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276 *Trypanosoma* Species (American Trypanosomiasis, Chagas Disease): Biology of Trypanosomes

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SHORT VIEW SUMMARY

Definition
- Chagas disease, or American trypanosomiasis, is an infection caused by the single-cell protozoan parasite *Trypanosoma cruzi*.

Microbiology
- *T. cruzi* is spread among its various mammalian hosts, including domestic and wild animals as well as humans, by blood-sucking triatomine insects, also called cone-nosed or kissing bugs.
- The parasites multiply in the gut of these insects, and their feces contain forms that can infect mammals. When contaminated feces touch vulnerable mammalian tissues such as the conjunctivae, oral and nasal mucosal surfaces, or skin abrasions, transmission can take place.
- Once the parasites gain a foothold in a mammalian host, they alternate between multiplying intracellular forms and free-swimming forms in the bloodstream that spread the infection internally or get swept up by feeding vectors, thus completing the cycle.
- *T. cruzi* can also be transmitted from mother to fetus, by ingestion of contaminated food and drink, through blood products and organs obtained from infected donors, and in laboratory accidents.
- Infection with *T. cruzi* in humans is lifelong.

Epidemiology
- Chagas disease is endemic in Mexico, as well as all of Central and South America.
- The infection is not endemic in any of the Caribbean islands.
- About 8 million persons are chronically infected with *T. cruzi*, roughly 56,000 new infections occur each year, and about 12,000 persons die of the illness annually. An estimated 238,000 immigrants with Chagas disease currently live in the United States.
- During recent decades, large numbers of people in the endemic countries have been migrating from rural areas to cities, and at the same time many millions of people have emigrated from endemic countries to industrialized regions, particularly the United States and the European Union, thus urbanizing and globalizing the disease.

Clinical Manifestations
- Between 10% and 30% of persons who are chronically infected with *T. cruzi* ultimately develop cardiac or gastrointestinal symptoms caused by pathologic processes related to the persistent presence of the parasite.
- Chronic cardiac Chagas disease typically involves rhythm disturbances and cardiomyopathy.
- Gastrointestinal problems can include megaesophagus and megacolon.
- Immunosuppression of persons who harbor *T. cruzi* chronically can result in life-threatening reactivation of the infection.

Diagnosis
- The diagnosis of acute or congenital Chagas disease is made by parasitologic methods, typically direct microscopic examination of blood or polymerase chain reaction–based assays.
- Chronic *T. cruzi* infection is diagnosed serologically, and many accurate enzyme-linked immunosorbent assays, immunofluorescence assays, and chemiluminescent tests are available commercially for this purpose.

Therapy
- Benznidazole and nifurtimox (Lampit; Bayer, Berlin, Germany) are the only two drugs available for treating *T. cruzi* infections. Benznidazole is approved by the US Food and Drug Administration for treatment of children 2 to 12 years of age and can be obtained from Exeltis (Florham Park, NJ; 877-303-7181, fastaccess@exeltis.com). Nifurtimox is available from the CDC Drug Service (404-639-3670, drugservice@cdc.gov).
- Parasitologic cure rates for these drugs are high for acute and congenital infections but unfortunately very low in persons with long-standing infections.
- There are no convincing data from randomized controlled trials indicating that treatment of chronically infected adults with either drug significantly delays pathogenesis or affects long-term outcomes.

Prevention
- No vaccine or prophylactic drugs are available for reducing transmission of *T. cruzi*.
- In endemic countries, reducing vector-borne transmission depends primarily on educating at-risk populations, housing improvement, and spraying insecticides to eliminate vectors in dwellings.
- Serologic screening of blood and organ donors is also a key element in the control of Chagas disease.
- In the majority of endemic countries, enormous progress has been made in reducing transmission through vector control and blood screening, and effective programs for the latter have been implemented in the United States, Canada, and several countries in the European Union.

The protozoan genus *Trypanosoma* consists of several dozen species.[1,2] Two of the three species that infect humans are pathogenic, and several other species cause severe and economically important diseases in domestic mammals. Broadly defined, the organisms belonging to this genus are protozoan flagellates of the family Trypanosomatidae, order Kinetoplastida, that pass through different morphologic stages (epimastigote, amastigote, and trypomastigote) in their vertebrate and invertebrate hosts. The criterion of three morphologic stages, however, is not fulfilled by each species in the genus. For example, only *Trypanosoma cruzi*, the etiologic agent of American trypanosomiasis, or Chagas disease, and one other species multiply in mammalian hosts as intracellular amastigotes similar to those seen in infections caused by organisms belonging to the genus *Leishmania*. In contrast, African trypanosomes, which cause sleeping sickness in humans and varying degrees of morbidity in wild and domestic mammals, do not have an intracellular form and multiply as trypomastigotes that circulate in the mammalian bloodstream and other extracellular spaces.

The trypomastigote form has a single flagellum originating near the kinetoplast, which is a DNA-containing structure located in the parasite's single, complex mitochondrion. The flagellum runs alongside the body of the parasite and is enveloped in an undulating membrane. It extends beyond the body as a free, threadlike structure. The undulating membrane and the free portion of the flagellum give the organism considerable motility.

According to their course of development in the vector, trypanosomes have been classified into two major groups:

1. *Stercoraria:* Multiplication in the mammalian host is discontinuous, taking place in the amastigote stage. Development in the vector (triatomines, or kissing bugs) is completed in the hindgut (posterior station), and mammalian hosts become infected by contaminative transmission. The subgenus *Schizotrypanum* belongs to this group and includes *T. cruzi.*
2. *Salivaria:* Multiplication in the mammalian host is continuous, taking place in the trypomastigote stage. Development in the vector (*Glossina,* or tsetse fly) is completed in the salivary glands (anterior station), and inoculative transmission to mammalian hosts occurs. The subgenus *Trypanozoon* belongs to this group and includes, among others, the subspecies *Trypanosoma brucei brucei,* which causes disease in animals but does not infect humans. *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense,* the two causative agents of African sleeping sickness, or human African trypanosomiasis, are also found in this subgenus. As a group, these three subspecies are often referred to as the *T. brucei* complex. Endemic areas of Chagas disease and African sleeping sickness do not overlap (Fig. 276.1). Moreover, there are such important differences in the transmission, pathogenesis, and clinical course of the two diseases that they have little in common except the genetic and morphologic similarities of the causative agents.

CHAGAS DISEASE

Life Cycle and Transmission

T. cruzi, the causative agent of American trypanosomiasis, is transmitted by various species of blood-sucking triatomine insects, or kissing bugs (Fig. 276.2).[3,4]

These vectors are found in large numbers in the wild, where they transmit the parasite among many mammalian species that constitute the natural reservoir; in endemic areas, they live in the nooks and crannies of substandard dwellings. The insects become infected by sucking blood from humans or other mammals that have circulating trypomastigotes (Fig. 276.3). The ingested parasites multiply in the midgut of the insects as epimastigotes, which are flagellates of a distinct morphologic type, and in the hindgut transform into infective metacyclic trypomastigotes that are discharged with the feces at the time of subsequent blood meals. Transmission to another vertebrate host occurs when mucous membranes, conjunctivae, or breaks in the skin are contaminated with bug feces containing the infective forms. The parasites then enter a variety of host cell types and multiply in the cytoplasm after transformation into amastigotes. When multiplying amastigotes fill the host cell, they differentiate into trypomastigotes and the cell ruptures. The parasites released invade local tissues or spread hematogenously to distant sites, thus initiating further cycles of multiplication, largely in muscle cells, and maintaining a parasitemia infective for vectors.

Transmission of *T. cruzi* also occurs through blood transfusions,[5,6] and historically this typically took place in cities when infected but asymptomatic migrants from endemic rural areas donated blood. Serologic screening of donated blood essentially has eliminated transmission by this route in most endemic countries. *T. cruzi* can also be transmitted by transplantation of organs obtained from chronically infected persons.[7,8,9] Roughly 5% to 10% of infants born to *T. cruzi*–infected women have congenital Chagas disease. Although some of these infants have severe problems as a result of the infection, most are completely asymptomatic.[10,11,12,13,14] Numerous laboratory accidents resulting in acute Chagas disease have occurred as a consequence of the ease with which highly infective parasite forms can be produced in the laboratory, but no reports of such events have appeared in recent years.[15,16] Transmission of *T. cruzi* by ingestion of food and drink contaminated by infected vectors has also been reported.[17,18]

FIG. 276.2 ***Rhodnius prolixus,*** **a common vector of** ***Trypanosoma cruzi.*** First- and second-stage nymphs, eggs, and adult.

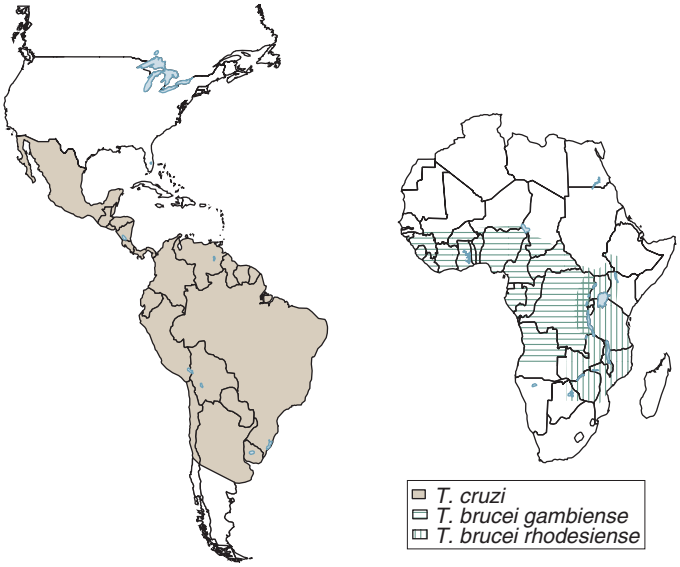

FIG. 276.1 **Distribution of human trypanosomiasis.**

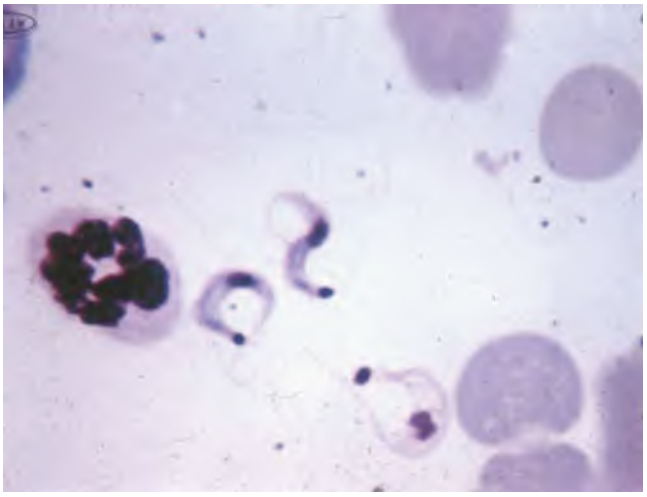

FIG. 276.3 ***Trypanosoma cruzi*** **trypomastigotes in a smear of mouse blood. (Giemsa stain; magnification ×625).** *(Courtesy Dr. Herbert B. Tanowitz, New York, NY.)*

Pathology

In acute Chagas disease, the inflammatory lesion caused by *T. cruzi* at the site of entry is called a *chagoma.*[19] Local histologic changes include intracellular parasitism of muscle and other subcutaneous tissues, interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. Trypomastigotes released when infected host cells rupture can often be detected by microscopic examination of fresh blood. Muscles, including the myocardium, are the most heavily parasitized tissues. Myocarditis may develop in association with patchy areas of infected cells and necrosis.[20–22]

The characteristic "pseudocysts" seen in sections of infected tissues are aggregates of intracellular amastigotes (Fig. 276.4). Lymphocytosis accompanies the high parasitemias of the acute illness, and mild elevation of transaminase levels is occasionally seen. In some patients, parasites can be found in the cerebrospinal fluid.[23,24]

The heart is the organ most commonly affected in chronic Chagas disease. Gross examination of the hearts of chronic chagasic patients who died of heart failure reveals marked bilateral ventricular enlargement, often involving the right side of the heart more than the left. Thinning of the ventricular walls is common, as are apical aneurysms and mural thrombi. Widespread lymphocytic infiltration is present, accompanied by diffuse interstitial fibrosis and atrophy of myocardial cells. Parasites are rarely seen in stained sections of myocardial tissue, but studies using polymerase chain reaction (PCR) assays have demonstrated the presence of parasites in areas of focal inflammation.[25–27]

Pathologic changes are also common in the conduction system of chronic chagasic hearts. Dense fibrosis and chronic inflammatory lesions most frequently involve the right branch and the left anterior branch of the bundle of His, but lesions of this type are found in other parts of the conduction system as well.[28]

The striking features apparent on gross examination of the esophagus or colon of a patient with chronic Chagas disease of the digestive tract (megadisease) are the enormous dilatation and muscular hypertrophy of the affected organs.[29,30] On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen. A marked reduction in the number of neurons in the myenteric plexus is also apparent, and periganglionic and intraganglionic fibrosis in the presence of Schwann cell proliferation and lymphocytosis is found. In most patients the clinical effects of this parasympathetic denervation are confined to the esophagus or the colon, or both, but similar lesions have been observed in the biliary tree, the ureters, and other hollow viscera.

The pathogenesis of the cardiac and gastrointestinal lesions of chronic Chagas disease was debated for many years. Starting in the early 1990s, however, convincing evidence has accumulated indicating that the persistence of parasites in heart muscle stimulates a chronic inflammatory process that often results in rhythm disturbances and cardiomyopathy.[31,32]

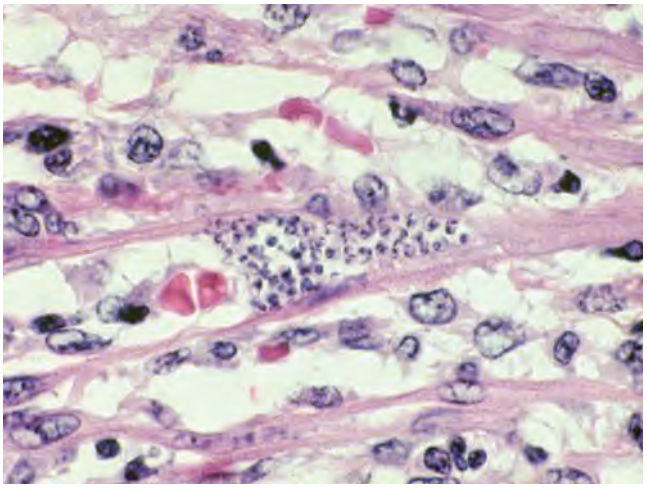

FIG. 276.4 ***Trypanosoma cruzi*** **in the cardiac muscle of a child who died of acute Chagas disease in Texas (see reference 20). (Hematoxylin & eosin stain; magnification ×900).**

Epidemiology

T. cruzi infection is a zoonosis, and humans are merely unfortunate hosts whose involvement in the cycle of transmission is not necessary for the perpetuation of the parasite in nature. The triatomine vectors necessary for natural transmission of *T. cruzi* are found in the Americas from the southern half of the United States to southern Argentina.[3] Infected insects have been found in uneven distributions throughout this range. Burrows, hollow trees, palm trees, and other animal shelters are sites where transmission of *T. cruzi* occurs among infected insects and nonhuman mammalian hosts. The ingestion of infected insects likely plays a major role in *T. cruzi* transmission among the latter, and experimental data relating to oral transmission support this concept.[33–35] Interestingly, outbreaks of acute Chagas disease in humans have been reported in several endemic countries and attributed to oral transmission through ingestion of food or drink contaminated with *T. cruzi*–infected vectors or their excreta.[18,36,37] In these incidents, the first of which was reported in Brazil in 1968, many dozens of people became infected and some even died of acute Chagas disease. The occurrence of these outbreaks also underscores the ease with which *T. cruzi* can be transmitted orally[16] and the need to keep vectors out of areas where food and drink are prepared and consumed. The marked reduction of vector-borne and transfusion transmission of *T. cruzi* in much of the endemic range has made oral and particularly congenital transmission proportionally more important.

T. cruzi has been isolated from more than 150 species of wild and domestic mammals. The ability of the parasite to adapt to such a wide variety of hosts, coupled with the long-term parasitemias in infected mammals, results in the presence of an enormous sylvatic and domestic reservoir in enzootic areas. Infected mammals are widely distributed in the southern United States[38–40] and from there southward to central Argentina and Chile.[34,41,42]

Typically, humans become involved in the cycle of transmission while living in rural enzootic areas where vector species adaptable to living in human dwellings, such as *Rhodnius prolixus* and *Triatoma infestans,* are prevalent. The insects live in niches in the settlers' primitive wood, mud, and stone houses, and emerge at night to take blood meals from both domestic animals and humans.[43–45] Thus human *T. cruzi* infection in endemic countries historically has been primarily a public health problem among poor persons who live in rural areas. This pattern has changed dramatically during the past few decades, however, as many millions of at-risk persons have migrated to cities in endemic regions as well as to countries outside the endemic range, thus urbanizing and globalizing the problem of Chagas disease.[46–51] Most new vector-borne infections occur in children younger than 10 years old. In one early study of selected patients the case-fatality rate for untreated acute Chagas disease was 12%,[52] but such a high rate likely reflects the fact that only seriously ill patients came to medical attention. The rate for all new infections is probably less than 1%.

The Pan American Health Organization currently estimates that 8 million people are infected with *T. cruzi,* 56,000 new cases occur each year, and annually 12,000 persons die of Chagas disease.[53–55] The endemic range of Chagas disease includes Mexico as well as all countries in Central and South America. Chagas disease is not endemic in any of the Caribbean nations. A recent estimate has put the global annual cost of Chagas disease at $7.19 billion US dollars.[56] Despite this bleak picture, the current situation relating to the transmission of *T. cruzi* is much brighter. A major international control program in the Southern Cone nations of South America (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay), initiated in 1991, has achieved a marked reduction in transmission rates through education of at-risk populations, vector control, and serologic screening of donated blood. Gradual reduction in prevalence rates in younger age groups and progressive reduction in the percentage of blood donors infected with *T. cruzi* stand as clear evidence of the success of the program.[57–59,60,61] Uruguay was certified as free of vector-borne transmission in 1997, and Chile followed in 1999. Brazil was declared transmission-free in 2006 and Paraguay in 2018, and it is likely that Argentina will be added to the list within a few years. Similar control programs in the Andean nations and in Central America have achieved considerable success. Historically, relatively less attention has been paid to Chagas disease by public health authorities

in Mexico, where the overall prevalence is likely to be 0.5% to 1.0%. Vector control programs have made progress in limited areas, but despite the 2012 federal mandate that all donations be tested for Chagas disease, a substantial proportion of donated blood is still not screened,[62] and testing for congenital transmission of *T. cruzi* is rarely done.[63,64] Taking a broad view of the problem of Chagas disease, it is fair to say that the barriers hindering the elimination of *T. cruzi* transmission to humans throughout the endemic range and elsewhere are economic and political, and no technical breakthroughs are necessary for its completion.

Only 10% to 30% of persons with chronic *T. cruzi* infections develop symptomatic Chagas disease.[65] The age distribution of the onset of the two types of chronic disease is broad. The relatively high frequency of sudden death in young adults observed in some regions in the past was attributed to the disturbances of cardiac rhythm associated with Chagas disease; decades ago in one highly endemic area in Brazil, chagasic cardiac disease was found to be the leading cause of death in young adults.[66] There is considerable geographic variation in the prevalence of symptomatic chronic Chagas disease among infected persons. The prevalence of cardiac disease among persons who harbor the parasite chronically is lower in Venezuela, Colombia, Central America, and Mexico than in the rest of the endemic range. Moreover, megaesophagus and megacolon associated with *T. cruzi* infection are virtually unknown in the northern endemic range, whereas their prevalence reaches 15% to 20% in the southern endemic regions. It is not known what roles are played by host genetic factors or parasite strain differences in the geographic variation in the patterns of disease.[67,68]

Despite the presence of *T. cruzi*–infected triatomine vectors in many parts of the southern and western United States, only seven autochthonous cases of acute Chagas disease have been reported: four in Texas and one each in California, Tennessee, and Louisiana.[20,69–71] Moreover, screening of US blood donors for Chagas disease, which began in January 2007 and during the first 3 years involved the testing of more than 30 million units, turned up only 17 donors who appeared to have acquired *T. cruzi* infection from vectors in the United States.[72] These data suggest that autochthonous transmission here might be slightly more common than previously thought. It is important to recognize, however, that these 17 donors, who appear to have autochthonously acquired chronic *T. cruzi* infection, came to light through what basically is a cross-sectional prevalence study that looked back over their entire lives. In view of this, then, their identification presents an extremely limited perspective on the overall incidence of vector-borne transmission and certainly says absolutely nothing regarding the secular trend of such transmission.

In a recent review focused solely on studies of Chagas disease in Texas, the authors tabulated the results of earlier heterogeneous prevalence studies published over several decades.[72a] The aggregated data suggest that autochthonous transmission may be a bit more common than previously thought. Nonetheless, in my view the potential pitfalls inherent in aggregating data from such methodologically heterogeneous and chronologically isolated studies cast a long shadow over the authors' conclusion in this regard. In any event, as in the case of the 17 chronically infected donors, no inferences can be drawn from the aggregated data in terms of a secular trend of the incidence of vector-borne *T. cruzi* in Texas. Taking a broad perspective, then, it is clear that vector-borne transmission of *T. cruzi* is a rare event in the enzootic regions of the United States, and there is no clear evidence that the incidence is increasing. Importantly, the last reported acute case of autochthonous transmission of *T. cruzi* in the United States occurred more than a decade ago.[70]

The rarity of transmission of *T. cruzi* to humans in the United States probably results from our relatively high housing standards and the low overall vector density. In the past 30 years, about 15 laboratory-acquired and imported cases of acute Chagas disease have been reported to the Centers for Disease Control and Prevention (CDC), but only one in the latter group occurred in a returning tourist.[73] However, three instances of tourists returning to Europe from endemic countries with acute *T. cruzi* infections have been reported, as well as one similar case in Canada.[74–76]

In contrast, in recent decades the number of persons in the United States with chronic *T. cruzi* infections has grown considerably. It is estimated that 23 million persons born in countries in which Chagas disease is endemic currently reside in the United States. Roughly 17 million of these immigrants are from Mexico,[77,78] where, as noted, the overall prevalence of Chagas disease likely is 0.5% to 1.0%. Moreover, a sizable proportion of these immigrants have come from Central America and Bolivia, areas in which the prevalence of *T. cruzi* infection is substantially higher than in Mexico. A study of Salvadoran and Nicaraguan immigrants done 30 years ago in Washington, DC, found a 5% prevalence of *T. cruzi* infection.[79] Prior to the implementation of donor screening, *T. cruzi* infection rates of 1 in 3285 and 1 in 5995 were found in blood donors in Los Angeles, California, and Tucson, Arizona, respectively.[80] More recently, in Los Angeles a cross-sectional serologic study in immigrants from endemic countries showed a prevalence of 1.24%,[81] which merely confirmed an earlier estimate,[47] and a prospective cohort study of immigrants from endemic countries with nonischemic cardiomyopathy found that Chagas disease was present in 19%.[82]

A recent estimate based on country-specific census data for immigrants from Chagas-endemic countries and the prevalence rates of Chagas disease in those countries suggests that 238,000 persons with Chagas disease currently reside in the United States.[51]

Before the implementation of donor screening, the presence of infected immigrants posed a risk for transfusion-associated transmission of *T. cruzi;* seven such cases had been reported in the United States and Canada[83] and two additional instances were found in trace-back studies done after screening started.[84,85] The confirmed rate of *T. cruzi* infection found in blood donors since the implementation of screening in January 2007 has been about 1 in 13,300.[86] The transplantation of organs obtained from three chronically infected immigrants resulted in five cases of acute Chagas disease, one of which was fatal.[8,87] Regarding congenital transmission, although a reasonable estimate would put the number of infants born in the United States each year with congenital Chagas disease at 63 to 315,[47,88,89] only 2 such cases have been reported to date.[12,90] Several factors likely underlie the lack of reported US cases of congenital transmission, but the low level of knowledge among caregivers about Chagas disease and the risk for congenital transmission certainly play major roles.[91,92]

Clinical Manifestations

The clinical syndromes of acute *T. cruzi* infection and chronic Chagas disease are quite different. Acute illness results from the first encounter of the host with the parasite, and chronic disease involves persistent infection and, in many infected persons, late sequelae.

Acute Chagas disease[19] is usually an illness of children, but can occur at any age. Only a small portion of acute infections caused by *T. cruzi* are recognized as such because of the mild and nonspecific nature of the symptoms in most patients and the lack of access to medical care. The first signs of illness occur a week or so after invasion by the parasites. When the parasites have entered through a break in the skin, a chagoma may appear, consisting of an indurated area of erythema and swelling accompanied by local lymph node involvement. The Romaña sign (Fig. 276.5), the classic sign of acute Chagas disease, consists of painless edema of the palpebrae and periocular tissues and may appear when the conjunctiva is the portal of entry. These initial local signs can be followed by fever, malaise, anorexia, and edema of the face and lower extremities. Generalized lymphadenopathy and hepatosplenomegaly may also appear.

Overt central nervous system signs are not common, but meningoencephalitis develops in some patients and is associated with a poor prognosis.[93] Severe myocarditis also develops in a small proportion of patients with acute disease, and most deaths are due to resulting congestive heart failure.[20,21] Nonspecific electrocardiographic changes are seen, but the life-threatening arrhythmias that are frequent in chronic Chagas disease generally do not occur. In untreated patients, symptoms resolve gradually over a period of weeks to months. Areas of local reaction around the eye or other sites of parasite entry can persist for several weeks, as can the lymphadenopathy and splenomegaly. After spontaneous resolution of the acute illness, the patient enters what is called the indeterminate phase of Chagas disease, which is characterized by asymptomatic and subpatent parasitemia and antibodies to a variety of *T. cruzi* antigens.

FIG. 276.5 Romaña sign in an Argentinean child with acute chagas disease. *(Courtesy Dr. Humberto Lugones, Santiago del Estero, Argentina.)*

FIG. 276.6 Chest radiograph of a Bolivian patient with chronic *Trypanosoma cruzi* infection, congestive heart failure, and rhythm disturbances (see reference 96). Pacemaker wires are present in the area of the left ventricle.

FIG. 276.7 Barium swallow radiographic study of a Brazilian patient with chronic *Trypanosoma cruzi* infection and megaesophagus. The markedly increased diameter of the esophagus as well as its failure to empty are typical findings in chagasic patients with megaesophagus. *(Courtesy Dr. Franklin A. Neva, Bethesda, MD.)*

Chronic symptomatic Chagas disease becomes apparent years or even decades after initial infection. The heart is the organ most commonly involved, and symptoms reflect the rhythm disturbances, congestive heart failure, and thromboembolism that are characteristic of the chronic illness (Fig. 276.6).[94–98] Dizziness, syncope, and, less commonly, seizures result from a wide variety of arrhythmias. The cardiomyopathy that develops insidiously often primarily affects the right ventricle, and the classic signs of right-sided heart failure are frequently present. As in patients with arrhythmias, the progression of symptoms related to the cardiomyopathy may be gradual, and a validated risk-score tool for following progression has been developed.[99] The clinical course is frequently complicated by emboli to the brain or other areas.

In patients with megaesophagus, symptoms are similar to those of idiopathic achalasia and may include dysphagia, odynophagia, chest pain, cough, and regurgitation (Fig. 276.7).[100,101] Hypersalivation and salivary gland hypertrophy have been observed. Aspiration can occur, especially during sleep, and in untreated patients repeated episodes of aspiration pneumonitis are common. Weight loss and even cachexia in patients with megaesophagus can combine with pulmonary infection to result in death. As in idiopathic achalasia, an increased incidence of cancer of the esophagus has been reported in patients with chagasic esophageal disease.

Patients with chagasic megacolon are plagued by chronic constipation and abdominal pain (Fig. 276.8).[102,103] Individuals with advanced disease can go for several weeks between bowel movements, and acute obstruction, occasionally with volvulus, can lead to perforation, septicemia, and death.

Immunosuppression and Transplantation in *T. Cruzi*–Infected Patients

When persons who harbor *T. cruzi* chronically become immunosuppressed, reactivation of the infection can occur, sometimes with a severity greater than is typical of acute Chagas disease in immunocompetent patients.[104–107] The incidence of reactivation in *T. cruzi*–infected patients who become immunosuppressed is not known. Immunosuppressed patients in whom chronic *T. cruzi* infection reactivates often develop skin lesions and cerebral mass lesions, neither of which occurs in immunocompetent persons infected with the parasite.[108–110] There have been several reports of reactivations of chronic *T. cruzi* infections after renal transplantation, and in two of these instances the central nervous system was involved. Nonetheless, *T. cruzi* infection should not be a contraindication for kidney transplantation. Infected patients who do undergo the procedure, however, should be monitored periodically for

FIG. 276.8 Air-contrast barium enema of a constipated Bolivian patient with megacolon and chronic Chagas disease (see reference 96). The markedly increased diameters of the ascending, transverse, and sigmoid segments of the colon are readily apparent.

signs and symptoms of acute Chagas disease, and a specific search for *T. cruzi,* including careful neurologic evaluation, should be performed when acute illnesses occur postoperatively.

Immunosuppression caused by the human immunodeficiency virus (HIV) can also lead to recrudescence of chronic *T. cruzi* infection. To date, dozens of such patients have been described, the first of whom was a Central American immigrant living in the United States.[107,111–113,114] As with other immunosuppressed patients, many of these coinfected patients developed *T. cruzi* brain abscesses. Calculations based on the epidemiologies of HIV and *T. cruzi* infections in endemic countries suggest that the incidence of brain abscesses caused by the latter in coinfected persons is low. Moreover, it is likely that the incidence of *T. cruzi* brain abscesses in HIV-infected patients has decreased markedly in the era of highly active antiretroviral therapy.

Heart transplantation is an option in patients with end-stage Chagas cardiac disease, and several hundred *T. cruzi*–infected patients have undergone the procedure, mostly in Brazil.[115,116] Because *T. cruzi* cannot reliably be eliminated by antiparasitic treatment before heart transplantation, reactivation of the infection is a frequent problem and is complicated by the fact that the parasitologic approaches usually used to detect acute *T. cruzi* infections often are not sensitive detectors of reactivation.[117] Moreover, a higher than expected incidence of malignancies was observed in the Brazilian patients.[118,119] It is also noteworthy that patients who have received transplants for Chagas heart disease occasionally develop cutaneous lesions containing large numbers of parasites,[120] as has been reported in Chagas disease patients who received renal transplants[121] and in coinfected persons with HIV/acquired immunodeficiency syndrome.[122] Despite these problems, the long-term survival of Chagas disease patients with heart transplants is greater than that of persons who receive transplants for other reasons, probably because the pathology of chronic *T. cruzi* infection is generally limited to the heart.[115]

Diagnosis

The first consideration in the diagnosis of acute Chagas disease is a history consistent with exposure to *T. cruzi.* This includes residence in an environment in which vector-borne transmission is known to occur, a recent transfusion in an endemic area where effective blood screening programs are not in place, birth of an infant to a *T. cruzi*–infected mother, risk of involvement in a foodborne outbreak, or a laboratory accident involving the parasite. It is important to keep in mind, moreover, that autochthonous transmission of *T. cruzi* in the United States is extremely rare and that only one imported case among tourists returning to the United States has been reported,[73] even though many millions of people travel from the United States to endemic countries each year.

The diagnosis of acute Chagas disease is made by detecting parasites, and testing for anti–*T. cruzi* IgM is not useful. Circulating parasites are motile and can often be seen in wet preparations of anticoagulated blood or buffy coat viewed under a coverslip or in microhematocrit tubes. In many cases the parasites can also be seen in Giemsa-stained smears. In acutely infected immunocompetent patients, examination of blood preparations is the cornerstone of detecting *T. cruzi.* In immunocompromised patients suspected of having acute Chagas disease, however, other specimens such as lymph node and bone marrow aspirates, pericardial fluid, and cerebrospinal fluid should be examined microscopically. When these methods fail to detect *T. cruzi* in a patient whose clinical and epidemiologic histories suggest that the parasite is present, as is often the case, efforts to grow the organism can be undertaken. This can be attempted by culturing blood (hemoculture) or other specimens in liquid medium.[123] Major problems with hemoculture are that its sensitivity may be no greater than 50% even in acutely infected patients and that it takes at least several weeks to complete, which is beyond the time at which a decision regarding drug treatment must be made. When available, PCR assays are a better alternative because the sensitivity is higher and completion time is relatively short (see later). The diagnosis of congenital Chagas disease also must be parasitologic (microscopic examination of cord blood or PCR assay) when performed right after birth because of the presence of maternal anti–*T. cruzi* antibodies. Serologic testing for specific IgG should be performed at least 9 months later if the initial parasitologic studies are negative.[10,124]

Chronic *T. cruzi* infection is usually diagnosed by detecting IgG antibodies that bind specifically to parasite antigens, and detecting the presence of the organism is not of primary importance. Currently, more than 30 assays for serologic diagnosis of *T. cruzi* infection are available commercially. The majority are based on enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination, and chemiluminescent and indirect immunofluorescence formats, and are used widely in the endemic countries for clinical testing and for screening blood and organ donors.[125,126] In recent decades enormous efforts have been invested in the development and validation of these tests, and their sensitivities and specificities are generally at the level of the best assays for other infectious diseases. Nonetheless occasional false-positive reactions do occur, typically with specimens from patients having leishmaniasis, malaria, syphilis, and other parasitic and nonparasitic diseases. Because of this issue, the World Health Organization recommends that samples be tested in two assays based on different formats before diagnostic decisions are made.[127]

The results of a recent evaluation of 11 commercially available rapid diagnostic tests indicate that their sensitivities and specificities generally are not high enough to warrant their use for making treatment decisions, even when they are used in highly controlled laboratory settings.[128]

Three serologic assays have been cleared by the US Food and Drug Administration (FDA) for clinical testing: the Hemagen Chagas Kit (Hemagen Diagnostics, Inc., Columbia, MD),[126] the Chagatest ELISA recombinante (Laboratorios Wiener, Rosario, Argentina),[126] and the Chagas Detect *Plus* Rapid Test (Inbios International, Inc., Seattle, WA).[129] The Abbott Architect Chagas Assay (Abbott Laboratories, Chicago, IL),[130,131] which is an accurate chemiluminescence test based on a mixture of four chimeric recombinant proteins, has not been cleared yet for use in the United States but is approved and used widely for both clinical and donor testing in many endemic countries.

The Ortho *T. cruzi* ELISA Test System (Ortho Clinical Diagnostics, Raritan, NJ), an ELISA based on a parasite lysate,[125] and the Abbott Prism Chagas Assay,[132] a highly automated chemiluminescent microparticle immunoassay based on the same mixture of recombinant proteins used in the Abbott Architect Chagas Assay, have been approved by the FDA for donor testing. These latter two assays are currently being used to screen the US blood supply in a selective testing protocol in which an initial donation at a given donor center is tested for Chagas disease, and if the result is negative, subsequent donations by the same person at that site are not tested. The Abbott ESA (Enzyme Strip Assay) Chagas, also based on the group of recombinant antigens used in the Architect Chagas Assay, has been approved by the FDA for confirmatory testing of screen-positive donor samples (i.e., positive in the Abbott Prism

Chagas Assay or the Ortho ELISA).[133] In addition, a Clinical Laboratory Improvement Amendments–approved radioimmunoprecipitation assay (Chagas RIPA)[126,134] was used from 2007 to 2014 for confirmatory testing of donated units that were positive in the Abbott Prism Chagas Assay or the Ortho ELISA, and is currently available in my laboratory for testing clinical and research specimens.

The possibility of using PCR assays for detecting *T. cruzi* infection has been studied extensively. The number of parasites in the blood of patients with chronic *T. cruzi* infection is extremely low, but PCR assays have the potential for detecting such low numbers because the organisms have highly repetitive nuclear and kinetoplast DNA sequences that can be amplified. Three decades ago, two of my colleagues and I described a PCR test in which a 188–base pair nuclear repetitive DNA sequence is amplified (TCZ1-TCZ2 primers).[135] Each parasite contains approximately 100,000 copies of this sequence, and in contrived experiments as little as 0.5% of the genome of a single parasite gave a positive result. Studies in mice with acute and chronic *T. cruzi* infections indicated clearly that this PCR assay is much more sensitive than microscopic examination of blood.[136] In a second PCR test, described at the same time by Sturm and coworkers, a 330–base pair segment of the *T. cruzi* kinetoplast mini-circle is amplified (S35-S36 primers).[137] Each parasite is believed to have approximately 120,000 copies of this sequence, and in mixing experiments the authors were able to detect 0.1% of one parasite genome. The results of the five head-to-head comparisons of PCR assays based on these two primer pairs published to date suggest that the TCZ1-TCZ2 assay has an edge in terms of sensitivity.[136,138–140]

Since the publication of these two original reports in 1989,[135,137] hundreds of articles focused on PCR detection of *T. cruzi* have been published. Importantly, in a group of nine key human studies published in the 1990s, the sensitivities of the PCR assays ranged from 44.7% to 100%.[123,141,142] Three more recent major studies showed sensitivities of 60% to 75% in persons chronically infected with *T. cruzi,* thus confirming that the lack of sensitivity of PCR assays continues to be a major issue.[139,140,143] Clearly this level of sensitivity is not high enough to allow use of these assays for confirmatory testing of screen-positive blood donations. Nonetheless, PCR assays are useful for detecting *T. cruzi* in persons with borderline serologic results, in infected individuals who have received specific treatment, and in patients suspected of having acute or congenital Chagas disease in whom parasites are not detected microscopically. In all such persons, only positive results can be taken as truly indicative of their infection status. At the present time no PCR test for the detection of *T. cruzi* is available commercially, but detailed guidance for optimization of assays has been published.[140]

Therapy

Current therapy for persons infected with *T. cruzi* is unsatisfactory from a variety of perspectives. Two drugs are currently used to treat patients infected with *T. cruzi.*[144] The first is the nitroimidazole derivative benznidazole (Exeltis), which is viewed as the drug of choice by most specialists and is used widely in the endemic countries.[144] In acute and congenital Chagas disease, benznidazole markedly reduces the duration and severity of the illness and decreases mortality. However, it results in parasitologic cure in only about 70% of acute patients, can cause severe side effects, and must be taken for prolonged periods. Therapy with benznidazole should be initiated as early as possible in cases of acute or congenital Chagas disease. Moreover, when a laboratory accident occurs in which there is a reasonable likelihood that *T. cruzi* infection will become established, therapy should be started without waiting for clinical or parasitologic indications of infection.

Side effects of benznidazole are common and include peripheral neuropathy, rash, and granulocytopenia.[145,146–149] High rates of discontinuation due to adverse reactions have been observed recently in studies done in nonendemic areas (20% in the United States; 32% in Milan, Italy).[150,151] The rash may associated with a Th2 response in patients who carry an HLA-B*3505 allele.[152] To address the high rate of discontinuation due to rash, a progressive regimen was proposed that increases the daily dose by one pill until the daily weight-based recommended dose is reached, and this led to a discontinuation rate of only 1 of 30 patients.[153] Experimental data indicate that benznidazole crosses the placenta and has teratogenic effects, and thus it should not be given to pregnant women. The recommended oral dosage of benznidazole is 5 mg/kg/day for 60 days.

The second drug used to treat Chagas disease is the nitrofuran derivative nifurtimox, which has been in use for more than 4 decades, and extensive clinical experience has accumulated.[154] The efficacy of nifurtimox is similar to that of benznidazole. A large proportion of patients treated with nifurtimox experience adverse side effects. Gastrointestinal complaints include abdominal pain, nausea, vomiting, anorexia, and weight loss. Possible neurologic symptoms include restlessness, insomnia, twitching, paresthesias, and seizures. These symptoms generally resolve when the dosage is reduced or therapy is discontinued. Nifurtimox should not be given to pregnant women.

Nifurtimox is supplied as 30- and 120-mg tablets. The recommended oral dosage for adults is 8 to 10 mg/kg/day. The dosage for adolescents is 12.5 to 15 mg/kg/day, and for children 1 to 10 years of age it is 15 to 20 mg/kg/day. The drug should be given in four divided doses each day, and therapy should be continued for 90 to 120 days. Nifurtimox is available from the Parasitic Disease Drug Service of the CDC.

In terms of which groups of *T. cruzi*–infected persons should be given specific treatment, there is broad consensus that all persons with acute *T. cruzi* infection, including infants with congenital Chagas disease, should be treated. In addition, all chronically infected persons up to 18 years old should be treated. This latter perspective is supported by data from older clinical trials in which reduced anti–*T. cruzi* antibody levels were observed in a substantial proportion of treated patients in this age group. Nonetheless, data regarding parasitologic cure in treated patients up to 18 years of age are not available, in large measure because of a lack of a workable diagnostic tool to assess cure. It merits mention, moreover, that the recent FDA approval of benznidazole for treating chronically infected 2- to -12-year-old children was based on surrogate antibody level reduction data rather than evidence of parasitologic cure.[155–157,158]

The question of whether adults in the indeterminate or chronic symptomatic phases of *T. cruzi* infection should be treated with benznidazole or nifurtimox has been debated for many years. This is a thorny issue because these two drugs have to be taken for 2 to 4 months, frequently cause bothersome side effects, and result in parasitologic cure in less than 10% of persons with long-standing *T. cruzi* infections.[159,160–162] Moreover, there is no convincing evidence from properly controlled trials that treatment with either of the drugs improves long-term outcomes in adults with chronic *T. cruzi* infection.[163] The issue is complicated further by the lack of sensitivity of parasitologic assays, which ideally would be used in trials to look for treatment failure because antibody titers can remain positive for years even when parasitologic cure has occurred. A panel of experts convened by the CDC in 2007 suggested that treatment be offered to adults with presumably long-standing indeterminate phase infections.[157] A major trial involving approximately 5000 study subjects in Argentina, Bolivia, Brazil, Colombia, and El Salvador (the BENEFIT Multicenter Trial) analyzed the effects of benznidazole therapy in seropositive patients with incipient Chagas cardiomyopathy. The outcomes of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter-defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic events were not significantly different between benznidazole and placebo recipients, with a mean follow-up of 5.4 years.[164]

The usefulness of fluconazole, ketoconazole, itraconazole, posaconazole,[165,166] and several other azoles, as well as allopurinol, has been studied extensively in *T. cruzi*–infected laboratory animals and to a lesser extent in persons with Chagas disease. None of these drugs should be used to treat patients with acute or chronic Chagas disease.

Most patients with acute Chagas disease require no therapy other than benznidazole or nifurtimox because symptoms are generally self-limited even in the absence of drug treatment. The management of the occasional severely ill acute-phase patient with myocarditis or meningoencephalitis is largely supportive. The treatment of patients with chronic chagasic heart disease is also supportive. Chronically infected persons should have electrocardiograms performed every 6 months or so because pacemakers have been shown to be useful in the management of arrhythmias seen in chronic Chagas disease. The congestive heart failure

of cardiomyopathic Chagas disease is generally treated with measures used in patients with cardiomyopathies resulting from other causes.[30,167–169] The usefulness of implantable cardioverter-defibrillators in patients with advanced chagasic cardiac disease is controversial.[170,171–173]

Megaesophagus associated with Chagas disease generally should be managed as for idiopathic achalasia.[30,101,174] The first approach to relieving symptoms is balloon dilation of the lower esophageal sphincter. Patients who fail to respond to repeated attempts at this approach are treated surgically. The procedure used most frequently is wide esophagocardiomyectomy of the anterior gastroesophageal junction, combined with valvuloplasty to reduce reflux. Patients with extreme megaesophagus are often treated with esophageal resection with reconstruction using an esophagogastroplasty. In industrialized countries, laparoscopic myotomy is often used to treat idiopathic achalasia. This relatively simple procedure may become the approach of choice for both idiopathic achalasia and Chagas megaesophagus. Patients in the early stages of colonic dysfunction associated with chronic Chagas disease can be managed with a high-fiber diet and occasional laxatives and enemas. Fecal impaction necessitating manual disimpaction may occur, as can toxic megacolon, which requires surgical treatment. Another complication of chagasic megacolon that requires immediate attention is volvulus. This usually occurs when the lengthened and enlarged sigmoid colon twists and folds on itself, causing a constellation of symptoms resulting from obstruction and vascular compromise. Endoscopic emptying can be performed initially in patients without radiographic, clinical, or endoscopic signs of ischemia in the affected area. Complicated cases should be treated with surgical decompression. In either event, however, surgical treatment of the megacolon is eventually necessary because of the high probability of recurrence of the volvulus. A number of surgical procedures have been used to treat advanced chagasic megacolon, and all include resection of the sigmoid colon as well as removal of part of the rectum.[175] The latter is performed to avoid recurrence of megacolon in the segment of the colon that is anastomosed to the rectum.

Prevention

In view of the possible serious consequences of chronic *T. cruzi* infection, all immigrants from endemic regions and children of immigrant mothers with geographic risk for Chagas disease who are not known to be seronegative should be screened serologically. Identification of infected persons is important so that they can be monitored for rhythm disturbances and other signs of cardiac disease, as well as gastrointestinal dysfunction, and treated appropriately when indicated. The possibility of congenital transmission is another justification for screening. Over the past decade, substantial evidence has accumulated indicating that treating chronically infected girls and women of childbearing age markedly reduces the probability of congenital transmission to their babies conceived after treatment.[176,177,178–180] Summarizing the data presented in these five somewhat heterogeneous studies, 171 girls and women had received specific treatment for chronic *T. cruzi* infection prior to pregnancies that all told resulted in 296 evaluable babies. None of these babies had any evidence of *T. cruzi* infection, which is surprising given that the historical rate of congenital Chagas disease in infants born to infected mothers is 5% to 10%. Moreover, it is noteworthy that many if not most of the girls and women so treated likely were not cured parasitologically, and in some instances many years had elapsed between treatment and the pregnancies. These data suggest strongly that specific prepregnancy treatment of chronic *T. cruzi* infection has a marked suppressive effect on the likelihood of subsequent congenital transmission, and it seems likely that treating all infected women of childbearing age will become the standard of care (the current consensus foresees that all persons of both sexes 18 years old or less will be treated). It merits mention, moreover, that given the potential fetal toxicity of benznidazole and nifurtimox, care must be taken to ensure that chronically infected women of childbearing age are not pregnant when treatment is initiated and that they do not become pregnant during treatment.

As noted earlier, to date nine cases of transfusion-associated transmission of *T. cruzi* have been reported in the United States and Canada. The courses of acute Chagas disease in seven of these patients were particularly fulminant because of immunosuppressive therapy, which certainly contributed to the definitive diagnoses. The question as to how best to avoid transmission of the parasite via transfusion in the United States was debated for more than a decade before December 2006, when an FDA-approved screening test first became available. Common sense suggested that if serologic screening was warranted in endemic countries from which the 23 million at-risk immigrants living in the United States had come, they should be screened when they presented for donation here. In the end, governmental and blood industry authorities embraced this view, and, as noted earlier, an FDA-approved selective screening protocol is currently implemented and essentially eliminates the risk of *T. cruzi* transmission by transfusion in the United States.[86,181]

A panel of experts recently reviewed the limited data available relating to the transplantation of organs obtained from *T. cruzi*–infected donors.[7] They and others[182] have concluded that, with informed consent, transplantation of livers and kidneys from infected donors is reasonable but cautioned that careful postoperative and long-term monitoring for *T. cruzi* infection in the recipients should be performed. Hearts from *T. cruzi*–infected donors should not be transplanted.[183]

T. cruzi is a Risk Group 2 organism, and laboratorians working with it should use personal protective measures consistent with this classification.[184,185] Persons traveling in endemic areas should avoid sleeping in dilapidated dwellings and should use insect repellent and bed nets to reduce exposure to vectors.[186,187] No vaccine is available for the prevention of transmission of *T. cruzi*.[188,189] Special precautions beyond the usual measures for reducing the insect exposure of campers, hunters, and others engaging in outdoor activities in the United States are not warranted.

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The complete reference list is available online at Expert Consult.

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277 Agents of African Trypanosomiasis (Sleeping Sickness)

Louis V. Kirchhoff[a]

SHORT VIEW SUMMARY

Definition
- Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by two protozoan parasite subspecies: *Trypanosoma brucei gambiense* (West African trypanosomiasis) and *Trypanosoma brucei rhodesiense* (East African trypanosomiasis).

Microbiology
- The trypanosomes that cause HAT are transmitted among their mammalian hosts by tsetse flies. The flies become infected when they take a blood meal from an infected mammal. There is a developmental cycle in the flies, after which infective parasites migrate to the salivary glands and are injected into a new host when the flies take subsequent blood meals. In their mammalian hosts African trypanosomes are found primarily in the bloodstream and, to a lesser extent, in perivascular areas of the brain and other tissues. In contrast to *Trypanosoma cruzi,* the parasite that causes Chagas disease, African trypanosomes do not have an intracellular phase. They avoid immune destruction by antibodies by periodically changing their glycoprotein coats through a molecular process called *antigenic variation.*

Epidemiology
- HAT occurs only in sub-Saharan Africa, where endemic foci are found in about two dozen countries.
- HAT is much less of a problem today than in the past. Only 2184 new cases were reported to the World Health Organization in 2016. Although this number reflects substantial underreporting, there is no doubt that control efforts implemented in many endemic countries during the past 25 years have achieved considerable success. Each year in industrialized countries HAT is diagnosed in a sprinkling of persons who have traveled to endemic areas, but given the large numbers of persons who make such trips, the incidence of such cases is extremely low.

Clinical Manifestations
- Two clinical stages exist. Stage 1 (hemolymphatic disease) is characterized by fever, adenopathy, and headache. Stage 2 (central nervous system or encephalitic disease) involves mainly neuropsychiatric signs and symptoms.
- The primary difference between the clinical patterns of *gambiense* and *rhodesiense* HAT is that the latter follows a much more rapid course and can lead to death in a matter of months, whereas *gambiense* HAT typically develops a chronic pattern that can last for years.
- Untreated HAT almost inevitably ends in death.
- It is important for caregivers attending to travelers with fever and other nonspecific symptoms who have been in endemic areas to include HAT in the differential diagnosis.

Diagnosis
- Given the life-threatening nature of untreated HAT, a high index of suspicion should be maintained with persons who have been in areas endemic for HAT.
- Numerous other illnesses common in the tropics cause symptoms similar to those seen in both the early and late stages of sleeping sickness.
- A definitive diagnosis of African trypanosomiasis requires demonstration of the parasite. Examination of blood smears and cerebrospinal fluid for parasites is the cornerstone of HAT diagnosis.
- There is a growing role for polymerase chain reaction and related molecular methods in the diagnosis of HAT.
- Diagnostic approaches and treatment should be discussed in detail with appropriate staff at the Centers for Disease Control and Prevention.

Therapy
- Treatment is complicated because it varies according to the clinical stage of the disease and the trypanosome subspecies causing the infection.
- Toxicity of the drugs used to treat HAT is a major problem.

Prevention
- Individuals can reduce their risk of acquiring infections with African trypanosomes by avoiding areas known to harbor infected insects, wearing clothing that reduces the biting of the flies, and using insect repellent.
- Chemoprophylaxis is not recommended because of the high toxicity of the drugs that are active against African trypanosomes, and no vaccine is available to prevent transmission of the parasites.

PARASITES AND THEIR TRANSMISSION

The agents of human African trypanosomiasis (HAT, sleeping sickness) are flagellated protozoan parasites that belong to the genus *Trypanosoma,* subgenus *Trypanozoon.*[1,2] A general description of the members of this genus and specific characteristics of the subgenus are presented in the introduction to Chapter 276. Three trypanosome subspecies, *Trypanosoma brucei brucei, T. brucei rhodesiense,* and *T. brucei gambiense,* are considered here. They are indistinguishable morphologically, and as a group they are often referred to as the *T. brucei* complex. *T. b. brucei* is a parasite of wild and domestic animals that is not infectious to humans. In contrast, *T. b. rhodesiense,* which is primarily a parasite of wild game, can infect humans, and this difference in host specificity forms the primary basis of the distinction between the two subspecies. *T. b. gambiense* primarily infects humans, and infections of wild and domestic animals are of limited importance.

The members of the *T. brucei* complex are transmitted by various species of tsetse flies that belong to the genus *Glossina.*[3,4] These bloodsucking insects are found only in Africa, where their range covers millions of square kilometers of rain forest and savanna. The parasites undergo a developmental cycle in the insect vectors. Tsetse flies of both sexes become infected with trypanosomes when they ingest blood from infected mammalian hosts that contains trypomastigotes, the form of the parasite that circulates in the bloodstream. There are two forms of circulating trypomastigotes: long, slender organisms that are capable

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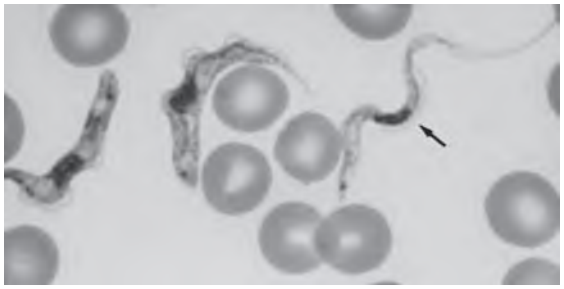

FIG. 277.1 *Trypanosoma brucei rhodesiense* trypomastigotes in rat blood. The parasite indicated by the arrow is typical of the long, slender forms capable of multiplying in the mammalian host. The other two organisms represent the stumpy, nondividing forms infective for the insect vector (Giemsa stain, ×1250). *(Courtesy Dr. G.A. Cook, Madison, WI.)*

of dividing and short, stumpy forms thought to be nondividing parasites that are infective for the insect vectors (Fig. 277.1). Once in the midgut of the tsetse flies, stumpy trypomastigotes transform into relatively long, slender procyclic trypomastigotes. After many cycles of multiplication the procyclic forms migrate to the salivary glands, where they differentiate into epimastigotes and continue to multiply. A final transformation occurs as the epimastigotes become nondividing metacyclic trypomastigotes. Transmission takes place when these infective forms are inoculated during a subsequent blood meal. The cycle is completed when the injected metacyclic forms become bloodstream trypomastigotes and begin to multiply in the blood or other extracellular spaces. The capacity of African trypanosomes to multiply in the bloodstream of their mammalian hosts, where they are continually exposed to humoral defenses, constitutes a fundamental difference between the agents of sleeping sickness and *Trypanosoma cruzi,* the cause of Chagas disease in the Americas. The African trypanosomes are able to evade immune destruction indefinitely because they undergo antigenic variation, a process in which they periodically change the antigenic structure of the coat of glycoproteins that covers the surface of the parasite. The molecular mechanisms that control this complex process have been studied intensively.[5–7] When epimastigotes transform into metacyclic trypomastigotes in the salivary glands of the tsetse fly, each parasite synthesizes a surface coat made up of one of about a dozen types of antigenic glycoproteins, called variant antigen types (VATs). Presumably, this occurs as a preadaptation to the relatively hostile environment of the mammalian host into which the metacyclics must be inoculated if they are to survive. After injection into a mammalian host, the parasites express metacyclic VATs for approximately 5 days, after which they switch to the expression of bloodstream VATs. Over time, the host sequentially mounts specific humoral responses directed against the predominantly expressed VATs. The population of parasites survives because an intrinsic rate of VAT switching provides an apparently endless supply of parasites that have surface glycoprotein coats to which the host has not been exposed previously.

Virtually all transmission of African trypanosomes to both wild and domestic animals, as well as to humans, takes place in the cyclic fashion just described. There is no evidence that these parasites can be transmitted by insects other than tsetse flies, and mechanical transmission by vectors is not important, although it may occur occasionally. Congenital transmission can occur, but in humans it is extremely rare,[8,9] as is transmission by blood transfusion. A small number of laboratory accidents resulting in infection with African trypanosomes have been reported.[10]

PATHOGENESIS AND PATHOLOGY

The pathogenesis of African sleeping sickness is complex, and many aspects of the process are poorly understood.[11–13] The first sign of infection with African trypanosomes can be the acute inflammatory lesion (trypanosomal chancre) that appears a week or so after the bite of an infected tsetse fly and resolves spontaneously over several weeks. Interstitial multiplication of the trypanosomes takes place within the chancre, and there is an intense mononuclear cell reaction to the parasites, as well as edema and local tissue destruction.

After this initial local response the infection evolves over weeks and months into a systemic hemolymphatic illness as the parasites disseminate widely through the lymphatic system and the bloodstream. Systemic African trypanosomiasis without central nervous system (CNS) involvement is generally referred to as stage 1 disease. The parasites first travel from the site of inoculation to regional lymph nodes, where they proliferate and cause an inflammatory response. They then move through the lymphatics into the bloodstream, where multiplication continues. Egress of trypanosomes from vessels into interstitial spaces, where multiplication also takes place, is thought to be facilitated by increased vascular permeability.

In stage 1 trypanosomiasis there is widespread lymphadenopathy and histiocytic proliferation, which may be followed by fibrosis. Morular cells (Mott cells) are also often present in tissue. These cells are plasmacytes with vacuolated cytoplasm and pyknotic nuclei that are thought to play a role in the production of immunoglobulin M (IgM).[14] The spleen may be enlarged, with generalized cellular proliferation, congestion, and focal necrosis. As the disease evolves, an endarteritis with perivascular infiltration of both parasites and lymphocytes may develop in lymph nodes and the spleen.

The heart is frequently involved in this stage of the disease, especially with *T. b. rhodesiense* infections. A pancarditis may develop involving all layers of the heart, including the mural and valvular endocardia.[15] The conduction system may also be affected, and involvement of the autonomic innervation of the heart has also been reported.[16] At the cellular level, pathologic changes include intense mononuclear infiltration consisting of lymphocytes, plasmacytes, and morular cells. As the infection progresses, myocytolysis and fibrosis may develop.

A number of hematologic manifestations accompany the development of stage 1 disease. Normocytic anemia is a regular feature in this phase of the illness and is usually accompanied by a brisk reticulocytosis. Several factors are thought to contribute to the anemia, and immune-mediated hemolysis may be important. Platelet counts are often reduced, especially in infections with *T. b. rhodesiense,* and disseminated intravascular coagulation before and during therapy has also been described. A moderate degree of leukocytosis is usually present, especially in the early months of the infection, and this is accompanied by polyclonal B-cell activation. High titers of immunoglobulins are a striking and constant feature of the illness. They consist primarily of polyclonal IgM that, for the most part, is not directed against specific parasite antigens. A number of other factors, including heterophile antibodies, rheumatoid factor, and anti-DNA antibodies, are often detectable. In addition, high levels of circulating antigen-antibody complexes are uniformly present, and these may play a role in the anemia, tissue damage, and increased vascular permeability that facilitate the dissemination of the parasites. Erythrocyte sedimentation rates are elevated, and hypocomplementemia has also been noted.

Stage 2 African trypanosomiasis involves invasion of the CNS. Parasites reach the brain and meninges via the bloodstream and cause meningoencephalitis or meningomyelitis, or both.[17–19] In the brain they are found mainly in the frontal lobes, pons, and medulla, but other areas may be parasitized as well. Edema and hemorrhages may be evident on gross examination of affected areas at autopsy. Trypanosomes are present in perivascular areas, and nests of organisms can be found without apparent relation to blood vessels. The presence of parasites in the CNS is associated with infiltration of mononuclear cells that are predominantly lymphocytes, plasmacytes, and morular cells. The presence of parasites in the CNS is heralded by abnormal findings in the cerebrospinal fluid (CSF). The CSF may be under increased pressure, and the total protein concentration is elevated, with mononuclear cells predominating in addition to small numbers of morular cells and eosinophils. Trypanosomes are frequently present in the CSF as well. A model of *T. brucei* infection in rats has been developed that differs from a standard view of disease and highlights the prominent role of penetration and residence of parasites in the pia mater, an immune-privileged site.[20] According to this model, the production of prostaglandin D_2 may influence the development of sleeping sickness, and brain parenchymal disease proceeds from this chronic infection. The authors suggest that

a better understanding of the physiology of disease might influence assumptions about the pharmacokinetic characteristics of drugs in development.

EPIDEMIOLOGY

HAT, which is limited to sub-Saharan Africa, was a much greater problem in the past than it is at present.[21] Hundreds of thousands of people died in major epidemics around the beginning of the 20th century and between 1920 and 1948. Between World War II and independence, the colonial powers invested heavily in controlling HAT and succeeded to the point where the disease was almost eliminated. In the decades after independence, however, in the context of continuing poverty and civil strife in many areas, control programs were neglected and HAT underwent a resurgence that reached a peak in the late 1990s. Angola, Uganda, South Sudan, and the Democratic Republic of Congo were particularly affected, and even today 80% of reported cases occur in the latter. Since then, efforts of the World Health Organization (WHO), governments of the endemic countries, and nongovernmental organizations have resulted in effective control in many affected areas, so much so that the annual number of reported cases decreased to 9878 in 2009 and to 2184 by 2016, which is roughly equivalent to the low point reached in the early 1960s. Although underreporting is a persistent problem, there is no doubt, to the credit of the many organizations involved in these efforts, that the level of control reached to date is impressive.[22] In 2012 a panel of experts convened by WHO to review the then-current situation and developed a vision for the elimination of HAT.[23,24] The current view at WHO is that efforts are on track for achieving, by 2020, the elimination of HAT as a public health problem, which is defined as fewer than 1000 reported cases per year.[25]

West African *(gambiense)* trypanosomiasis and East African *(rhodesiense)* trypanosomiasis are epidemiologically distinct diseases. The general geographic distributions of these two illnesses are presented in Fig. 276.1 in Chapter 276, and the remaining foci where transmission is known to occur are found in the indicated areas. Distinguishing epidemiologic and clinical features of the two diseases are presented in Table 277.1.

West African Trypanosomiasis

West African trypanosomiasis is caused by *T. b. gambiense,* which is transmitted primarily by tsetse flies belonging to the *palpalis* group: *Glossina palpalis, Glossina tachinoides,* and *Glossina fuscipes*. These vectors inhabit forests and wooded areas along rivers, where conditions of temperature, moisture, and darkness favorable for them are combined with the availability of mammalian blood. This distribution of the vectors restricts the occurrence of human infection to the tropical rain forests of Central and West Africa. Despite the facts that these tsetse flies adapt to feeding on a variety of mammals and *T. b. gambiense* has been found in several wild animal species, infected humans apparently constitute the only epidemiologically important reservoir of this subspecies. The primary determinant of the risk of acquiring the infection is the frequency of contact with the vector. This risk increases during the dry season, when the density of both vectors and humans increases around limited numbers of water holes. Because of this pattern of transmission, West African trypanosomiasis is primarily a problem in rural populations, and tourists rarely become infected with *T. b. gambiense.* The course of the illness caused by *T. b. gambiense* is less severe than that caused by *T. b. rhodesiense,* although both forms almost always lead to death if not treated.[26,27] In fact, many persons infected with *T. b. gambiense* are asymptomatic for long periods and continue to have contact with the vectors. This may be an important element in the persistence of the infection in the reservoir between epidemics.

TABLE 277.1 Comparisons of West African and East African Trypanosomiasis

	WEST AFRICAN *(GAMBIENSE)*	EAST AFRICAN *(RHODESIENSE)*
Organism	*Trypanosoma brucei gambiense*	*Trypanosoma brucei rhodesiense*
Vectors	Tsetse flies (*palpalis* group)	Tsetse flies (*morsitans* group)
Primary reservoir	Humans	Antelope and cattle
Human illness	Chronic (late CNS disease)	Acute (early CNS disease)
Duration of illness	Months to years	<9 mo
Lymphadenopathy	Prominent	Minimal
Parasitemia	Low	High
Epidemiology	Rural populations	Tourists in game parks; workers in wild areas; rural populations

CNS, Central nervous system.

East African Trypanosomiasis

The etiologic agent of East African trypanosomiasis is *T. b. rhodesiense.* This subspecies is transmitted by tsetse flies of the *morsitans* group, principally *Glossina morsitans, Glossina pallidipes,* and *Glossina swynnertoni.* These vectors are widely distributed in savanna and woodland areas of Central and East Africa. Wild animals are the reservoir of this organism, principally antelope such as the bushbuck and hartebeest. These animals are trypanotolerant and generally do not suffer significant morbidity unless weakened by other illnesses. Cattle are the only domestic animals that can serve as a reservoir of *T. b. rhodesiense,* and infection with the parasite usually causes death if left untreated. Many other wild and domestic animals can be infected with these parasites, but their importance as reservoirs is minimal because parasitemias are either low or they succumb quickly to the infection. The presence of the reservoir of *T. b. rhodesiense* and other trypanosome species in wild game in vast areas of Africa makes opening these lands for livestock difficult. Humans become infected with *T. b. rhodesiense* only incidentally because for the most part risk results from contact with tsetse flies that principally feed on wild animals. Thus the illness is an occupational hazard for persons such as game wardens who work in areas where infected wild animals and vectors are present. In addition, sporadic cases of *T. b. rhodesiense* infection occur among non-African tourists who visit game parks in East Africa.

The natural cycle of the African trypanosomes does not exist outside Africa, and HAT in the United States and other nonendemic countries is limited to occasional imported cases, most of which are caused by *T. b. rhodesiense.*[28,29] During the past 25 years, roughly two dozen cases of imported African trypanosomiasis have been reported to the Centers for Disease Control and Prevention (CDC), several of whom had CNS involvement.

CLINICAL COURSE

West African Trypanosomiasis

An indurated, painful trypanosomal chancre may develop at the site where parasites were inoculated by an infected tsetse fly. This lesion usually appears 1 to 2 weeks after the bite of the infected fly and resolves spontaneously over several weeks. The chancre may ulcerate and reach a diameter of several centimeters; regional lymphadenopathy may also develop. However, the trypanosomal chancre is seldom seen in clinical practice. Thus most patients develop systemic trypanosomiasis without experiencing the symptoms of localized disease.

The development of stage 1 (hemolymphatic) disease with dissemination of the parasites is marked by fever, which may appear weeks or months after the acquisition of the infection. The fever is characterized by intermittent bouts of high temperatures lasting for several days, and extended periods may intervene during which the patient is afebrile. As the chronic illness evolves, a wide variety of other signs and symptoms develop. Lymphadenopathy is a fairly constant feature of *gambiense* trypanosomiasis. The nodes are typically discrete, movable, rubbery, and nontender. With time they frequently become indurated as fibrosis develops. Supraclavicular and cervical nodes are often visibly discernible, and enlargement of the nodes of the posterior cervical triangle, or Winterbottom sign, is a classic finding in persons infected with *T. b. gambiense*. Hepatosplenomegaly may be present as well.

Transient edema is a frequent sign during the hemolymphatic phase of the illness and can occur in the face, as well as in the hands, feet,

and other periarticular areas. Pruritus is common, and an irregular circinate rash is often present. The rash is typically located on the trunk, shoulders, buttocks, and thighs and consists of erythematous areas 5 to 10 cm in diameter with clear centers.[30] Other inconstant findings include malaise, headache, weakness, weight loss, arthralgias, and tachycardia.

Stage 2 (meningoencephalitic) disease is characterized by the insidious development of protean neurologic manifestations, accompanied by progressive alterations in the composition of the CSF.[17,18] In *gambiense* trypanosomiasis CNS findings may develop months or even years after the initiation of the infection. Irritability, personality change, and loss of the ability to concentrate may develop before changes in the CSF become evident, and this underscores the somewhat arbitrary nature of the distinction between the hemolymphatic and CNS stages of the illness. A picture of progressive indifference develops, associated with daytime somnolence, sometimes alternating with restlessness and insomnia at night. Severe headache is common. The frequency and progressive nature of the somnolence result in the use of the term *sleeping sickness*. A listless gaze reflects a loss of spontaneity, and speech may become indistinct. Extrapyramidal signs often develop and may include choreiform movements of the trunk, neck, and extremities; tremors of the tongue and fingers; and fasciculations of a variety of muscle groups. Ataxia is a frequent sign, and the patient may appear to have Parkinson disease, as a shuffling gait, hypertonia, tremors, and slurred speech develop. The final phase of the CNS disease is one of progressive neurologic impairment ending in coma and death. During the weeks and months of stage 2 disease, patients often develop signs and symptoms of hypothyroidism and adrenal insufficiency, but in general these diagnoses are not supported by laboratory data.[31,32]

Trypanosomiasis in children, which is relatively uncommon because they have less exposure to the vectors, does not differ greatly from the clinical illness seen in adults. However, the illness tends to run a more acute course, and the distinction between the hemolymphatic and CNS stages may be difficult to make.[17,33,34] Moreover, due to the protean nature of the symptoms and the lack of pathognomonic signs, the diagnosis is often missed in the early stages of the infection and is made only after neurologic impairment has developed.[35]

East African Trypanosomiasis

The most striking general difference between West African and East African trypanosomiases is that the latter illness tends to follow a more acute course, presumably reflecting a relatively less effective adaptation of *T. b. rhodesiense* to humans.[17,36,37] The onset of symptoms usually occurs a few days after the patient has been bitten by an infected tsetse fly, but the incubation period may be as long as several weeks. Typically in tourists, systemic signs of infection such as fever, malaise, and headache appear before the end of the trip or shortly after their return home. As the illness progresses, the pattern of intermittent fever develops, and rash is a nearly constant feature of the early weeks of the illness. Lymph node swelling is not prominent in *rhodesiense* trypanosomiasis, and thus the Winterbottom sign is generally absent. Persistent tachycardia unrelated to the fevers is frequently present early in the course of the illness, and in some patients death may result from arrhythmias and congestive heart failure due to pancarditis even before CNS disease develops. In general, untreated *rhodesiense* trypanosomiasis usually leads to death in a matter of weeks to months, often without a clear distinction between the hemolymphatic and CNS stages.

DIAGNOSIS

Epidemiologic information and clinical findings often combine to suggest the diagnosis of African trypanosomiasis, and a high index of suspicion should be maintained with persons who have been in endemic areas. However, there are numerous other illnesses common in the tropics that cause symptoms similar to those seen in both the early and late stages of sleeping sickness, and a definitive diagnosis of African trypanosomiasis requires demonstration of the parasite.[18,38,39]

If a chancre is present, fluid should be expressed and examined directly under light microscopy for the highly motile trypanosomes. Part of the specimen should be fixed and stained with Giemsa. Aspiration of soft lymph nodes early in the course of the infection can also be used to demonstrate the presence of parasites. This method is more effective in patients with West African trypanosomiasis because of the prominence of lymphadenopathy, but even in such patients, multiple aspirates are sometimes necessary before parasites are found. An enlarged node should be punctured and kneaded gently during aspiration, and the sample obtained should be examined directly and also after staining.

Examination of wet preparations and Giemsa-stained thin and thick smears of peripheral blood is also a sensitive method for detection of infection with African trypanosomes (see Fig. 277.1). This approach is more likely to be successful in the hemolymphatic stage of the illness, and it is much more useful in patients infected with *T. b. rhodesiense* because of the relatively high parasitemias. Because parasitemias may vary considerably from one day to the next, serial specimens should be examined. If parasites are not seen in blood from a patient whose history and clinical findings point to African trypanosomiasis as a possible diagnosis, efforts should be made to concentrate the organisms. This can be done by microscopic examination of buffy coat obtained by centrifuging 10 to 15 mL of anticoagulated blood as a wet preparation and after Giemsa staining. Miniature anion exchange columns, which retain blood cells but not trypanosomes, can also be useful in detecting parasites,[40] and refinements of these approaches are being developed.[41]

Considerable work has been done on the development of polymerase chain reaction (PCR)-based assays for the detection of African trypanosomes, and more than a dozen articles have been published on the subject.[42] Although these studies have shown clearly that PCR-based assays can have high levels of sensitivity and specificity, the lack of technical facilities in many of the areas of active transmission of the parasites makes implementation in the field difficult. Loop-mediated isothermal amplification of DNA (LAMP) methodology has also been applied to the development of assays for HAT diagnosis, but it too will require further work before it can be applied broadly in field conditions.[43,44]

Examination of the CSF is mandatory in all patients suspected of having African trypanosomiasis.[12] An increase in the CSF cell count is the first abnormality to be detected. Increased opening pressure of the fluid develops later, as do an elevated IgM level and total protein concentration. Examination of CSF processed by single or double centrifugation methods often reveals trypanosomes in patients with CNS involvement.[45] Any CSF abnormality in a patient in whom trypanosomes have been found in specimens from other sites must be viewed as indicative of CNS involvement, and this has implications for treatment that are discussed later. CSF cell counts and IgM levels may remain elevated for long periods after curative therapy.

Accurate diagnostic staging of HAT is crucial because treatment for stage 2 disease can be far more toxic than that given for stage 1 illness. WHO criteria for stage 2 disease are the presence of trypanosomes in the CSF or a whole blood cell count (WBC) greater than 5 cells/μL. The latter criterion is controversial, however, and some experts have recommended that a WBC greater than 10 cells/μL be taken as indicative of stage 2 disease.[18] This controversy has driven a search for other biomarkers that would be more accurate indicators of stage 2 disease, but to date none of the parameters investigated have found their way into use, in large measure because there is no gold standard for stage 2 disease that can serve as a benchmark for determining the accuracy of new methods.[46–48]

An additional approach to patients in whom parasites cannot be demonstrated by the previously described methods is bone marrow aspiration. Trypanosomes may be found by careful examination of Giemsa-stained specimens. Moreover, material aspirated from the bone marrow can be inoculated into special liquid culture medium, as can blood, CSF, or lymph node aspirates obtained from the patient in whom trypanosomiasis is suspected.[49] Simple agglutination tests for trypanosomes performed on cards (card agglutination trypanosomosis test [CATT])[38,39] are available commercially and are easy to use under field conditions. These card assays are the cornerstone for screening populations at risk, after which parasitologic studies are done on persons having positive results. Immune trypanolysis, a test with high positive and negative predictive values for infection with *T. b. gambiense*, detects specific antibodies by measuring the lysis of trypanosomes mixed with patient serum, but it is performed only in reference centers. Commercial rapid diagnostic tests (RDTs) are now used for the diagnosis of *T. b. gambiense,* and have the advantage of not requiring a cold chain, but

they are not appropriate for large-scale screening. HAT Sero-K-Set (Coris BioConcept; Gembloux, Belgium) and SD Bioline HAT (SD Diagnostics, Giheung-gu, South Korea) have been compared, with immune trypanolysis as a gold standard. No significant difference between RDTs was found, and both of the tests have acceptable sensitivity, but specificity has not been sufficient.[50] Thus the RDTs performed in fixed health centers require confirmation, either parasitologically or with trypanolysis. Cost concerns with RDTs remain paramount, as they would presumably increase health care costs in areas of high prevalence.

THERAPY

The treatment of HAT is complex, and currently recommended protocols have been reviewed in detail elsewhere.[18,51] Assessment of the efficacy of treatment of HAT can be difficult and prolonged, and this complicates the development of new drugs.[52] Suramin, pentamidine, and organic arsenicals have been the mainstay for treating African trypanosomiasis for more than 50 years. Eflornithine (difluoromethylornithine [DFMO], Ornidyl; Sanofi, Bridgewater, NJ), which is effective in both the hemolymphatic and CNS stages of West African trypanosomiasis, was added to the group in 1990. Therapy of *gambiense* and *rhodesiense* trypanosomiases must be individualized based on the absence or presence of CNS disease, side effects, and occasionally drug resistance[53,54] of the infecting organisms. Suramin and pentamidine do not penetrate the CNS adequately. Thus eflornithine should be used in patients with *gambiense* trypanosomiasis who have CNS disease, but because of its relative lack of activity against *T. b. rhodesiense,*[55,56] patients with stage 2 *rhodesiense* trypanosomiasis must be treated with the arsenical melarsoprol, which is highly toxic (Table 277.2). In the United States these drugs can be obtained from the Drug Service of the CDC.

Patients with the hemolymphatic stage of *gambiense* trypanosomiasis and normal CSF (stage 1 disease) should be treated with pentamidine isethionate (Lomidine).[57] The dosage for both adults and children is 4 mg/kg, up to 300 mg/day, intravenous (IV) or intramuscular (IM) for 10 days. IM injections of pentamidine are painful and may cause sterile abscesses. Immediate side effects of pentamidine can include nausea, vomiting, hypotension, and tachycardia. These reactions are generally transient and do not warrant discontinuation of therapy. Other side effects include nephrotoxicity, elevation of hepatic transaminases, neutropenia, rashes, and hypoglycemia.

Eflornithine is highly effective in both the hemolymphatic and CNS stages of *gambiense* trypanosomiasis.[58] This drug produces a dramatic reduction of symptoms and rapid clearing of parasites from blood and CSF. For adults the recommended dosage is 400 mg/kg per day IV in four divided doses for 14 days, and for children it is 500 to 600 mg/kg per day on the same schedule. Anemia, leukopenia, and thrombocytopenia are frequent in patients treated with eflornithine, but generally they are not clinically significant. Seizures and hearing loss have been reported rarely. Major disadvantages of eflornithine are the requirement that it be given IV, the amount of drug that must be given, and the duration of therapy. These factors make widespread use difficult, leaving pentamidine as the better choice for stage 1 *gambiense* disease. For patients with *gambiense* disease and CNS involvement, until recently eflornithine has been the drug of choice because it is as effective as melarsoprol but has far fewer side effects. However, recent field trials of nifurtimox (Bay 2502 and Lampit; Bayer, Leverkusen, Germany) in combination with eflornithine (nifurtimox-eflornithine combination treatment, or NECT) for stage 2 *T. b. gambiense* disease have been carried out.[59,60] NECT is given as eflornithine 200 mg/kg every 12 hours IV for 7 days plus nifurtimox 15 mg/kg/day orally in three divided doses for 10 days.

TABLE 277.2 Drugs Recommended for Treatment of the African Trypanosomiases

	CLINICAL STAGE	
CAUSATIVE AGENT	**1**	**2**
Trypanosoma brucei gambiense	Pentamidine Alternative: suramin	Eflornithine Alternatives: eflornithine/nifurtimox; melarsoprol
Trypanosoma brucei rhodesiense	Suramin	Melarsoprol

The safety and efficacy of the combined regimen have been amply demonstrated,[61–63] and in comparison with eflornithine monotherapy, NECT is markedly less complicated to administer and costs less overall. Thus, if available, NECT is the recommended treatment for stage 2 *T. b. gambiense* disease. The extent to which human immunodeficiency virus coinfection affects the course of African trypanosomiasis and the efficacy of treatment is not clear and merits further investigation.[64,65]

Suramin (Bayer 205, Naphuride, Antrypol; Bayer, Leverkusen, Germany) is the first-choice drug for stage 1 *rhodesiense* trypanosomiasis. A 100- to 200-mg test dose is recommended, although anaphylactic reactions are rare. The treatment regimen for both adults and children, beginning 24 hours after the test dose, is 5 mg/kg on day 1, 10 mg/kg on day 3, and 20 mg/kg on days 5, 11, 17, 23, and 30 (1 g/day max). The exact spacing of the doses most likely is not important because suramin has a long half-life. The drug is administered by slow IV infusion of a freshly prepared 10% aqueous solution. Suramin causes a number of side effects and must be administered under the supervision of a physician knowledgeable on its use. Approximately 1 patient in 20,000 has an immediate, severe, and potentially fatal reaction to the drug consisting of nausea, vomiting, seizures, and shock. A number of less severe reactions can also occur, including fever, pruritus, photophobia, arthralgias, and skin eruptions. The most important side effect of suramin is renal damage. Transient proteinuria is often seen during treatment. Urinalysis should be done before each dose, and if proteinuria increases or casts and red cells appear in the urine sediment, the drug should be discontinued. Suramin should not be used in patients with renal insufficiency.

The drug of choice for *rhodesiense* trypanosomiasis with CNS involvement is the arsenical melarsoprol (mel B, Melarsen-BAL, Arsobal).[66–69] Melarsoprol cures both stages of the disease. Thus it is also indicated for treatment of the hemolymphatic stage in patients in whom suramin or pentamidine has failed or could not be tolerated. However, it should never be the first choice for therapy of stage 1 trypanosomiasis because of its relatively high toxicity. The "short course" of melarsoprol currently recommended has been shown to be noninferior to the previous treatment course for *T. b. rhodesiense,*[70,71] which was administered over several weeks and was more toxic. The short-course regimen is 10 daily doses of 2.2 mg/kg IV given with prednisolone 1 mg/kg. Melarsoprol is a highly toxic drug and should be administered with great care. The most important side effects involve the CNS. A substantial percentage of patients treated with melarsoprol develop reactive encephalopathy. The risk of this immune-mediated phenomenon and its associated mortality is reduced significantly by concomitant administration of prednisolone. Thus all patients treated with melarsoprol should be given prednisolone at a dose of 1 mg/kg up to 40 mg per day, starting a day or two before initiation of melarsoprol therapy, continued through the period of treatment, and then tapered over several days.[72] Clinical indications of reactive encephalopathy include high fever, headache, tremor, impaired speech, seizures, and finally coma and death. Melarsoprol should be discontinued at the first sign of encephalopathy. It may be restarted cautiously with smaller doses a few days after the signs have resolved.

A number of other side effects are associated with melarsoprol therapy. Extravasation of the drug results in intense local reactions and, as with administration of other heavy metals, abdominal pain and vomiting are commonly observed. Jarisch-Herxheimer-type reactions have been reported, as have nephrotoxicity, abnormal liver function tests, and myocardial damage.

If a patient with *gambiense* CNS disease cannot tolerate eflornithine, or if the latter is not available, melarsoprol should be given at the dose listed earlier. This compressed regimen for stage 2 *gambiense* disease has been shown in a randomized trial to be equally effective and no more toxic than the traditional regimen outlined previously.[70]

Finally, the oral drug fexinidazole was recently shown in a randomized phase 2/3 trial to be noninferior to NECT for the treatment of patients with stage 2 gambiense HAT.[73] If fexinidazole is approved by regulatory authorities and becomes available commercially, the fact that it is an oral drug may ultimately result in its becoming the definitive tool in

the elimination of West African HAT. Fexinidazole is discussed at some length in Chapter 42.

PREVENTION

The trypanosomiases constitute complex public health and epizootic problems in many developing countries in Africa. Control programs that focus on eradication of vectors and drug treatment of infected people have been in operation in most endemic regions for decades. As noted, enormous progress has been made to the extent that a vision for the elimination of HAT as a public health problem by 2020 has been developed. Individuals can reduce their risk of acquiring infections with trypanosomes by avoiding areas known to harbor infected insects, wearing clothing that reduces the biting of the flies, and using insect repellent. Chemoprophylaxis is not recommended because of the high toxicity of the drugs that are active against African trypanosomes, and no vaccine is available to prevent transmission of the parasites.

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278 *Toxoplasma gondii*

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SHORT VIEW SUMMARY

Definition

- *Toxoplasma gondii* is a ubiquitous coccidian protozoan that usually causes asymptomatic infection in humans but can cause significant disease in congenitally infected infants and immunodeficient patients and occasionally in immunocompetent individuals.

Epidemiology

- Toxoplasmosis is a worldwide zoonosis that can infect a wide range of animals and birds.
- Transmission to humans is mainly by ingestion of viable tissue cysts in meat or of oocysts in food or water. Transmission can also occur via the placenta or a transplanted organ.
- Positive immunoglobulin G (IgG) representing prior infection increases with age; seroprevalence is ≈11% in the United States and up to ≈78% in other parts of the world.
- Congenital transmission occurs almost exclusively when a seronegative mother becomes infected during pregnancy but can also occur among immunosuppressed mothers who reactivate toxoplasmosis during gestation. Retinochoroiditis can occur after congenital infection or recently acquired infection. Infection in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome patients almost always results from reactivation of latent infection. Among organ transplant patients, disease can result from either newly acquired infection from the transplanted organ or from reactivation of latent infection in the setting of hematopoietic cell transplantation. Reactivation has also been observed among patients who are immunosuppressed with the expanding armamentarium of biologics that significantly depress adaptive immunity.

Microbiology

- *Toxoplasma* organisms are exclusively intracellular. The sexual phase occurs in felines. Excreted oocysts require 1 to 5 days to become infectious. Tachyzoites actively replicate in essentially all cell types. Tissue cysts with intracystic bradyzoites maintain organism viability during latent infection.
- Tachyzoites replicate well in tissue culture and are responsible for clinical manifestations during primary infection or reactivation of latent infection.
- Multiple strains are identified by genotyping. Strains differ in virulence, with the most virulent strains so far reported being found in Latin America.

Diagnosis

- Direct detection of the organism is by polymerase chain reaction (PCR) assays, histopathology with immunoperoxidase staining, or, rarely, by tissue culture or mouse inoculation.
- Serologic assays can help distinguish acute from chronic infection and can identify patients at risk for reactivation. Immunoglobulin M (IgM)-positive test results should be confirmed at a reference laboratory (e.g., the Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory [PAMF-TSL]; www.pamf.org/serology/; 650-853-4828).
- Maternal infection is often asymptomatic; serology shows acute infection, and IgM-positive test results must be confirmed at a reference laboratory. Congenital infection may be asymptomatic or appear with neurologic or ocular manifestations; this form is diagnosed in utero by PCR of amniotic fluid or after birth by serology or PCR.
- Chorioretinitis may be asymptomatic or show visual loss; ophthalmologic examination can reveal typical lesions, and PCR of vitreous or aqueous fluid should be considered in cases with atypical lesions or inadequate response to therapy. The Goldmann-Witmer coefficient (anti-*Toxoplasma* IgG/total IgG in aqueous fluid divided by anti-*Toxoplasma* IgG/total IgG in serum) can be helpful.
- HIV-infected patients usually present with focal neurologic symptoms. Patients are usually IgG positive and IgM negative, computed tomography or magnetic resonance imaging may show one or more contrast-enhancing lesions, cerebrospinal fluid PCR is specific but not sensitive, brain biopsy sensitivity is improved by immunoperoxidase staining, and diagnosis is often presumptive and extends to a response to empirical therapy.
- Immunodeficient patients present with encephalopathy, seizures, pneumonia, and fever. Diagnosis is based on positive PCR or histopathology. Hematopoietic stem cell transplantation (HSCT) requires pretransplant serology in the recipient; solid-organ transplantation requires pretransplant serology in the donor and recipient.

Therapy

- Immunocompetent patients: These patients usually require no therapy if asymptomatic; they may benefit from treatment if symptoms are severe or persist.
- Immunocompromised patients: The therapy of choice is pyrimethamine (200-mg load, then 50–75 mg/day) plus sulfadiazine (1000–1500 mg every 6 hours) plus leucovorin (10–20 mg/day). The dosage is then decreased to maintenance dosing of pyrimethamine (25–50 mg/day) plus sulfadiazine (500–1000 mg every 6 hours) plus leucovorin (10–20 mg/day) after 3 to 6 weeks if a clinical response occurs. Alternatives include pyrimethamine, as above, plus leucovorin plus either clindamycin (intravenous [IV] or oral [PO]; 600 mg every 6 hours) or atovaquone (1500 mg every 12 hours). Other alternatives include trimethoprim-sulfamethoxazole (TMP-SMX) (IV or PO; 5 mg/kg of TMP every 12 hours) or sulfadiazine plus atovaquone. Corticosteroids are given only for clinically significant edema or mass effect, and anticonvulsants are given only after a seizure.
- HIV patients: Start antiretroviral therapy (ART) after 2 to 3 weeks. Consider stopping anti-*Toxoplasma* medications if the CD4 count is >200 cells/mm^3 for more than 6 months. High relapse rate occurs without ART and maintenance therapy.
- Acute infection in pregnant women less than 14 weeks of gestation: Give spiramycin (1 g every 8 hours; available at no cost through the PAMF-TSL and the US Food and Drug Administration) until delivery. If infection in the fetus is documented or suspected, or if maternal infection at 14 weeks of gestation or later, give pyrimethamine (50 mg every 12 hours for 2 days, then 50 mg/day) plus sulfadiazine (initial dose 75 mg/kg, followed by 50 mg/kg every 12 hours; maximum, 4 g/day), plus folinic acid (10–20 mg/day). Before 14 weeks of gestation, give no pyrimethamine or leucovorin.
- Congenitally infected infant: Give pyrimethamine (1 mg/kg every 12 hours for

SHORT VIEW SUMMARY—cont'd

2 days, then 1 mg/kg/day for 2 or 6 months); then this dose is given every Monday, Wednesday, and Friday; plus sulfadiazine (50 mg/kg every 12 hours) plus folinic acid (10 mg three times weekly) for at least 12 months.
- Chorioretinitis patients: If therapy is clinically indicated, give pyrimethamine (100-mg loading dose over 24 hours, then 25–50 mg/day) plus sulfadiazine (1 g every 6 hours) plus leucovorin (10–20 mg/day) for 4 to 6 weeks. TMP-SMX, one single-strength tablet every day, can prevent relapse.

Prevention and Prophylaxis
- Avoid undercooked meat and potentially contaminated food or water; clean cat litter daily.
- Immunocompromised patients: Give TMP-SMX, one double-strength or single-strength tablet daily. An alternative is dapsone (50 mg/day) plus pyrimethamine (50 mg/wk) plus leucovorin (25 mg/wk). If the patient has HIV, start if the CD4 count is less than 100 to 200 cells/mm^3; discontinue if the patient is on ART and the CD4 count is greater than 200 cells/mm^3 for at least 3 months (primary prophylaxis) or 6 months (chronic maintenance). For *Toxoplasma* seropositive HSCT recipients, start TMP-SMX after engraftment and/or consider preemptive strategy with weekly peripheral blood *Toxoplasma* PCR until posttransplantion day +100. If the patient is a solid-organ transplant recipient, start at transplantation if classified as seropositive donor (D^+) or seropositive recipient (R^+).

Although *Toxoplasma gondii* infects a large proportion of the world's human population, it is an uncommon cause of disease. Certain individuals, however, are at high risk for severe or life-threatening disease because of this parasite. These include congenitally infected fetuses and newborns and immunologically impaired individuals. Congenital toxoplasmosis is the result of maternal infection acquired during gestation, an infection that is most often clinically inapparent. In immunodeficient patients toxoplasmosis most often occurs in persons with significant defects in T-cell and/or B-cell–mediated immunity, such as those receiving corticosteroids, anti–tumor necrosis factor (TNF) therapies, certain monoclonal antibodies, or cytotoxic drugs, and in those with hematologic malignancies, organ transplants, or acquired immunodeficiency syndrome (AIDS). In the vast majority of otherwise immunocompetent individuals, primary or chronic (latent) infection with *T. gondii* is asymptomatic; after the acute infection a small percentage suffer chorioretinitis, lymphadenitis, mononucleosis-like syndrome, flulike symptoms, or, even more rarely, hepatitis, pneumonia, brain abscesses, myocarditis, and polymyositis.[2]

T. gondii was first observed in the North African rodent *Ctenodactylus gundi* by Nicolle and Manceaux in 1908[2] and was recognized as a cause of human disease in an 11-month-old congenitally infected child by Janku[3] in 1923. It was reported as a cause of encephalitis by Wolf, Cowen, and Paige,[4] who in 1939 observed it in a newborn who presented with seizures, intracranial calcifications, hydrocephalus, and chorioretinitis.

Although relatively few cases of severe toxoplasmosis in adults were reported during the ensuing years, the remarkable report in 1968 by Vietzke and his colleagues,[5] from the National Cancer Institute of the National Institutes of Health, highlighted *T. gondii* as a cause of life-threatening infection in patients with malignancy, predominantly in those with hematologic malignancies. Brain involvement with focal areas of encephalitis was the primary finding at autopsy in these patients. Since that time, several hundred cases in non-AIDS immunodeficient patients have been recorded in the literature.[6] In 1983 the first report of toxoplasmosis in AIDS patients appeared.[7] Toxoplasmic encephalitis (TE) subsequently was recognized as the major cause of space-occupying lesions in the brains of these patients, almost all of whom had serologic evidence of prior exposure to the parasite.[7] Between 2003–12 more than 6000 estimated cases of toxoplasmosis occurred in the United States, based on International Classification of Disease(s)–9 coding of privately insured patients: 38% with eye disease, 5% with meningoencephalitis, and 45% with unspecified toxoplasmosis.[8] Despite the significant advances that have been achieved in the recent past, major challenges remain in the areas of prevention and management of the acute infection in pregnancy, the fetus, and the newborn[9]; in understanding the correlation between parasite strains and geographic origin versus disease outcomes[10]; immune responses in humans[11]; contribution of the chronic infection to human behavior and psychiatric and other disorders[12,13]; and in the understanding and treatment of toxoplasmic chorioretinitis[14] and infection in immunocompromised individuals.[1,6,15]

ETIOLOGY

T. gondii is a coccidian parasite of felids, with humans and other warm-blooded animals serving as intermediate hosts. It belongs to the subphylum Apicomplexa, class Sporozoa, and can exist in many forms: macrogametes and microgametes, the oocyst (which releases sporozoites), the tissue cyst (which contains and may release bradyzoites), and the tachyzoite (Fig. 278.1).[16]

Population genetic analysis has demonstrated that, at least within Europe and North America, most organisms isolated from both domesticated animals and humans can be grouped into one of three clonal genotypes—types I to III—that may identify clinically relevant biologic differences.[17] Clear differences have been observed in the frequency of parasite genotypes when *T. gondii* isolates from animals were compared with those of humans. Type III strains are common in animals but observed significantly less often in cases of human toxoplasmosis; most cases in humans in Europe and North America are caused by type II strains. Type II strains are significantly more often associated with reactivation of chronic infections and accounted for 65% of strains isolated from AIDS patients.[18] Both type I and type II strains have been associated with human congenital toxoplasmosis.[18–21] Multiple genotypes have been associated with ocular disease; in Germany an unusual nonreactive serotype was associated with ocular disease and with more frequent recurrences.[22–24] Atypical and recombinant strains have been identified with increasing frequency in regions other than the United States and Europe and from animals other than humans and domestic animals; some of these strains appear to be associated with more severe disease, suggesting greater virulence, even in immunocompetent individuals.[25,26] The most exhaustive studies have now identified six major population clades,[27] although detailed sequence analysis indicates there is a varied amount of genetic exchange within and between these clades.[28,29] Hence, although the "three-dominant-strain" paradigm is holding for humans in Europe and North America, the situation appears much more complex in other regions and in other animal hosts.

ORGANISM STAGES

Oocyst

Cats eventually shed oocysts after they ingest any of the forms of the parasite, at which time an enteroepithelial cycle begins. This sexual form of reproduction begins when the parasites penetrate the epithelial cells of the small intestine and initiate development of asexual and sexual (gametogony) forms of the parasite. Oocyst wall formation begins around the fertilized gamete, and when still immature, oocysts are discharged into the intestinal lumen by rupture of intestinal epithelial cells.[16] Unsporulated oocysts are subspherical to spherical and measure 10 × 12 µm in diameter (see Fig. 278.1A). Oocysts are formed in the small intestine only in felids and are excreted in the feces for periods varying from 7 to 20 days. More than 100 million oocysts may be shed in the feces in a single day.[16] Sporulation, required for oocysts to become infectious, occurs outside the cat within 1 to 5 days, depending on temperature and the availability of oxygen. Sporulated oocysts contain two sporocysts (see Fig. 278.1A), each of which contains four sporozoites. Maturation is more rapid at warm temperatures (2–3 days at 24°C compared with 14–21 days at 11°C).[16] Oocysts may remain viable for as long as 18 months in moist soil; this results in an environmental reservoir from which incidental hosts may be infected. Recent clues to