pigment-bearing macrophages in its outer layers and in the vitreous. The retina may be detached, with proteinaceous exudate between it and the choroid (Fig 12.59). The choroid is heavily infiltrated with plasma cells, lymphocytes, and mononuclear cells, and may be necrotic (Figs 12.60 & 12.61). The retinal pigment epithelium shows focal proliferation and diffuse necrosis. Tachyzoites and cysts may be seen in all retinal layers and the choroid (Figs 12.62 & 12.63). Panophthalmitis, orbital cellulitis, and hemorrhage are rare (Figs 12.64 & 12.65).[52,53] In AIDS patients with toxoplasmosis, if the full thickness of the retina is involved, miliary toxoplasmic retinitis lesions may become confluent and the retina may detach (Figs 12.59, 12.66, & 12.67).

Lymph Node

Among AIDS patients with disseminated toxoplasmosis, lymph nodes are rarely involved. Immunocompromised patients who do develop toxoplasmic lymphadenitis show effacement of nodal architecture (Fig 12.68) and areas of massive necrosis that usually contain *T. gondii* cysts and tachyzoites (Fig 12.69).

Lung

In toxoplasmic pneumonia, the inflammatory reaction is mononuclear and intra-alveolar (Fig 12.70). Vasculitis may be prominent (Fig 12.71). Tachyzoites, groups, and cysts may be diffuse or in foci of coagulation necrosis (Figs 12.72 to 12.74).

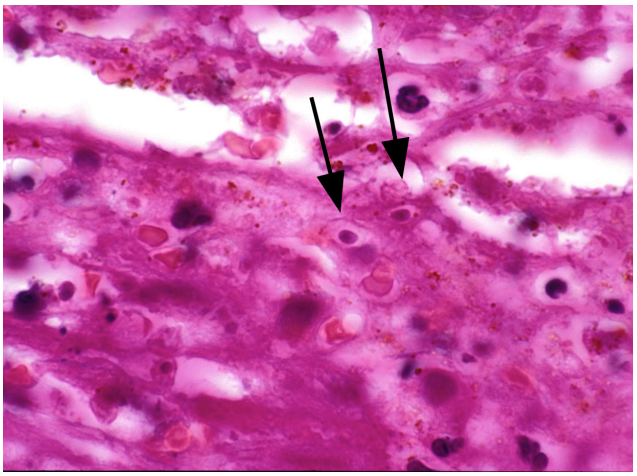

Figure 12.63
Two *Toxoplasma* tachyzoites in necrotic choroid (arrows) in enucleated eye from patient described in Figures 12.59 to 12.62. H&E x750

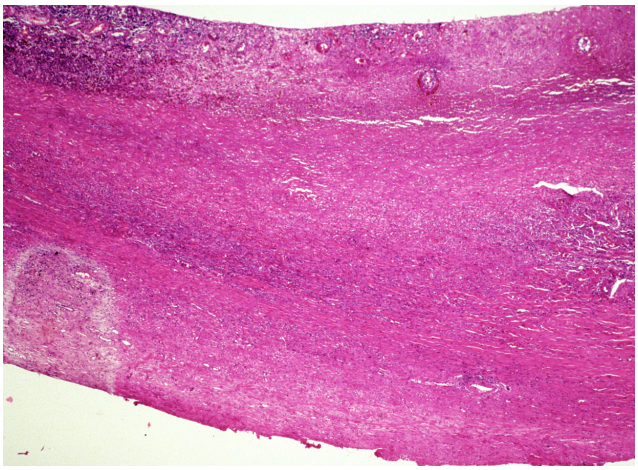

Figure 12.64
Panophthalmitis in enucleated eye from patient described in Figures 12.59 to 12.63. Note necrotic sclera. H&E x19

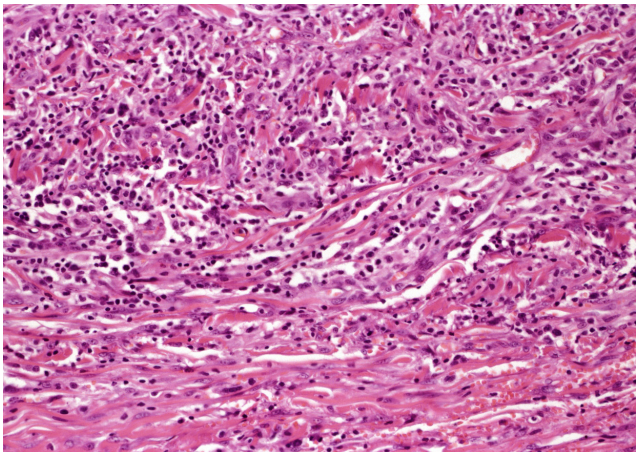

Figure 12.65
Panophthalmitis in enucleated eye from patient described in Figures 12.59 to 12.64. Note chronic scleritis. H&E x125

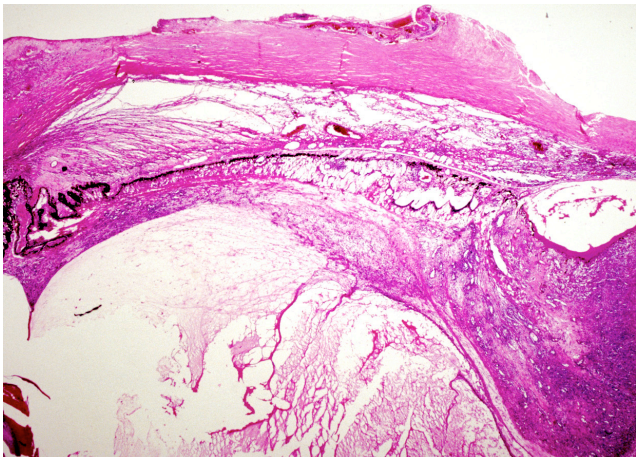

Figure 12.66
Panophthalmitis in enucleated eye from patient described in Figures 12.59 to 12.65. Both ciliary body and detached retina are necrotic. H&E x5

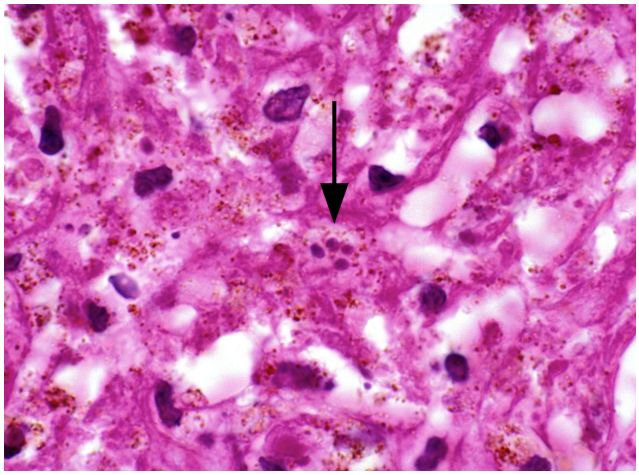

Figure 12.67
Four *Toxoplasma* tachyzoites (arrow) in necrotic ciliary body depicted in Figure 12.66. H&E x750

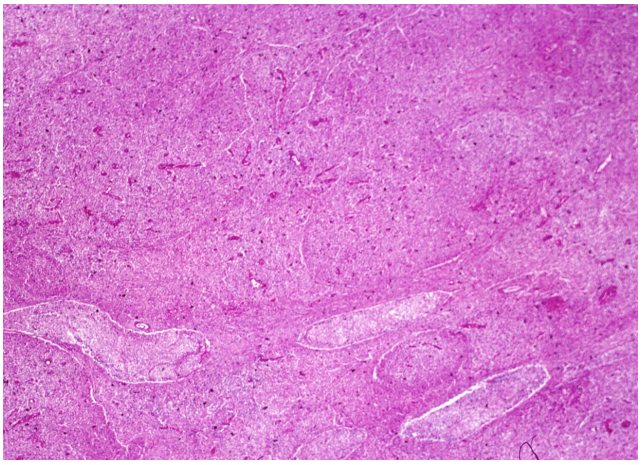

Figure 12.68
Massive necrosis in effaced lymph node from immunocompromised patient. H&E x25

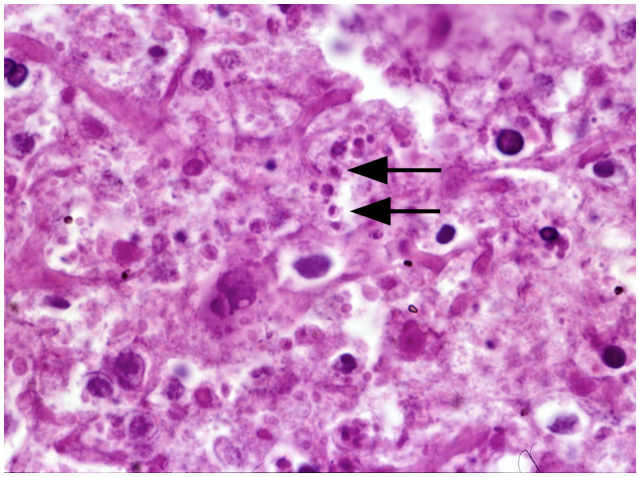

Figure 12.69
Several *Toxoplasma* tachyzoites (arrows) in necrotic lymph node shown in Figure 12.68. H&E x800

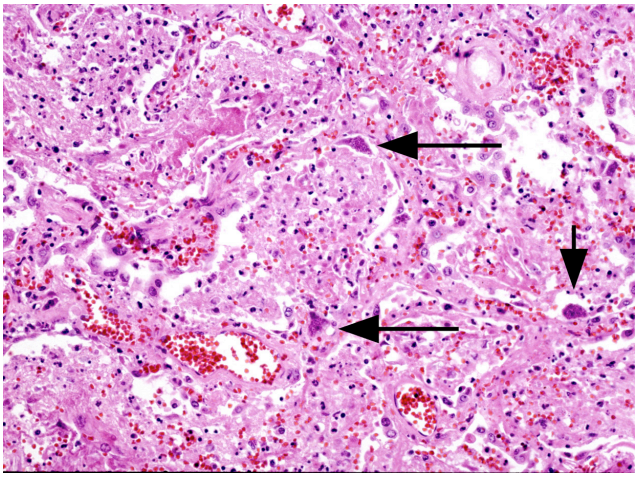

Figure 12.70
Toxoplasmic pneumonia with characteristic necrosis, intra-alveolar exudate and cysts (arrows). H&E x125

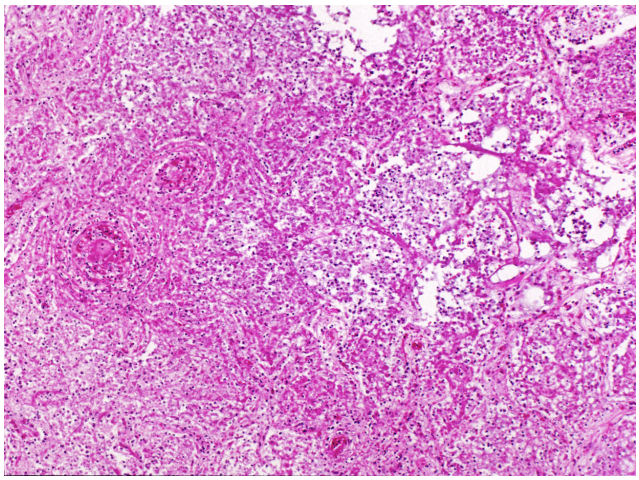

Figure 12.71
Toxoplasmic pneumonia with necrosis and prominent vasculitis. H&E x60

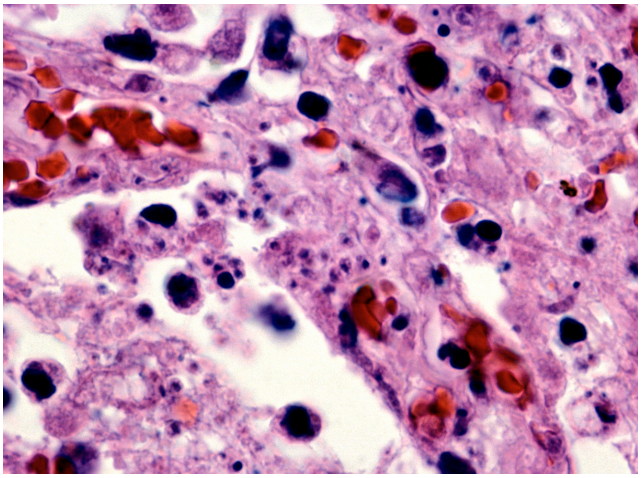

Figure 12.72
Intra- and extracellular *Toxoplasma* tachyzoites in necrotic lung. H&E x735

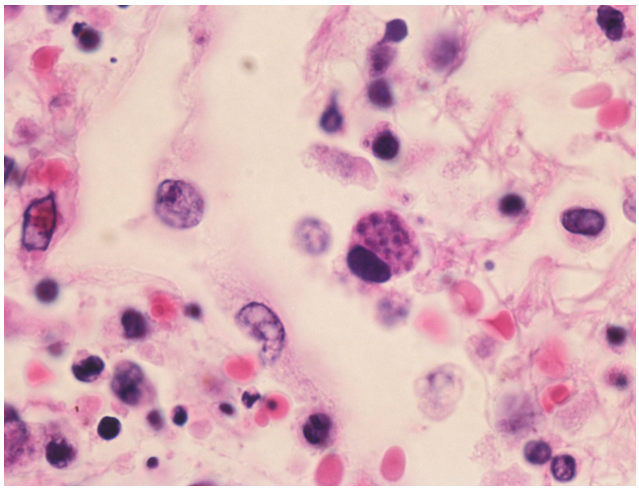

Figure 12.73
Group of *Toxoplasma* tachyzoites within histiocyte in lung. H&E x755

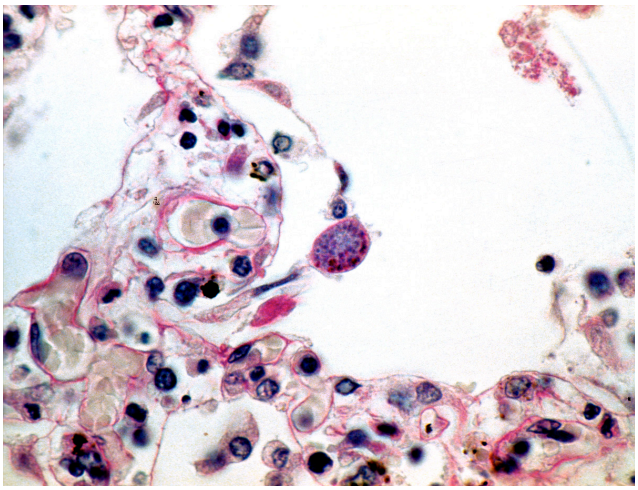

Figure 12.74
Toxoplasma cyst with bradyzoites in lung. Few organisms are PAS-positive. PAS x450

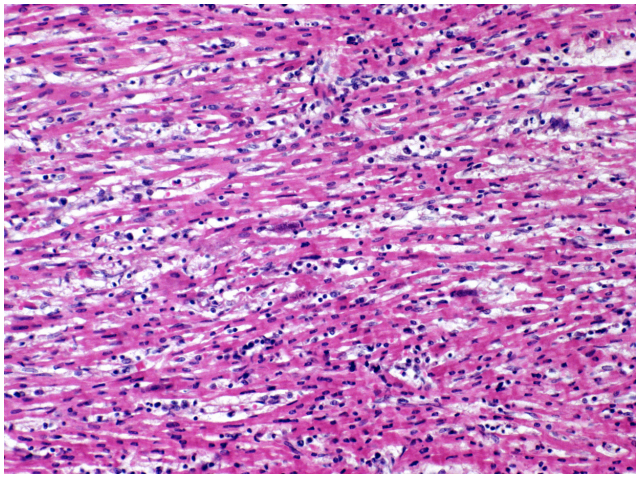

Figure 12.75
Toxoplasmic myocarditis characterized by mononuclear inflammatory infiltrate. H&E x130

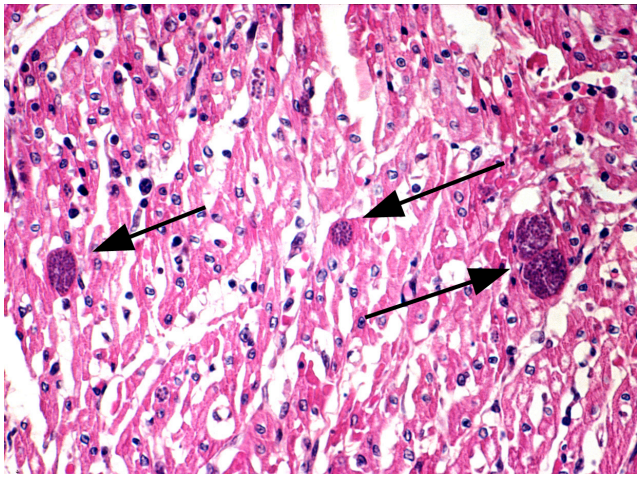

Figure 12.76
Toxoplasma organisms (arrows) parasitize individual heart muscle fibers. H&E x250

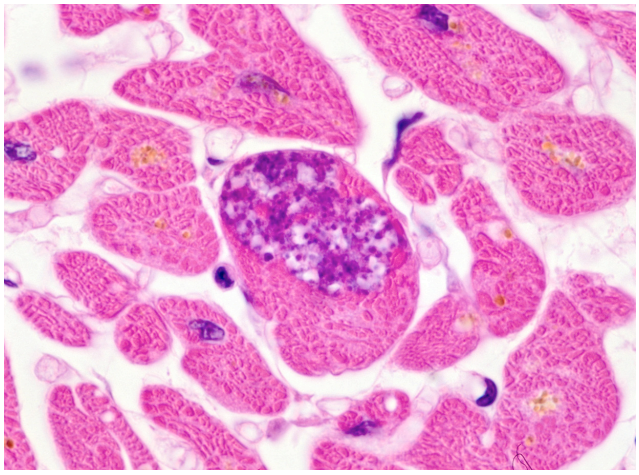

Figure 12.77
Toxoplasma organisms in heart muscle fiber. Note absence of inflammation. H&E x630

Heart

Toxoplasmic myocarditis is characterized by a mononuclear inflammatory infiltrate (Fig 12.75). *Toxoplasma* organisms may parasitize individual heart muscle fibers, provoking no inflammatory reaction (Figs 12.76 & 12.77).

Liver

Liver involvement in toxoplasmosis is rare and generally diagnosed on the basis of abnormal liver function tests and serology. *Toxoplasma* organisms are rarely identified in the liver (Fig 12.4).

Diagnosis

Toxoplasma organisms in lesions are best revealed with hematoxylin, immunoperoxidase, or in situ DNA hybridization. PCR tests are highly sensitive and specific for detecting toxoplasmic encephalitis,[54] and are particularly useful when patients have undergone chemotherapy and no organisms are visible in sections.[42] Real-time PCR detection methods for *Toxoplasma* DNA have been developed.[55,56] Used on blood samples, PCR may help to detect recent infections in patients midway through pregnancy.[57] Multicopy sequences specific for *T. gondii*, such as the B1 gene or the 529-bp sequence, are especially useful in molecular tests. Molecular methods are also employed for genotypic characterization of *T. gondii* isolates; analysis of polymorphic sequences determines the precise type.[58] If the patient is immunocompetent, antibody titers should be commensurate with levels usually found in such disease states.[59] Finding tachyzoites in lesions, along with a rising antibody titer, is diagnostic of acute infection. Conversely, finding both *Toxoplasma* cysts and tachyzoites in an enucleated eye may be associated with a low, stable antibody titer indicative of chronic infection.

The most useful serologic tests are the dye test, direct *Toxoplasma* agglutination test, and indirect fluorescent antibody test, each of which is highly sensitive.[60-62] However, interpretation of antibody tests is not dependable in immuno-compromised patients, so diagnosis should be based on identifying the etiologic agent, its antigens, or its DNA.

Toxoplasma can be isolated in cell cultures but is best isolated by inoculating suspected material into mice previously shown to be free of *Toxoplasma* antibody. After intraperitoneal inoculation, *Toxoplasma* tachyzoites may be found in the peritoneal exudate that develops after 4 to 6 days. If the mice show no clinical changes on primary inoculation, diagnosis must be based on finding antibody in the mice after 3 to 4 weeks, or finding *Toxoplasma* cysts in the brain after 1 or 2 months. *Toxoplasma* cysts must be differentiated from any *Encephalitozoon* pseudocysts that may be encountered. Because *Toxoplasma* organisms persist through asymptomatic chronic infection, isolation of organisms is not by itself indicative of disease from *Toxoplasma*, but must be correlated with antibody response,

symptoms, and lesions.

In histologic sections, a variety of microorganisms, including those that cause histoplasmosis, pneumocystosis, microsporidiosis, leishmaniasis, American trypanosomiasis, and sarcocystosis, and intracytoplasmic inclusions of cytomegalovirus (CMV) may be mistaken for *Toxoplasma* (Fig 12.78). Intracytoplasmic CMV inclusions stain well with H&E, are round, basophilic to amphophilic, and 1µm to 4µm in diameter; unlike *T. gondii*, however, they have no nucleus (Fig 12.79). *Histoplasma capsulatum* yeast cells are round to oval and frequently contain vacuoles (Fig 12.80), but they reproduce by budding (Fig 12.81), which distinguishes them from *T. gondii*. Microsporidian spores are readily observed with H&E stain (Fig 12.82), but special stains can reveal distinguishing characteristics of some spores, such as a PAS-positive polar granule at the anterior end (Fig 12.83) or a gram-positive band (Fig 12.84).

Amastigotes of *Leishmania* sp and *Trypanosoma cruzi* may be mistaken for *T. gondii* since they stain well with H&E and are about the same size. They can be distinguished from *T. gondii*, however, by the presence of a rod-shaped kinetoplast (Fig 12.85 to 12.89). Brown-Hopps modified Gram stain may help to identify the kinetoplast in tissue sections (Fig 12.86). The kinetoplast stains dark blue by the Giemsa method in smears, scrapings, and imprints (Fig 12.87). *Sarcocystis* sp, which also can mimic *T. gondii*, form sarcocysts that contain various stages of the parasite (Figs 12.90 &12.91), including mature, banana-shaped bradyzoites (Fig 12.92). Distinguishing characteristics of *Sarcocystis* sp include septations in the sarcocyst and bradyzoites that are larger than those of *T. gondii*. Occasionally, unidentified structures that mimic *T. gondii* are found in tissue sections (Figs 12.93–12.96), but careful examination shows none of the pertinent morphologic features. *Toxoplasma gondii* can be cultured and distinguished from other similar microorganisms by their characteristic ultrastructural features (Fig 12.97).

Treatment and Prevention

Drug therapy of toxoplasmosis is complex considering all the disease forms and status of the patient. Thus the clinician should consult appropriate specialized literature before starting treatment. Following are a few generalized suggestions.

The treatment of choice for toxoplasmosis is chemotherapy with a combination of oral pyrimethamine and sulfadiazine.[63] Pyrimethamine is administered with a loading dose of 75 to 200 mg/day for the first 3 days and 25 to 50 mg/day thereafter. For toxoplasmic encephalitis, the higher dose should be maintained. Sulfadiazine is given as 500 to 1000 mg every 6 hours. Folinic acid (leucovorin, 1 to 20 mg/day) counteracts any hematologic side effects of this drug regimen without significantly impairing therapeutic action.

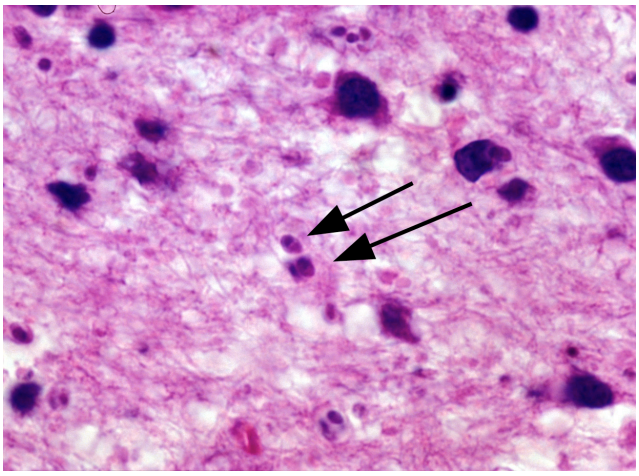

Figure 12.78
Typical *Toxoplasma gondii* tachyzoites (arrows), each with prominent nucleus, in biopsy of brain. H&E x780

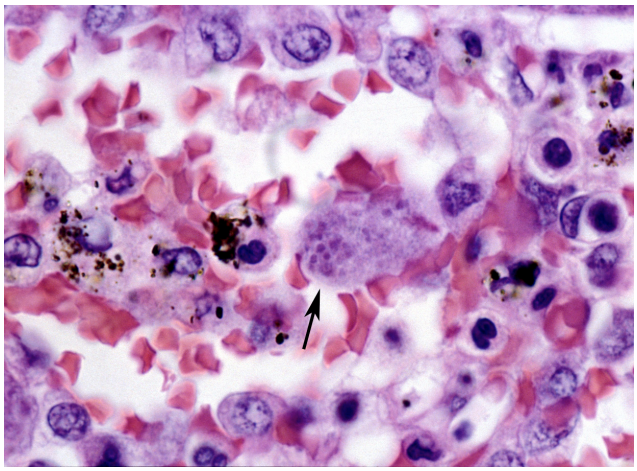

Figure 12.79
Intracytoplasmic inclusions of CMV (arrow) in lung are homogeneous and lack nuclei. H&E x710

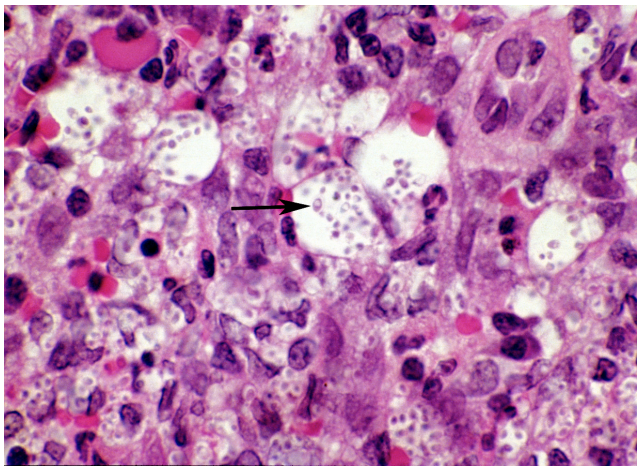

Figure 12.80
Histoplasma capsulatum yeast cells in cecal mass are round to oval and contain vacuoles (arrow). H&E x780

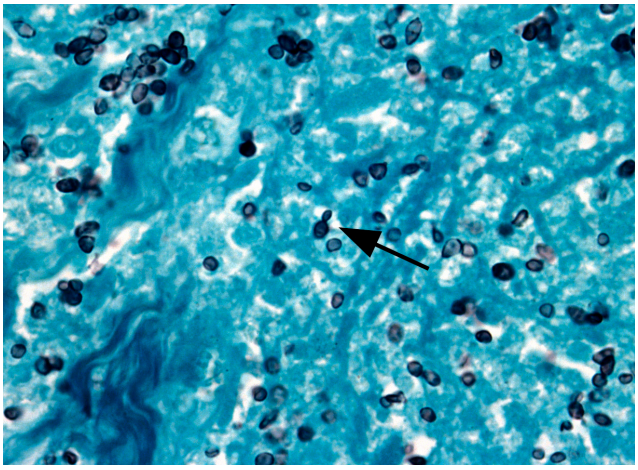

Figure 12.81
Histoplasma capsulatum yeast cells in necrotic lung, demonstrating narrow-neck budding (arrow) and silver positivity. GMS x590

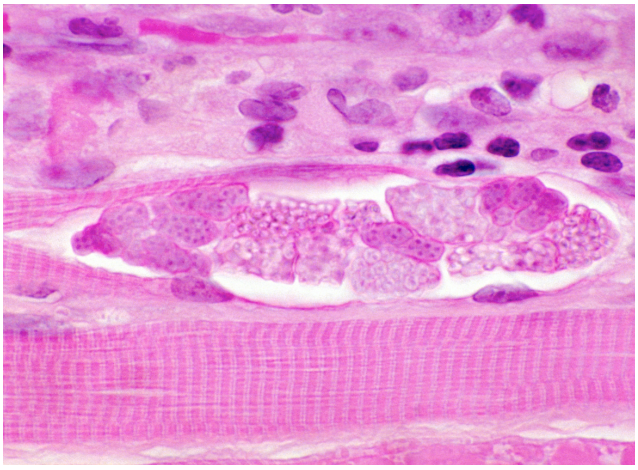

Figure 12.82
Microsporidian spores of *Pleistophora ronneafiei* in striated muscle are readily identified by H&E. H&E x800

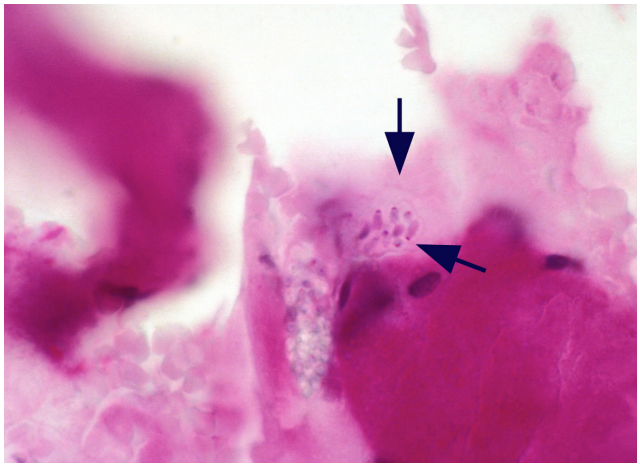

Figure 12.83
Microsporidian spores of *Pleistophora ronneafiei* in striated muscle, demonstrating PAS-positive polar granule (arrows) at anterior end of spore. PAS x800

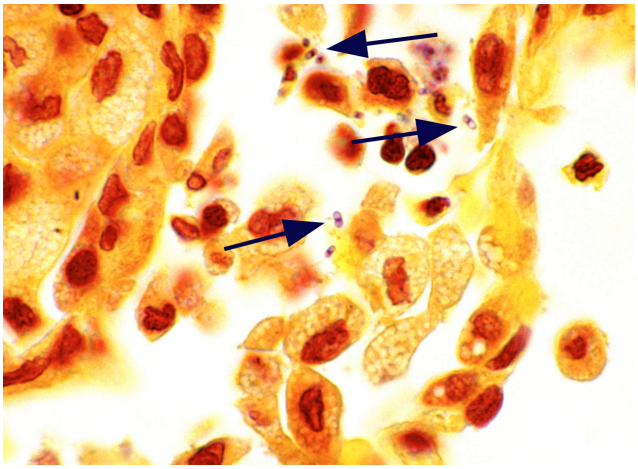

Figure 12.84
Microsporidian spores of *Encephalitozoon cuniculi* in lung of AIDS patient. Spores are extracellular and have band of gram-positive material (arrows). B&H x800

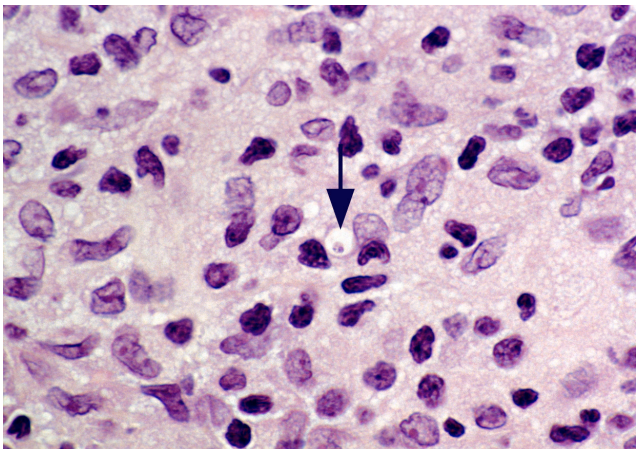

Figure 12.85
Single amastigote within vacuolated histiocyte in skin of patient with cutaneous leishmaniasis. Note tiny rod-shaped kinetoplast (arrow) to left of large spherical nucleus. H&E x590

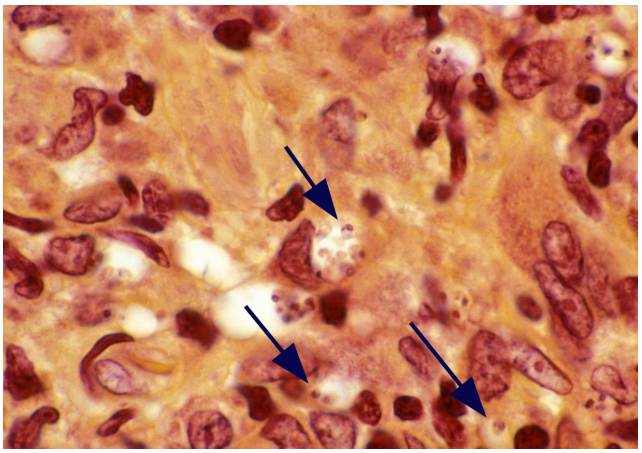

Figure 12.86
Several amastigotes of *Leishmania* sp in skin of patient with cutaneous leishmaniasis. Note yellow to pale cytoplasm, large red round nucleus, and tiny black rod-shaped kinetoplast (arrows). B&H x800

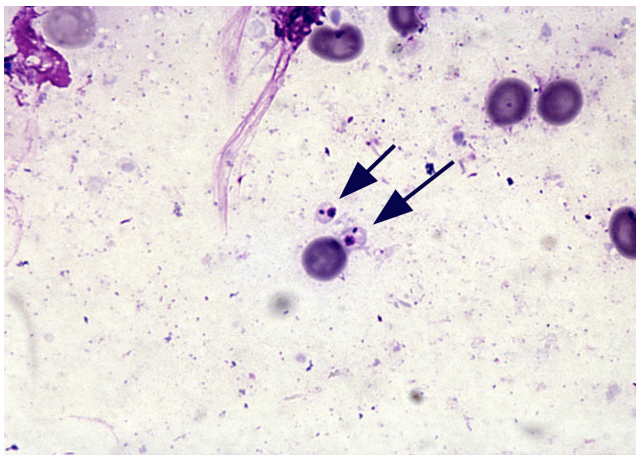

Figure 12.87
Smear of skin of patient with cutaneous leishmaniasis shows 2 *Leishmania* sp amastigotes (arrows). Note well-stained large round nucleus and deeply stained rod-shaped kinetoplast. Giemsa x830

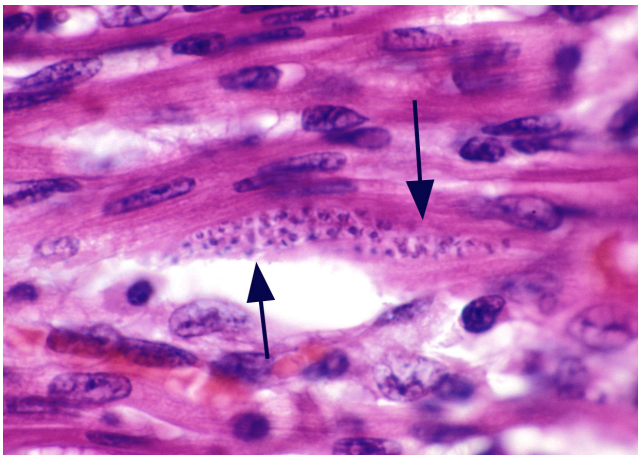

Figure 12.88
Cluster of *Trypanosoma cruzi* amastigotes in heart of patient who died of Chagas' disease. Note deeply stained rod-shaped kinetoplasts (arrows). H&E x930

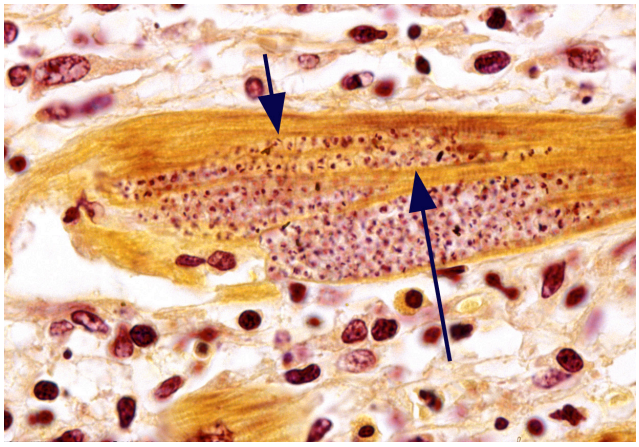

Figure 12.89
Cluster of *Trypanosoma cruzi* amastigotes in heart of patient who died of Chagas' disease. Note deeply stained rod-shaped kinetoplasts (arrows). B&H x670

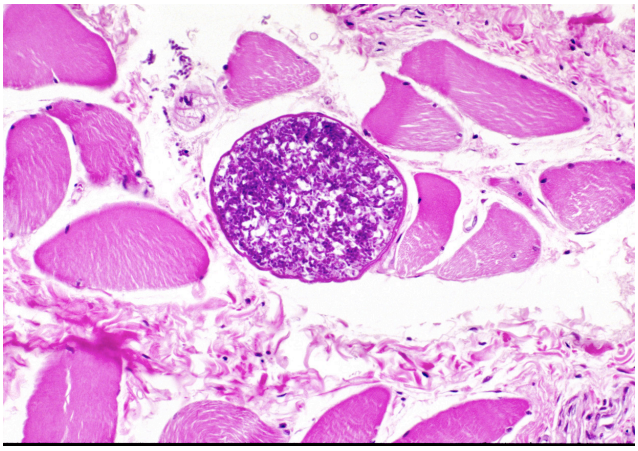

Figure 12.90
Mature *Sarcocystis* sp sarcocyst in African patient. Note well-stained bradyzoites and lack of inflammation. H&E x120

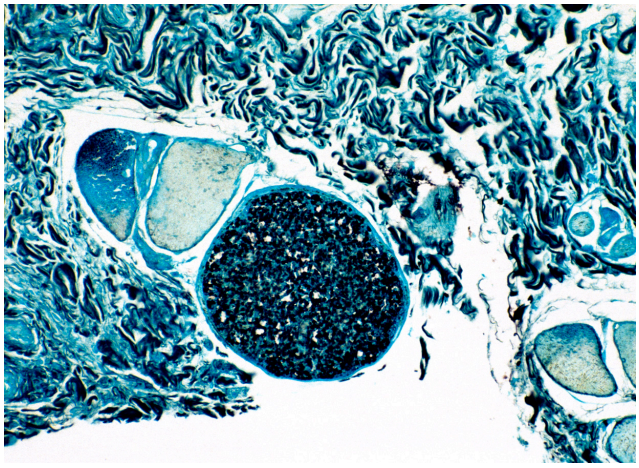

Figure 12.91
Same sarcocyst shown in Figure 12.90, demonstrating GMS-positive bradyzoites. GMS x120

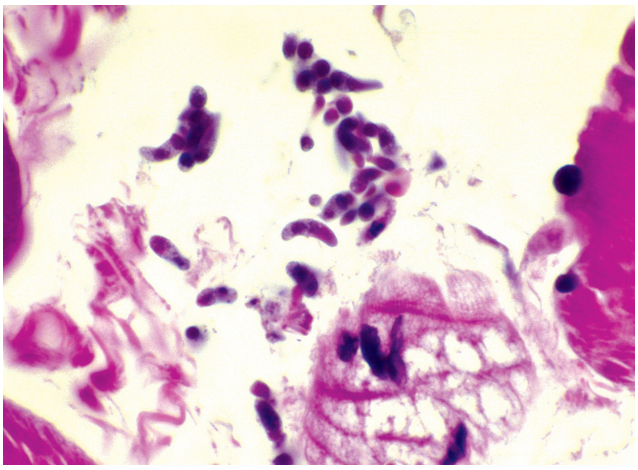

Figure 12.92
Extracellular bradyzoites from sarcocyst described in Figures 12.90 and 12.91. Bradyzoites are 9µm to 12µm by 2µm to 4µm and have rounded ends; each organism has prominent nucleus. H&E x650

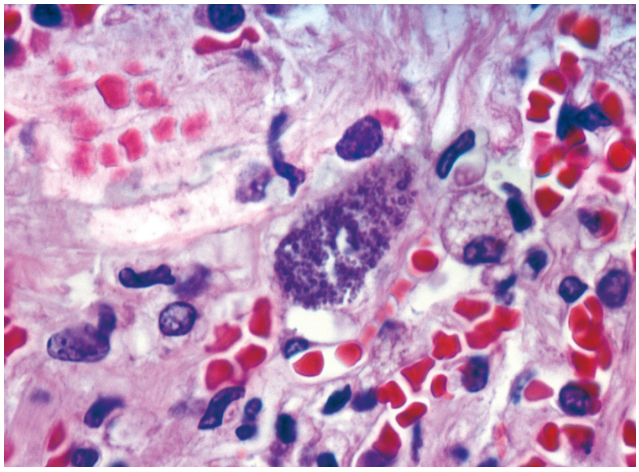

Figure 12.93
Calcification in lung mimicking *Toxoplasma gondii* cyst. H&E x830

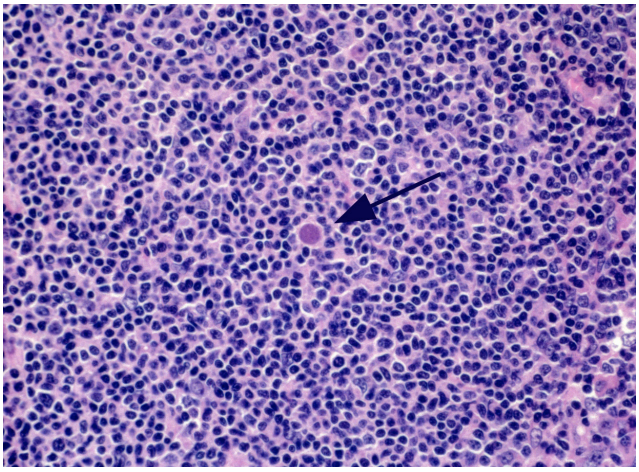

Figure 12.94
Unidentified artifact (arrow), initially identified as *Toxoplasma gondii*, in hypertrophic lymph node. H&E x100

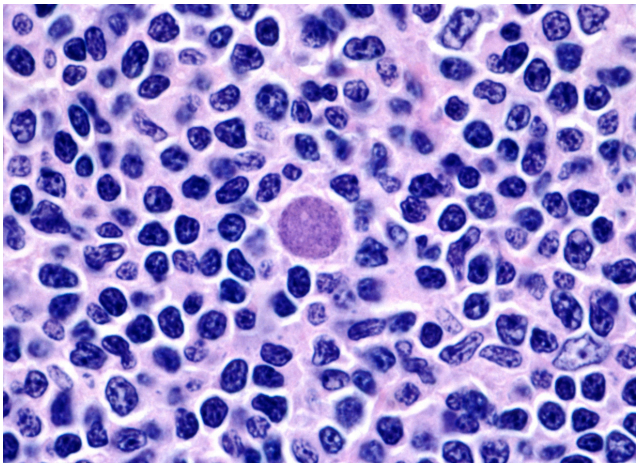

Figure 12.95
Higher magnification of structure shown in Figure 12.93. Unidentified artifact is 10 µm in diameter and contains neither bradyzoites nor tachyzoites. H&E x300

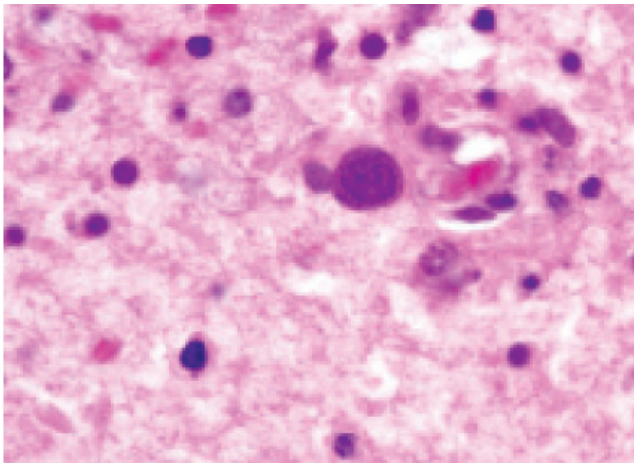

Figure 12.96
Unidentified cell in brain of patient with proven toxoplasmic encephalitis. The possibility of an atypical *Toxoplasma* cyst was entertained, but it lacked the pathognomonic features. The cell is 14 µm in diameter. H&E x535

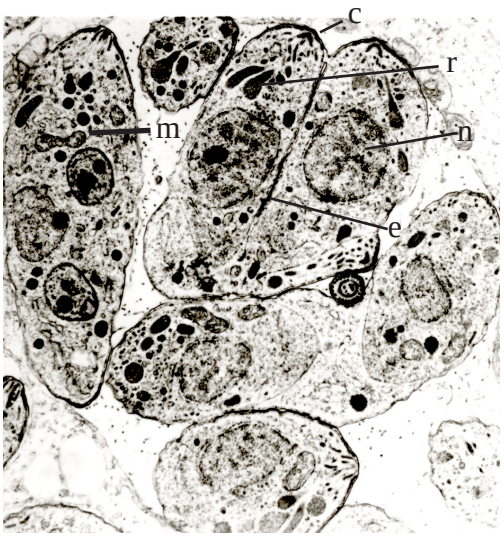

Figure 12.97
Toxoplasma tachyzoites in cultured cells showing conoid (c), nucleus (n), rhoptries (r), mitochondria (m), and division by endodyogeny (e). x9,430

Because the pyrimethamine-sulfadiazine combination is potentially teratogenic, pregnant patients should be given clindamycin (600 mg every 6 hours). Acute toxoplasmosis in pregnant women should receive speramycin 1 gram orally 3-4 times daily until term delivery. Other drugs with activity against *T. gondii* include, azithromycin, clarithromycin, atovaquone, minocycline, rifabutin, and dapsone. Post-transplant toxoplasmosis can be prevented by prophylaxis with trimethoprim-sulfamethoxazole.[64]

Toxoplasmosis can be prevented by observing a few simple precautions. Because infection is most severe in the perinatal period, pregnant women should avoid contact with outdoor cats that hunt rodents and birds, and soil and sand that may be contaminated with cat feces. Cover children's sandboxes when not in use and do not allow outdoor cats to defecate indoors. Litter boxes used exclusively by indoor cats that do not hunt are not likely to be contaminated. Cook all meat until it is well-done[65] and wash hands thoroughly after contact with any sources of infection.[13] There is no evidence of sexual transmission in humans.[66]

Ultimate control of toxoplasmosis demands an effective vaccine that stimulates both cellular and humoral mucosal immunity. Some vaccines that use attenuated parasites and DNA prime-booster techniques are in development, but have not yet been well-formulated or tested.[67-68] Proteomic research to identify new drug and vaccine targets and produce 2-dimensional gel electrophoresis maps of *T. gondii* tachyzoites is currently under way.[69]

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Figure 12.21
Courtesy of Centers for Disease Control and Prevention

Figure 12.22
Courtesy of JK Frenkel

Figure 2.23
Gardiner CH, Fayer R, Dubey JP. An Atlas of Protozoan Parasites in Animal Tissues. 2nd edition, Armed Forces Institute of Pathology, American Registry of Pathology, Washington, DC

Figure 12.24
Courtesy of Marvin Miller

Figure 12.97
Courtesy of Henry Azar