[Frontiers in Bioscience 9, 706-723, January 1, 2004]

PARASITIC DISEASES OF THE HEART

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. American trypanosomiasis (Chagas' disease)
- *3.1. The parasite and mechanisms of transmission*
- *3.2. Clinical manifestations*
  - *3.2.1. Acute and indeterminate phases of Chagas' disease*
  - *3.2.2. Chronic Chagas' heart disease*
  - *3.2.3. Chronic gastrointestinal Chagas' disease (megadisease)*
  - *3.2.4. Immunosuppression, HIV, and Trypanosoma cruzi infection*
  - *3.2.5. Congenital Chagas' disease*
- *3.3. Epidemiology of Chagas' disease*
  - *3.3.1. The burden of Chagas' disease*
  - *3.3.2. The Southern Cone Initiative*
  - *3.3.3. Chagas' disease in Mexico*
  - *3.3.4. Epidemiology of Trypanosoma cruzi infection in the United States*
- *3.4. Transmission in the United States by blood transfusion and organ transplantation*

4. Sleeping sickness (African trypanosomiasis)
- *4.1. The parasites and mechanisms of transmission*
- *4.2. Epidemiology*
- *4.3. Pathogenesis and pathology*
- *4.4. Clinical manifestations*
- *4.5. Diagnosis*
- *4.6. Treatment and prevention*

5. Amebic pericarditis (Entamoeba histolytica)
6. Hydatid disease of the heart caused by Echinococcus granulosus
7. Toxoplasmosis
- *7.1. Life cycle and epidemiology*
- *7.2. Toxoplasma myocarditis*

8. Cysticercosis
9. Trichinosis
10. Other parasites
11. Conclusions
12. References

1. ABSTRACT

The following chapter is one of a series of chapters in the volume entitled *Infections of the Myocardium* appearing in *Frontiers in Bioscience.* The full table of contents can be found at http://www.bioscience.org/current/special/tanowitz.htm. In this chapter, we review several parasitic infections involving the myocardium and pericardium. The most widely studied parasitic infection affecting the heart is Chagas' disease or American trypanosomiasis. In this chapter we describe issues relating to Chagas' disease not covered in detail in other chapters. African trypanosomiasis may also cause a myocarditis. The protozoan parasite, *Entamoeba histolytica* rarely causes a pericarditis while *Toxoplasma gondii* may cause myocarditis, usually in immunocompromised hosts. The larval forms of the tapeworms *Echinococcus* and *Taenia solium* may cause space-occupying lesions of the heart. Severe infection with the nematode *Trichinella spiralis* may cause myocarditis.

2. INTRODUCTION

In recent years interest in parasitic diseases of humans has increased. This heightened interest is the result of several factors including increased tourism, immigration, AIDS and wars. With the exception of Chagas' disease, the subject of parasitic diseases of the human heart has not received much attention. In this regard, it has been nearly forty years since Kean and Breslau published their monograph on parasites of the human heart (1) and nearly a decade since Tanowitz and colleagues published reviews on

the same subject (2, 3). Parasites can have direct and indirect effects on the heart. For example whereas *Trypanosoma cruzi* and *Toxoplasma gondii* directly cause myocarditis, infection with *Plasmodium falciparum* may cause pulmonary edema and a shock-like syndrome, thus indirectly affecting the heart (4). Moreover, infections with *Schistosoma* sp. may cause pulmonary hypertension and cor pulmonale without directly infecting the myocardium (5). In this chapter, however, we have only chosen to deal with parasites that directly cause myocarditis, pericarditis or space-occupying lesions of the myocardium.

3. CHAGAS' DISEASE

In the following section topics of special interest in Chagas' disease are discussed. Other chapters in this volume, *Infections of the Myocardium*, cover pathology, clinical syndromes, and clinical management, including cardiac imaging and immunology. In addition, other chapters describe the role of nitric oxide, endothelin and bradykinin in the pathogenesis of chagasic heart disease (http://www.bioscience.org/current/special/tanowitz.htm).

3.1. The parasite and mechanisms of transmission

Chagas' disease is caused by the protozoan parasite, *Trypanosoma cruzi.* Although there are many members of the genus to which *T. cruzi* belongs, only it and two African trypanosome subspecies are capable of causing disease in humans. *T. cruzi* has a complex life cycle that involves mammalian hosts and insect vectors. The vectors, often called triatomines or kissing bugs, become infected when they take a blood meal from mammals that have circulating trypomastigotes, which are non-dividing but infective forms of the parasite. Once inside the insect midgut the parasites transform into epimastigotes, which have a distinct morphology, and these organisms then multiply extracellularly. After migration to the hindgut, epimastigotes differentiate into non-dividing metacyclic trypomastigotes, which are then discharged with the feces when the bug takes a subsequent blood meal. Transmission to a second mammalian host occurs when breaks in the skin, mucous membranes, or conjunctivas are contaminated with insect feces containing infective metacyclic forms. The parasites can adhere to and penetrate a variety of host cell types and, having done so transform into amastigotes, which multiply intracellularly. When amastigotes fill the host cell, they differentiate into trypomastigotes, which are released as the cell ruptures. The released parasites invade adjacent tissues and spread via the lymphatics and bloodstream to distant sites where they go through further cycles of intracellular multiplication. As they cycle asynchronously in this manner humans maintain parasitemias infective for vectors, and thus the cycle of transmission is completed. *T. cruzi* can also be transmitted by blood transfusion by individuals chronically harboring the parasite (6-8), in laboratory accidents (9), and from mother to fetus (10).

3.2. Clinical manifestations of Chagas' disease

3.2.1. Acute and indeterminate phases of Chagas' disease

A chagoma, which is an indurated erythematous lesion at the site where *T. cruzi* entered 10-14 days earlier, can be the first sign of acute Chagas' disease (11). If the parasite enters through a conjunctiva, the patient may develop painless unilateral periorbital edema, which is called Romaña's sign. Dissemination of the parasites from the site of initial multiplication may be accompanied by malaise and fever, as well as edema of the face and lower extremities, generalized lymphadenopathy, and hepatosplenomegaly. Occasionally humans develop a morbilliform rash called schizotrypanides. Heavy parasitism of muscles can develop, and symptomatic myocarditis occurs in a small proportion of patients, occasionally resulting in fatal congestive heart failure (12, 13). Non-specific ECG abnormalities can be present, but the life-threatening rhythm disturbances that often are part of chronic cardiac Chagas' disease usually do not occur. In patients with acute Chagas' disease *T. cruzi* also can invade the central nervous system (14), but in general, neurological findings are uncommon. Meningoencephalitis is a rare occurrence and it is associated with a poor prognosis (15). The signs and symptoms of acute Chagas' disease resolve spontaneously in 4-8 weeks in the vast majority of patients, who then enter the *indeterminate phase* of the infection. This phase is characterized by a lack of symptoms, life-long subpatent parasitemia, and detectable antibodies to *T. cruzi* antigens.

3.2.2. Chronic Chagas' heart disease

Only 10-30% of patients with chronic *T. cruzi* infections ever develop symptomatic chronic Chagas' disease. Symptoms may first appear years or even decades after the infection was acquired. Myocardial dysfunction is the most frequent consequence of chronic *T. cruzi* infection and during the past decade convincing evidence has accumulated indicating that the persistent presence of parasites in heart muscle stimulates an inflammatory process (Figure 1) leading to organ dysfunction and in many cases death (16-19). The inflammatory process can cause a variety of dysrhythmias, including atrial bradyarrhythmias and fibrillation; bundle branch blocks, often of the right bundle; premature ventricular contractions; and third degree AV block. These abnormalities can cause dizziness and syncope, and sudden death is common (20, 21). Fibrosis and cardiomyopathy (Figure 2) can also develop, resulting in congestive failure, clot formation with thromboembolization and ventricular apical aneurysm. (22).

3.2.3. Chronic gastrointestinal Chagas' disease (mega disease)

The gastrointestinal tract is commonly affected in chronic *T. cruzi* infection. Symptoms caused by megaesophagus are the most typical clinical manifestations of megadisease, although problems related to megacolon are common as well. Patients with megaesophagus have complaints similar to those of idiopathic achalasia such as cough, chest pain, dysphagia, odynophagia, and regurgitation (23, 24). Parotid gland hypertrophy and hypersalivation also have been observed. Aspiration can occur, and repeated episodes of aspiration pneumonitis are common in patients with severe esophageal dysfunction who do not obtain medical attention. Poor nutritional status can combine with pulmonary infection to result in death in patients

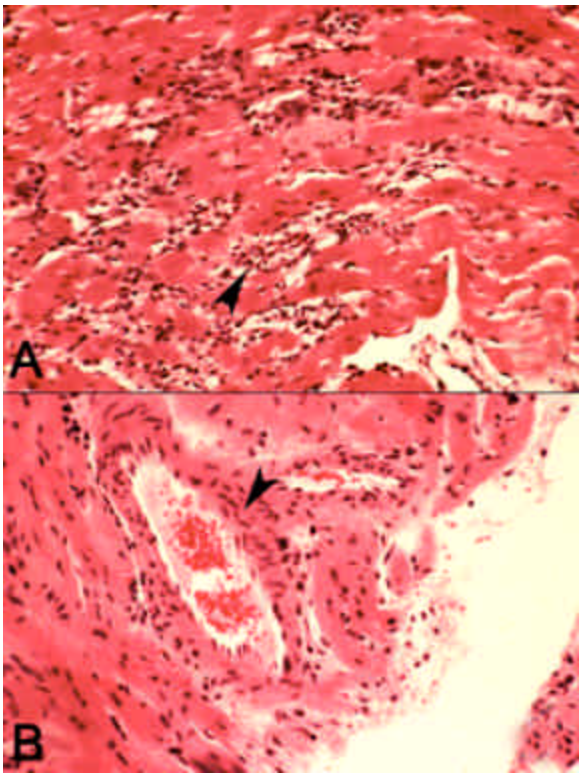

Figure 1. Acute chagasic myocarditis. A. Myocardial inflammation (arrow). B. Acute vasculitis and myocardial inflammation.

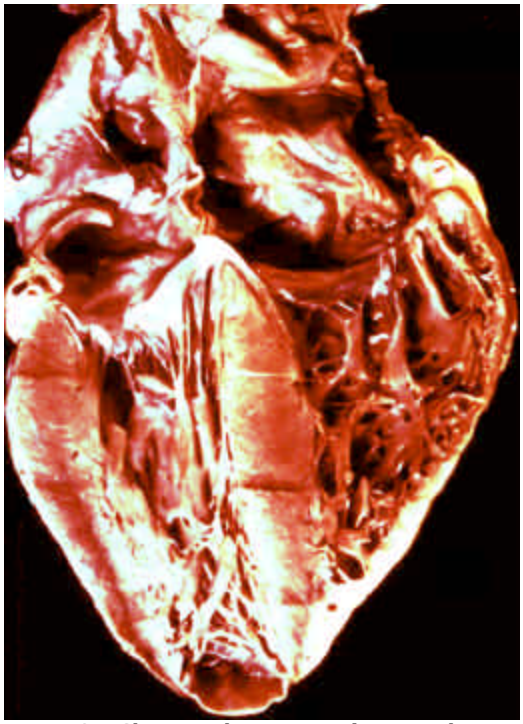

Figure 2. Chronic chagasic cardiomyopathy. Four-chamber enlargement is present, as is an apical aneurysm. (Permission from the Armed Forces Institute of Pathology, Washington, D.C.)

with megaesophagus, although this is uncommon today.

Patients with megacolon suffer from chronic constipation and abdominal pain. Patients with advanced megacolon can go for weeks between bowel movements, and acute obstruction, occasionally with volvulus, can lead to perforation, septicemia, and death (22, 25). Surgery is indicated in advanced cases.

3.2.4. Immunosuppression, HIV, and *Trypanosoma cruzi* infection

Immunosuppression of patients chronically infected with *T. cruzi* can lead to reactivation of the infection, sometimes with an intensity that is atypical of acute Chagas' disease in immunocompetent patients. Reactivation of *T. cruzi* in immunosuppressed patients who are chronically infected occurs in a minority of patients, but the exact incidence is not known. A handful of reports of reactivation after renal transplantation have appeared, and in rare cases the central nervous system was involved (26-28). Although chronic *T. cruzi* infection should not be considered a contraindication for renal transplantation, the possibility of reactivation should be kept in mind during follow-up care. Cardiac transplantation is an option in persons with severe Chagas' heart disease, and more than 100 *T. cruzi*-infected patients have undergone the procedure in Brazil and the United States (29, 30). It is noteworthy that long-term survival in these patients is greater than in patients transplanted for other types of cardiac disease. Endomyocardial biopsies have demonstrated that the parasites have invaded the transplanted hearts. Interestingly patients who have had transplants for chagasic heart disease often develop skin lesions containing high numbers of intracellular parasites (31). Such lesions have not been reported in *T. cruzi*-infected patients who have received other organs, nor have they occurred in persons with AIDS.

Serious reactivation disease can occur in persons co-infected with *T. cruzi* and AIDS. Several dozen such instances have been described (32-34). It merits mention that a large proportion of these patients developed *T. cruzi* brain abscesses. This does not occur in immunocompetent individuals with chronic Chagas' disease. Reactivation in the form of myocarditis is also common (35). Calculations based on the epidemiology of both HIV and *T. cruzi* in Latin America suggest that the incidence of *T. cruzi* brain abscesses in co-infected persons is extremely low, and thus prophylactic *T. cruzi* treatment cannot be recommended for all dually infected patients. The diagnosis of *T. cruzi* brain abscesses in HIV-infected persons is complicated by the fact that in imaging studies the lesions of cerebral toxoplasmosis are similar. The role of highly active anti-retroviral therapy in reducing the likelihood of *T. cruzi* reactivation is not known.

3.2.5. Congenital Chagas' disease

Congenital transmission of *T. cruzi* is a public health concern in endemic areas, as roughly five percent of infants born to infected mothers are in turn infected with the parasite (10). The usefulness of benznidazole or nifurtimox in preventing congenital transmission of *T. cruzi* has not been

studied, and the safety of these two agents in pregnancy has not been determined. Since primary prevention of congenital transmission is not an option, then, efforts need to be focused on diagnosing and treating infants with congenital Chagas' disease. As a first step, pregnant women at risk for *T. cruzi* infection should be tested serologically, and infants born to seropositive mothers should be evaluated parasitologically. Doing this is difficult in many endemic areas, however, because a large portion of pregnant women only come to health care facilities immediately before giving birth and coordinating serologic testing in this context can be difficult.

Testing infants for parasite-specific IgG is of no use because the results would only reflect the mother's serologic status, and unfortunately, testing for *T. cruzi*-specific IgM is not an effective approach for identifying infected infants. There are, however, several parasitologic options. Methods for detection of the parasite in blood samples taken around the time of birth include microhematocrit (36), hemoculture (37), and PCR assays (38). These approaches have sensitivities that vary with the geographic region in which they are done, the volume of blood studied, and the skills of the persons doing the tests. An alternative to examining for parasites around the time of birth is to perform IgG serology at six months of age. At that time maternal anti-*T. cruzi* antibodies should no longer be present and infected babies by then should have detectible levels of specific antibodies. This approach cannot be used in many endemic areas, however, because the percentage of mothers who return with their babies for follow-up is low. As was clearly evident at the International Colloquium on Congenital Chagas' Disease held in Cochabamba, Bolivia (November, 2002), there is no consensus regarding which approach for diagnosing congenital Chagas' disease is best. The approaches employed should in large measure be determined by the capabilities of the local laboratories and the characteristics of the patient population. Identifying infants with congenital *T. cruzi* infection should be a priority, moreover, given the roughly five percent transmission rate and the fact that more than 90 percent of babies treated before their first birthdays are cured parasitologically. Unfortunately, despite the epidemiological importance of congenital Chagas' disease and the window of opportunity to give curative therapy, with the exceptions of Chile and Paraguay, comprehensive programs for identifying and treating affected babies generally have not been implemented in endemic countries. Many thousands of are born each year with congenital *T. cruzi* infection. The number will decline gradually as vector-borne transmission comes under control.

The treatment of acute Chagas' disease is with benznidazole or nifurtimox. The issue of the drug treatment of chronic Chagas' disease, however, remains controversial (39).

3.3. EPIDEMIOLOGY OF CHAGAS DISEASE

3.3.1. The burden of Chagas' disease

Despite the fact that only 10-30% of *T. cruzi*-infected persons will ever develop chronic symptomatic Chagas' disease, the burden of mortality and disability in the endemic countries is enormous. For example, in the early 1990s it was estimated that in Brazil the yearly cost of early pension expenses and time lost by workers due to Chagas'-associated disability, as well as medical care, including pacemakers and surgery for gastrointestinal Chagas' disease, totaled several billion dollars. Calculations applied in other endemic countries have led to similar conclusions regarding the economic impact of Chagas' disease, and it is currently estimated that its total annual cost in all endemic countries is more than US$ 8 billion (40). When considered from a global perspective, Chagas' disease represents the third greatest tropical disease burden, after malaria and schistosomiasis. Despite the reductions in transfusion-associated and vector-borne transmission of *T. cruzi* achieved in many countries in recent years, this burden will be borne by the affected nations on a continuing basis, as millions of *T. cruzi*-infected persons gradually develop symptomatic Chagas' disease.

3.3.2. The Southern Cone Initiative

Even though the situation regarding the overall prevalence of *T. cruzi* infection and its impact in endemic countries is bleak, the situation relating to the current incidence rates of transmission is markedly brighter. In 1991 the countries of the Southern Cone of South America (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay) began an ambitious program called the Southern Cone Initiative (SCI) that is directed at interrupting the transmission of *T. cruzi* (41). The primary focus of the program is control of the triatomine vectors that transmit the parasite. This aspect of SCI involves spraying infested houses with residual insecticides, housing improvement to reduce infestation, and education of persons at risk about the cycle of transmission and the disease. The second major element of the program is the elimination of transfusion-associated transmission of the organism through improvement in serologic screening in blood banks. This effort involves technical enhancement of existing programs in addition to expanding coverage to all donated blood. During the first eight years of the initiative US$340 million was invested in SCI by the participating nations. Over two million houses have been treated with insecticides and donor screening programs have been expanded on a widespread basis.

After 12 years of activity, the SCI has achieved an impressive level of success. Ongoing epidemiologic surveillance has shown that transmission has been interrupted in vast regions of several endemic countries. Progressive reduction in prevalence rates in the younger age groups and a substantial reduction in the percent of *T. cruzi* infection among blood donors stand as clear evidence of the success of the initiative (42). Uruguay was certified free of transmission in 1997, and certification of Chile followed in 1999. Argentina and Brazil are expected to follow suit within several years. The highest prevalence rates of *T. cruzi* infection in the participating countries are found in Bolivia; the program has achieved the lowest rates of penetration there. The current goal is to eliminate *T. cruzi* transmission to humans throughout the Southern Cone by 2010. This would provide enormous social and medical benefits as well as substantial economic returns on the funds invested in the initiative. Programs similar to the

SCI have been initiated in the Andean countries and in Central America during the past five years, and major progress is being achieved by these efforts as well.

Finally, the impressive progress made to date in reducing vector-borne transmission of *T. cruzi* in Latin America has been achieved by straightforward, low-tech methods. Although enormous progress has been made in recent decades in understanding the genetics of *T. cruzi*, the immunology of its interaction with its mammalian hosts, and the pathogenic mechanisms that result in symptomatic Chagas' disease, essentially none of this information has contributed to the striking success in reducing transmission of the parasite from insects to people. Similarly, this vast amount of basic information has not resulted in the development of new drugs. This reality may have important implications for the control of other infectious diseases, both in industrialized countries as well as in developing nations.

3.3.3. Chagas' disease in Mexico

The epidemiology of Chagas' disease in Mexico is of major interest because it has been studied less intensively there than in other endemic countries and also because approximately eight million Mexicans now live in the United States. Reports describing patients with Chagas' disease from almost all Mexican states and the Federal District have been published. Moreover, in a national serologic survey of blood donors in Mexico carried out in the mid-1990s, a 1.5% overall prevalence rate of *T. cruzi* infection was found, with the highest rates in the states of Hidalgo (2.8%), Tlaxcala (1.9%), and Puebla (1.8%) (43). In a recent study of *T. cruzi* infection among blood donors in the states of Jalisco and neighboring Nayarit, Kirchhoff and colleagues found an overall prevalence rate of 0.7% (8). Importantly, four of the nine recipients of blood or platelets donated by *T. cruzi*-infected persons studied were infected with the parasite. These results indicate clearly that *T. cruzi* infection is common among blood donors in the region of Mexico where the study was done and that transmission of the parasite to recipients of contaminated blood is occurring. Transfusion-associated transmission of *T. cruzi* in Mexico had not been reported previously. Serologic testing of blood donors in Nayarit and Jalsico should be performed, and the epidemiologic data from other regions suggests that testing of donated blood throughout Mexico would be appropriate, especially in view of the major internal migrations that characterize Mexican demographics. Currently it is estimated that only 13% of blood donated in Mexico is screened for *T. cruzi.* Blood bank regulations are currently being revised at the federal level in Mexico and mandatory, country-wide screening for Chagas' disease is being considered. In terms of vector-borne transmission, a larger epizootiologic and epidemiologic database needs to be developed to facilitate effective focusing of control measures in the regions in which *T. cruzi* is most common. To date few programs specifically directed at reducing *T. cruzi* transmission have been implemented in Mexico.

3.3.4. Epidemiology of *T. cruzi* infection in the United States

The sylvatic cycle of *T. cruzi* transmission is present in large areas of the western and southern United States, but despite these observations only five cases of autochthonous transmission to humans here have been reported (13). The reason for this is uncertain but the low overall vector density and our relatively high housing standards likely underlie the rarity of vector-borne transmission of *T. cruzi* to people here. In the past three decades, a handful of imported cases of acute Chagas' disease have been reported to the Centers for Disease Control and Prevention (CDC), but none have occurred in returning tourists. Even though the number of autochthonous and imported cases of acute *T. cruzi* infection in the United States may be many times the number reported, the fact remains that the illness is rare here and it is unlikely to become more of a major public health concern.

In contrast, the number of persons living in the United States with chronic *T. cruzi* infections has increased enormously in recent years. Data from the 2000 census indicate that more than 12 million Latin Americans from Chagas'-endemic countries now reside here. Roughly eight million of these immigrants are Mexicans, where as noted above, *T. cruzi* infection is widespread, but a sizable percentage has also come from Central America, where *T. cruzi* prevalence is high (44,45). Over 15 years ago a 5% prevalence rate of *T. cruzi* infection among Nicaraguans and Salvadorans living in Washington, D.C. was reported (46). In a Los Angeles hospital where half of the donors are Hispanic it was found that between 1 in 1,000 and 1 in 500 donors had serology positive for *T. cruzi* infection (47, 48). In another study, carried out in seven blood banks in three Southwestern states, approximately 1 in 600 donors with Hispanic surnames was found to harbor *T. cruzi.* In a much larger investigation done in Miami and Los Angeles, the prevalence of Chagas' disease was found to be 1in 8,800 in the general donor population and 1 in 710 in donors who had spent more than a month in an endemic area (49). These findings, combined with data from the 2000 census, indicate that 80,000 to 100,000 *T. cruzi*-infected persons now live in the United States.

3.4. Transmission of *Trypanosoma cruzi* in the United States by transfusion and organ transplantation

T. cruzi can be transmitted by blood transfusion and organ transplantation. Eight cases of transfusion-associated transmission of *T. cruzi* have been reported in the United States, Canada, and Europe, all of which occurred in immune suppressed patients in whom the diagnosis was made because of the fulminant course of the illness (6, 50-53). Since most transfusions are given to immunocompetent patients in whom acute *T. cruzi* infection would be a mild illness, it is reasonable to assume that many undetected instances of transfusion-associated transmission of *T. cruzi* have occurred here. The risk of transfusion-transmitted Chagas' disease may have been reduced in the past three years by screening prospective blood donors with questions relating to residence in endemic countries, but the efficacy of the questions asked in identifying high-risk donors has not been studied.

The question of whether blood donated in the United States should be screened for *T. cruzi* has been

considered for at least a decade by both public and private entities involved in blood banking. A consensus has been developing at the Food and Drug Administration (FDA) and the American Red Cross in favor of serologic testing of our entire blood supply. Implementation of such a recommendation, however, is not an option currently because no test for *T. cruzi* infection has been cleared by the FDA for use in blood banks.

Several instances of transmission of *T. cruzi* by organ transplantation have been reported in Latin America. Transplantation-associated acute Chagas' disease is particularly worrisome in transplant recipients because of their relatively limited ability to control the infection. Most reports to date have described transmission of the parasite by transplantation of kidneys obtained from persons with chronic *T. cruzi* infections (27). An instance of transplantation-associated transmission of *T. cruzi* recently was reported in the United States (54), and its occurrence is not surprising given the number of infected immigrants currently living here. In this case, several organs were obtained from a *T. cruzi*-infected Central American immigrant and all three transplant recipients developed acute Chagas' disease. One patient died as a consequence of the *T. cruzi* infection and another died of unrelated causes. Incidents of this type could be eliminated by serologic screening of organ donors in endemic countries and those in the United States who are at geographic risk for *T. cruzi* infection, and then not transplanting organs from persons found to be infected. Such testing would be difficult to coordinate because of time constraints, however, and more importantly, this approach is simply not acceptable because of the chronic shortage of organs for transplantation. As an alternative, organ donors at risk for *T. cruzi* infection could be tested, followed by serial serologic testing and in symptomatic individuals, parasitological studies in the months following transplantation of organs obtained from *T. cruzi*-infected donors. A program for identifying *T. cruzi*-infected organ donors in the United States is being developed by staff of the CDC and the United Network for Organ Sharing.

4. SLEEPING SICKNESS (*TRYPANOSOMA BRUCEI RHODESIENSE* AND *T. BRUCEI GAMBIENSE*)

4.1. The parasites and mechanisms of transmission

Sleeping sickness, or human African trypanosomiasis (HAT), is caused by flagellated protozoan parasites that are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic dysfunction and death. The West African (*gambiense*) and the East African (*rhodesiense*) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies: *Trypanosoma brucei gambiense* and *T. brucei rhodesiense.* These organisms are morphologically indistinguishable but cause diseases that are clinically and epidemiologically distinct. The parasites are transmitted by several species of blood-sucking tsetse flies that belong to the genus *Glossina*. The insects become infected when they ingest blood from infected mammalian hosts. The parasites multiply in the midgut of the vectors and then migrate to the salivary glands. Transmission takes place when they are inoculated into another mammalian host during a subsequent blood meal. The injected trypanosomes multiply in the blood, lymph, and other extracellular spaces, first locally and then systemically. As the infection in a mammalian host progresses, the parasites evade immune destruction for long periods by undergoing antigenic variation, a process in which the surface coat of glycoproteins changes periodically (55-57).

4.2. Epidemiology

The trypanosomes that cause HAT are found only in Africa. Sleeping sickness has undergone a resurgence in recent years, with major epidemics involving tens of thousands of people in endemic areas of sub-Saharan Africa such as the Sudan, Ivory Coast, Chad, and the Central African Republic (58,59). Humans are the only important reservoir of *T. b. gambiense*, which occurs in widely distributed foci in tropical rain forests of West and Central Africa. Gambiense trypanosomiasis is mostly a problem in rural populations, and tourists rarely become infected. Trypanotolerant antelope species in savanna and woodland areas of East and Central Africa are the principal reservoirs of *T. b. rhodesiense.* Cattle also can become infected with the agents of HAT and other trypanosome species, and they generally succumb to the infection. This fact precludes the development of enormous areas of potentially productive grazing land in sub-Saharan Africa. Risk results primarily from contact with tsetse flies that feed on wild animals, and thus humans acquire *T. b. rhodesiense* infection only incidentally while working in areas where infected game and vectors are present. In addition, international visitors to game parks in East Africa occasionally become infected and some develop symptoms only after returning to their homelands (60, 61). The occurrence of secondary cases in non-endemic areas is not a possibility because adequate vectors are not present.

4.3. Pathogenesis and pathology

An inflammatory lesion, the trypanosomal chancre, may appear at the site of inoculation a week or so after the bite of an infected tsetse fly. A systemic febrile illness then develops as the parasites disseminate through the bloodstream and lymphatics. The organisms multiply in the blood and other extracellular spaces, and there is no intracellular phase, as is the case with *T. cruzi*, the cause of Chagas' disease. Systemic HAT without involvement of the central nervous system (CNS) is generally referred to as s*tage I* or *hemolymphatic disease.* In this stage, splenomegaly and widespread lymphadenopathy reflect marked lymphocytic and histiocytic proliferation and invasion of morular cells, which are plasmacytes that may produce parasite-specific IgM. Endarteritis, with perivascular infiltration of both parasites and lymphocytes, may develop in the spleen and lymph nodes. Myocarditis often develops in patients with *stage I disease*, especially in those infected with *T. b. rhodesiesne* (62-64).

Hematologic abnormalities that characterize s*tage I* HAT include anemia, moderate leukocytosis, and thrombocytopenia. High levels of immunoglobulins, consisting mainly of polyclonal IgM, are a constant feature, and rheumatoid factor, heterophile antibodies, anti-DNA

antibodies, and are often present. High levels of antigen-antibody complexes may play a role in the increased vascular permeability and tissue damage that appear to facilitate dissemination of the parasites. *Stage II disease* involves invasion of the CNS. The presence of trypanosomes in perivascular areas in brain parenchyma is accompanied by intense mononuclear cell infiltration (65, 66). Cerebrospinal fluid (CSF) abnormalities include increased pressure, pleocytosis, and elevated total protein concentration. Trypanosomes are frequently found in CSF.

4.4. Clinical manifestations

The trypanosomal chancre that develops at the site of the infecting bite may be painful. Hemolymphatic spread of the parasites (s*tage I disease*) is accompanied by fevers that do not follow a predictible chronological pattern. Often bouts of high temperatures lasting several days are separated by afebrile periods. Lymphadenopathy is prominent in *T. b. gambiense* trypanosomiasis, but not in rhodesiense disease. The nodes are nontender, discrete, movable, and rubbery. Enlarged cervical nodes often develop, and when located in the posterior cervical triangle are called Winterbottom's sign. Maculopapular rashes and pruritus are common. Less consistent findings include malaise, headache, tachycardia, arthralgias, edema, weight loss, and hepatosplenomegaly.

Invasion of the CNS (s*tage II disease*) is characterized by the insidious development of protean neurologic manifestations and progressive abnormalities in the CSF. Gradually, a picture of daytime somnolence (hence the term "sleeping sickness") and progressive indifference develops, in some patients alternating with insomnia and restlessness at night. A loss of spontaneity accompanies a listless gaze, and speech may become indistinct and halting. Extrapyramidal signs may include movement disorders including fasciculations, and tremors. Ataxia is common, and the patient may appear to have Parkinson's disease, with tremors, a shuffling gait, and hypertonia. Progressive neurological impairment ends in coma and death.

The most notable difference between the East African and West African trypanosomiasis is that the former tends to follow a more acute course. In infected tourists, who as noted generally have rhodesiense disease, systemic signs of infection, such as malaise, headache, and fever, may appear before the end of the trip or shortly after the return home. Persistent tachycardia unrelated to fever is common early in rhodesiense trypanosomiasis, and death may result from congestive heart failure and arrhythmias even before CNS disease develops. In general, untreated *T. b. rhodesiense* trypanosomiasis leads to death in a matter of weeks to months, frequently without a clear distinction between the hemolymphatic and CNS stages, whereas gambiense disease can smolder for months or even years.

4.5. Diagnosis

A definitive diagnosis of HAT requires detection of the parasite, and there are a variety of approaches for doing this. If a chancre is present, fluid should be expressed and examined by light microscopy for the highly motile organisms. The fluid also should be fixed and stained with Giemsa. Material obtained by aspirating lymph nodes early in the course of the illness should be studied similarly. Examination of wet preparations and Giemsa-stained thin and thick films of serial blood specimens may also useful. If parasites are not seen initially in blood, efforts should be made to concentrate the organisms. This can be done with quantitative buffy coat analysis tubes (67, 68) (QBC, Becton-Dickinson, Franklin Lakes, NJ). These tubes are coated with acridine orange, and after centrifugation any parasites present are easily seen under light microscopy because of the stain. Trypanosomes may be seen in bone marrow aspirates, and this material also can be inoculated into liquid culture medium, as can blood, buffy coat, lymph node aspirates, and CSF. Rodent inoculation can be used to detect *T. b. rhodesiense* infection, but not *T. b. gambiense* because of the host specificity of the latter subspecies.

It is essential to examine CSF from all patients in whom HAT is a diagnostic consideration. An increase in the CSF cell count may be the first detectable abnormality. Trypanosomes may be seen in the sediment of centrifuged CSF. Any patient with a CSF abnormality must be viewed as having s*tage II* disease if trypanosomes have been found at other sites, and thus must be given specific treatment for CNS disease.

Several serologic assays are available for diagnosing HAT, but their variable sensitivity and specificity require that treatment decisions be based on detection of the parasite (69-71). These tests are useful for epidemiologic surveys. Novel molecular methods for detecting HAT are being developed (72,73).

4.6. Treatment

The drugs used for treatment of HAT are suramin, pentamidine, the organic arsenicals, and eflornithine (difluoromethylornithine), which was approved by the FDA in November 1990 for the treatment of gambiense disease. In the United States these drugs can be obtained only from the CDC. Therapy for HAT must be individualized on the basis of the infecting organism (*T. b. gambiense* or *T. b. rhodesiense*) and the presence or absence of CNS disease (74).

4.7. Prevention

Trypanosomiasis poses complex public-health and epizootic problems in Africa. Considerable progress in reducing the burden of these diseases has been made in some areas through control programs that focus on eradication of vectors and drug treatment of infected humans. There is no consensus on the best approach for solving the overall problem (75), however, and major epidemics continue to occur. Individuals can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by using insect repellent, and by wearing protective clothing. Drug prophylaxis is not recommended, and no vaccine is available.

5. AMEBIC PERICARDITIS (*ENTAMOEBA HISTOLYTICA*)

Entamoeba histolytica is a pathogenic protozoan that is transmitted by the fecal-oral route and usually

resides in the large bowel. Historically it has been a major scourge of humankind, and prevalence rates continue to be quite high in many areas, particularly in the less developed nations in the tropics. Acquisition of *E. histolytica* is a serious risk for tourists who travel to areas where prevalence rates are high. *E. histolytica* is the third most important cause of parasitic death in the developing countries, after malaria and schistosomiasis (76).

E. histolytica has the capacity to break down tissue, and henceforth its name, but most persons who harbor *E. histolytica* have few if any symptoms. Nonetheless, in a substantial portion of infected people it causes acute inflammation and ulceration of the colonic mucosa, or rectocolitis. Symptoms associated with this chronic process often include dysentery, fever, abdominal pain, and weight loss. In a minority of patients, the acute rectocolitis evolves into fulminant colitis with perforation, toxic megacolon, and even perianal ulceration. Liver abscesses are the most common manifestation of extraintestinal amebic disease. Ironically, most patients with liver involvement do not have concomitant diarrhea. When left untreated, such abscesses can rupture and cause peritonitis, but more commonly they erode through the diaphragm, resulting in empyema or lung abscess. Both these complications are associated with a high mortality. Several drugs are used for treating *E. histolytica* infections and parasitologic cure rates are generally 90% or greater. The regimens used vary as a function of the type of clinical disease (77).

Amebic pericarditis is a rare but serious complication of liver abscess (78). Cardiac tamponade and even perforation can occur, but typically the course is more insidious and involves substernal chest pain as well as congestive heart failure. No reports of pericardial amebiasis have been published in the indexed literature for more than 10 years, and this may reflect a trend toward earlier diagnosis as well as the widespread use of effective treatment.

6. HYDATID DISEASE OF THE HEART CAUSED BY *ECHINOCOCCUS GRANULOSUS*

Echinococcus species are tapeworms that sporadically cause serious disease in humans. *Echinococcus granulosus* is the most common of the three species that infect humans. Wild and domestic canines constitute the definitive reservoirs of these parasites, and infective eggs are contained in their feces. A variety of ungulates, including sheep, goats, horses, camels and cervines, serve as intermediate hosts after becoming infected by ingesting eggs while grazing. The cycle is completed when canines eat entrails of infected ungulates and in doing so ingest larval forms of the parasite contained in hydatid cysts. *Echinococcus* species have a worldwide distribution, and the cycle of transmission involving livestock and domestic dogs is important in some areas. Humans become inadvertent intermediate hosts when they ingest eggs from the feces of infected dogs. Although there are several foci of infection in the western United States that results in occasional human cases there, most patients diagnosed with hydatid diseases in the United States are immigrants.

Once ingested by humans the eggs hatch, releasing oncospheres that penetrate the small intestine and spread distally via the circulation. The oncospheres encyst in various tissues and hydatid cysts containing infective larval forms develop over months and years. Hydatid cysts can become quite large and can even lead to organ failure and death. Occasionally, a cyst will rupture releasing fluid that can disseminate infective larvae and cause allergic reactions. Such severe disease is the exception rather than the rule, however, as it is thought that the majority of echinococcal cysts never get large enough to come to medical attention. This is due in part to the host immune defenses.

Most hydatid cysts are located in the liver, but a sizable proportion is also found in the lungs. Less than 10 percent end up in brain, bones, and the heart. Isolated hydatid cysts in the heart are uncommon. Single case reports and small series involving Greek and Italian patients with cardiac hydatid disease have been reported (79-84).

Unsuspected echinococcal disease is often diagnosed incidentally when imaging studies are done for unrelated complaints. When symptoms do occur, they are usually caused by the mass effect of the cysts, and ultrasound or tomographic studies are the mainstay of making the diagnosis. The echocardiogram is generally regarded as the best method of diagnosing myocardial or pericardial hydatid cysts (81) (Figure 3). An enzyme immunoassay and an immunoblot are available for serologic diagnosis of hydatid disease from commercial sources and the CDC. The sensitivity and specificity of this test are greater than 80% in patients with liver cysts, but it is considerably less sensitive in persons who have cysts in other sites.

The best method for managing hydatid cysts is surgical removal. Cysts should be punctured at the beginning of the procedure and a larvicidal solution instilled into the cyst cavity to kill the infective forms. After a 30 minute dwell time, the cyst should be removed entirely. Obviously, many hydatid cysts are inoperable, including many of those found in the heart. In such cases either albendazole or mebendazole should be used. Medical therapy results in improvement in most patients and about a third are cured parasitologically. Cysts caused by *E. multilocularis* tend to be more aggressive than those of *E. granulosus* and as the name suggests, reproduce by lateral budding and thus invade adjacent tissues. This process often leads to organ dysfunction and accompanying symptoms, and the masses are sometimes initially thought to be cancer. Surgical removal of the cysts is difficult in many patients infected with *E. multilocularis*.

7. TOXOPLASMOSIS

7.1. Life cycle and epidemiology

Toxoplasma gondii, an Apicomplexan protozoan with a world-wide distribution, is capable of causing several clinical syndromes. It is a very common human infection with seroprevalence rates in adults in the United

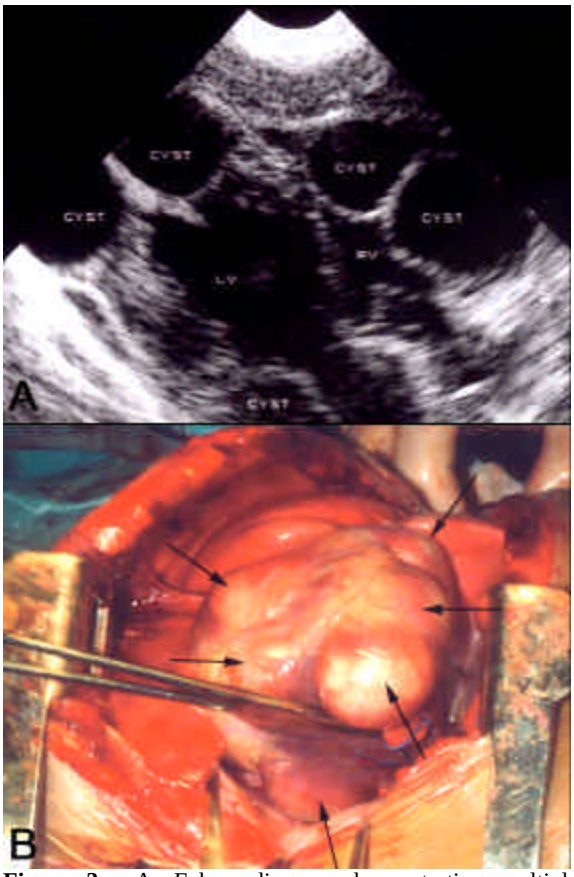

Figure 3. A. Echocardiogram demonstrating multiple hydatid cysts situated superficially in both ventricles. B. Intraoperative photograph demonstrating multiple hydatid cysts in the right and left ventricular walls. (Reprinted from reference 81 with permission of Dr. J.E. Bagg, Copyright 2002, Texas Heart Institute, Houston, TX).

States that vary from 20 to 70% depending on the geographic area. Most cases of acute toxoplasmosis are asymptomatic or involve a self-limited mononucleosis-like syndrome. During acute infection this organism forms cysts and thus establishes latent infection. A small number of acute infections, in immunocompetent hosts, result in clinically evident disseminated disease involving multiple organs (85). If acquired during pregnancy in a naïve host, *T. gondii* can be transmitted to the fetus resulting in congenital toxoplasmosis (86). Iatrogenic immunosuppression associated with chemotherapy and transplantation results in disseminated disease due to the reactivation of latent toxoplasmosis (87). The decline in cell mediated immunity associated with advanced HIV infection (CD4+ less than 100 cells/μl) may result in reactivation toxoplasmosis presenting as Toxoplasma encephalitis that may also be associated with dissemination to other organs (88,89).

Toxoplasma gondii has three morphologic forms: the tachyzoite, bradyzoite (tissue cyst) and oocyst. Gametogony occurs only in the small intestines of cats (the definitive host) resulting in the production of infectious oocysts (90). Humans and other animals become infected by ingesting oocysts contaminating food or water; by ingestion of bradyzoites (tissue cysts) in inadequately cooked meat; or by transplacental transmission. *Toxoplasma gondii* can also be transmitted by organ transplantation from a seropositive donor into a seronegative recipient (87). When a seropositive host is immunosuppressed reactivation of these latent foci can occur with the transformation of bradyzoites to tachyzoites and the development of clinical disease.

Infection with *T. gondii* is characterized by intracellular tachyzoite replication with hematogenous dissemination of these tachyzoites to virtually any cell type. The degree of tissue damage depends on the duration and intensity of tachyzoite multiplication and the organs involved. Autopsies of adults dying of disseminated toxoplasmosis demonstrate interstitial pneumonia, focal hepatitis, myocarditis, myositis, and encephalitis. Once the host develops an immune response, infection with *T. gondii* reaches a latent or chronic stage during which tissue cysts (bradyzoites) are present and parasitemia with tachyzoites is not evident. The development of cysts is due to a combination of host and parasite factors; however, cysts can form *in vitro* in the absence of host cell factors (91). Experimental evidence in animal models suggests that interferon γ is a critical factor in host defense against *T. gondii* (92).

7.2. Toxoplasma myocarditis

Toxoplasma myocarditis has been described as a complication of the immune suppression associated with HIV infection (87, 93-100). Hofman *et al* examined a series of 182 necropsies from 1987 to 1991 performed on HIV infected patients and found 12% (21 patients) with cardiac toxoplasmosis (100). In 86% of these cases (18/21) Toxoplasma encephalitis was also present. Twenty-eight percent of patients (6/21) had had cardiac symptoms. In an autopsy survey of 54 patients who died with AIDS prior to 1983, 30 patients (54%) had cardiac pathology of various etiologies (87). In 6 of these patients, 5 of whom had accompanying CNS toxoplasmosis, tachyzoites were present in the heart and was associated with lymphocytic infiltrates and myonecrosis (Figure 4). Herdy *et al* (99) reported 1 case of Toxoplasma myocarditis in 21 AIDS patients followed until death, and Matturri *et al* (94) reported 4 cases of Toxoplasma myocarditis among 18 consecutive autopsied patients with AIDS. Adair (94) reported a case of myocarditis in an AIDS patient with pericardial tamponade and a case of congenital cardiac toxoplasmosis in a 7 week old infant with AIDS presenting with heart failure due to hypertrophic cardiomyopathy has also been reported (98). Galium scanning may be useful in diagnosing toxoplasma myocarditis (101). In AIDS patients not allergic to sulfonamides, the synergistic combination of pyrimethamine (50-75 mg/day), sulfadiazine (6-8 gm/day) and folinic acid (10-20 mg/day) is the preferred therapy for patients with myocarditis (102,103). In AIDS patients allergic or intolerant to sulfadiazine, successful treatment of myocarditis has been reported with pyrimethamine and clindamycin (2400-4800 mg/d) (95). Alternative treatment pyrimethamine and atovaquone (1500-3000 mg/d) has been effective in some cases of Toxoplasma encephalitis.

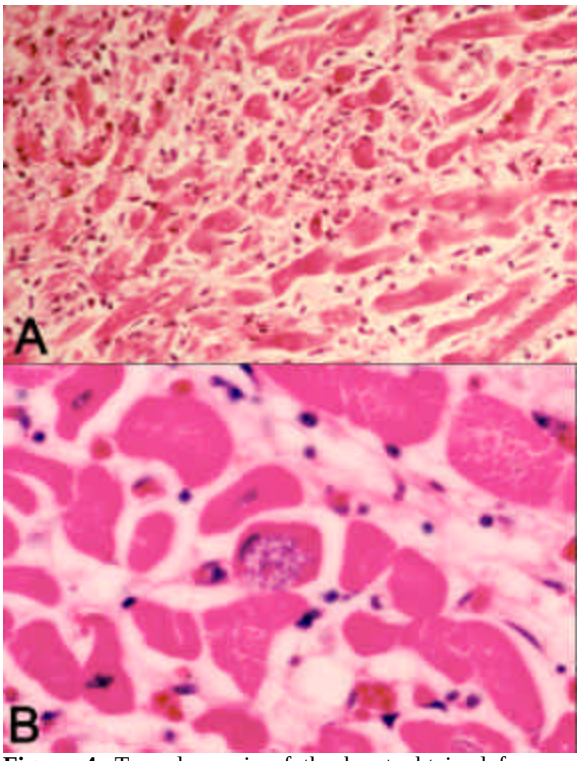

Figure 4. Toxoplasmosis of the heart obtained from an autopsy of an AIDS patient. A. Acute myocarditis with marked inflammation. B. *Toxoplasma gondii* in cardiac tissue (Courtesy of Dr. Stephen M. Factor, Jacobi Medical Center and the Albert Einstein College of Medicine, Bronx, NY).

Reactivation toxoplasmosis also occurs in other immunosuppressed hosts and has presented as disseminated disease involving the myocardium (Figure 4). In cases of fatal toxoplasmosis in immunocompromised patients, encephalitis was present clinically in 50% of patients and pathologically in 90% (104). It appears that Toxoplasma myocarditis in immunocompromised hosts is usually associated with involvement of other organ systems, most commonly the CNS. Several of these patients also had necrotizing myocarditis and pneumonitis (104). There are multiple case reports of cerebral and cardiac toxoplasmosis following bone marrow transplantation (105-109). Toxoplasma pericarditis has been reported in a patient with myelodysplastic syndrome (110). Treatment for toxoplasmosis in these immunocompromised patients is pyrimethamine (50-75 mg/day) and sulfadiazine (6-8 gm/day).

Disseminated toxoplasmosis has been described after heart (87, 110-117), liver (118,119), and kidney (120) transplantation. Toxoplasma encephalitis has been reported in 2 to 5% of cardiac transplant recipients (87,110-117). The highest risk of disseminated toxoplasmosis occurs when a seronegative recipient receives a heart from a seropositive donor (87,110-117). In a study of 31 seronegative patients undergoing heart transplantation 4 received hearts from seropositive donors and 3 developed life-threatening toxoplasmosis (114). Two of these patients developed systemic disease with evidence of encephalopathy, hepatitis and fever within 6 weeks of transplantation and the third developed chorioretinitis 6 months after transplantation and encephalitis 10 months after transplantation (114). The remaining 27 seronegative patients did not seroconvert or develop toxoplasmosis (114). In a study of 19 Toxoplasma seropositive patients undergoing heart transplantation, 10 had significant increases in serum IgM or IgG antibody titers within the first two months post-transplantation, but none developed clinical illness attributable to toxoplasmosis (114). These data are consistent with asymptomatic reactivation in these seropositive patients secondary to immunosuppression.

Treatment of transplant patients with azathioprine, corticosteroids, and anti-thymocyte globulin is associated with greater increases in Toxoplasma titers than patients receiving the combination of cyclosporine, corticosteroids and anti-thymocyte globulin. This may be a reflection the direct inhibitory effects of cyclosporin on *T. gondii* that have been observed in vitro (121).

Diagnosis of toxoplasmosis in seronegative patients who have undergone transplantation can be made if seroconversion occurs with the development of anti-Toxoplasma IgM (110-117). In patients with myocarditis after transplantation, diagnosis is best made by endomyocardial biopsy, which often demonstrates *T. gondii* tachyzoites in cases of acute Toxoplasma myocarditis following heart transplantation (87,113,114). Histopathological changes seen in these biopsies include myonecrosis, edema, and an inflammatory cell infiltrate consisting of plasma cells, macrophages, lymphocytes, and eosinophils. The most sensitive technique for the demonstration of tachyzoites in such biopsy specimens is the peroxidase-anti-toxoplasma antibody technique (113,122). Treatment of toxoplasmosis complicating transplantation has been successful with pyrimethamine (25-75 mg/day), sulfadiazine (4-8 gm/day) and folinic acid (5-10 mg/day) for a minimum of 6 weeks. Prophylaxis with pyrimethamine 25 mg/d (111,123,124) for 6 weeks after transplantation or with trimethoprin-sulfamethoxazole (124,125) has been successful in the prevention of acute toxoplasmosis in seronegative recipients of hearts from seropositive donors, thus expanding the available organ pool for these recipients.

Acute myocarditis associated with tachyzoites, focal inflammation and myonecrosis may accompany congenital toxoplasmosis (40,127) or acute infection in adults (128). Congenital toxoplasmosis involving the heart is usually asymptomatic with only cysts and no tachyzoites being present in the myocardium. One case (130) of extensive calcification of the right ventricle and intraventricular septum has been reported in congenital toxoplasmosis. In immunocompetent adults infection is also usually asymptomatic or causes a "mononucleosis-like" syndrome, however, there are occasional patients with acute infection who develop myocarditis (130), pancarditis (131) or pericarditis (110,132-134). Chronic pericardial effusion and constrictive pericarditis due to toxoplasmosis has also been reported (132, 134). In these cases of

pericarditis, tachyzoites were found either in pericardial fluid or in pericardial biopsies. Acute myocarditis and pericarditis have been reported to respond to pyrimethamine and sulfadiazine (131,132,133,135) in the same doses as used in toxoplasmosis complicating cardiac transplantation.

There are two case reports of congestive heart failure and myocarditis following seroconversion for *T. gondii* (128). Several studies have suggested that latent *T. gondii* (e.g. seropositivity) may be associated with a chronic cardiomyopathy (130,135,136) with arrhythmias and congestive heart failure. In these studies (134,135) patients were divided into two groups, those without congestive heart failure who had a short (<6 month) history of symptoms and those with congestive heart failure who had a longer illness. The first group had a good response to treatment (pyrimethamine, sulfadiazine and steroids) with improvement of ECG abnormalities and a decrease in heart size. This group presented with chest pain, tachyarrhythmias and conduction abnormalities (137) and appears to be similar to case reports of acute toxoplasmosis with pericarditis (110, 130-134). The second group of patients presented with cardiomegaly and congestive heart failure of longer duration. The response to pyrimethamine and sulfadiazine was variable (135,136) at best. In a minority of patients in each group organisms were either evident by microscopy or isolated by experimental inoculation of tissue into mice (135,136). All of the other patients reported to have chronic cardiomyopathy due to *T. gondii* had serological evidence of latent toxoplasmosis, but no histopathological evidence of myocardial infection (135,136). Overall the data are lacking that latent toxoplasmosis is etiologically linked to chronic cardiomyopathy, but are convincing that acute toxoplasmosis can result in myocardial damage and acute (subacute) congestive heart failure.

8. CYSTICERCOSIS

Cysticercosis results from the ingestion of ova of pork tapeworm, *Taenia solium*. Ingested ova hatch in the gastrointestinal tract. The hatched onchosperes penetrate the small intestine, disseminate hematogenously and lodge in multiple organs most notably brain and other portions of the central nervous system, skin, muscle and eye (138). Cysts have been observed in the heart as incidental findings at autopsy or during cardiac surgery for unrelated causes. In the heart the cysts are randomly distributed in the subpericardium, subendocardium or myocardium of the right or left ventricle, septum or papillary muscles. The cysts are usually multiple and are either ovoid or round (139,140). They measure from 10-30 mm and are readily discernible on gross examination. Occasionally, a large single cyst may be present (139). Microscopically, the scolex, hooklets and four suckers may be identified beneath a capsule that has been artificially wrinkled during histologic processing. The inflammatory response of the surrounding myocardium is variable (141,142). The degeneration of cysts in the myocardium may result in granuloma formation and fibrosis. The cysts and their degeneration, which may occur naturally or as a result of drug therapy, may result in arrhythmia and or conduction abnormalities. Echocardiography may be useful in detecting cysts (141). The usefulness of steroids and anti-parasitic drugs such as albendazole and praziquantel in patients with cardiac cysts has not been investigated.

9. TRICHINOSIS

Human infection with the nematode *Trichinella spiralis* and other *Trichinella* species is common world-wide and although its incidence in the United States has declined since the 1940s, outbreaks continue to occur. It is most commonly acquired by the ingestion of raw or undercooked pork containing the encysted *Trichinella* larvae. Trichinosis has also been reported after ingestion of bear, walrus, wild boar, cougar, and other animals (144).

In the human hosts encysted larvae in infected meat products excyst and penetrate the small intestine. During the acute enteric phase there is nausea, vomiting, diarrhea and abdominal pain. Following maturation and mating, female worm residing in the intestine produce many larvae which then migrate into the lymphatics and bloodstream finally encysting in striated muscle. The migratory phase may last several weeks to 2-3 months. Each cyst then becomes fully encapsulated within striated skeletal muscle. There is then a parasite induced transformation into a nurse cell which sustains the encysted larva. Cysts calcify over a period of many years. *Trichinella* larvae encyst in skeletal muscle. The nurse cell formation is specific for skeletal muscle and encystment does not occur in cardiac tissue.

The signs and symptoms of trichinosis are directly related to the number of larva ingested. The majority of infections are asymptomatic. The classic signs and symptoms of the migratory phase include fever, severe myalgia, periorbital edema, conjunctivitis, muscle tenderness and subungual hemorrhage. These findings are usually associated with a rising eosinophilia and increased muscle related enzymes. The usual method of confirming the diagnosis is by serology which, depending on the test, becomes positive in 2-3 weeks. Although muscle biopsy is most specific it is only positive in only 30-50% of cases. Most cases of trichinosis are either asymptomatic or mildly symptomatic. Severe morbidity and mortality usually occurs secondary to pneumonitis, encephalitis or myocarditis (145,146). These syndromes are caused by migrating larvae. The transient migration of larvae through the myocardium may be clinically manifested by ECG changes such as arrhythmias, T wave inversion, widening of the QRS complex and increased P-R interval, and heart block. Individuals may experience severe myocarditis, pericarditis and congestive heart failure (147-150). Pathological examination of the heart can reveal interstitial inflammatory infiltrate composed of lymphocytes, eosinophils, plasma cells and polymorphonuclear leukocytes. Animal studies have demonstrated that migrating larvae are surrounded by necrotic muscle cells and inflammation suggesting that the cardiac pathology is a direct result of migrating larvae and the local inflammatory response. Trichinosis is a self-limited illness. Treatment is usually with mebendazole or albendazole. Steroids are recommended for severe disease such as myocarditis.

10. OTHER PARASITIC INFECTIONS

Cardiovascular complications may be observed in other parasitic infections. The anemia that accompanies severe hookworm infections and visceral leishmaniasis may cause heart failure. Severe cases of visceral larval migrans may result in an eosinophilic myocarditis. Rarely other migrating nematode larvae have been described in the heart. Infections with the free-living ameba *Naegleria fowleri* have also been associated with myocarditis (151).

Endomyocardial fibrosis is a form of restrictive cardiomyopathy observed in tropical areas of Africa and South America. Initially there is an acute eosinophilic myocarditis with the subsequent appearance of an apical aneurysm. In the final phase there is healing with the formation of scar tissue that obliterates the ventricular cavities. The endocardium is most intensely involved in this process. Trypanosome and filarial infections have been discussed as possible etiologies (152-155).

11. CONCLUSIONS

It has been four decades since the original monograph by Kean and Breslau on parasites of the heart was published (1). Since then great strides have been made in defining the clinical characteristics and pathogenesis of chagasic heart disease, the most studied of the parasitic diseases of the heart. These advances have been well described in the current volume, *Infections of the Myocardium* (156-163). African trypanosomiasis (sleeping sickness) is now a recognized cause of myocarditis. Toxoplasmosis is an important opportunistic infection in immunocompromised hosts which may manifest itself as myocarditis. Helminths such as the larval stages of *Echinococcus* and *Taenia solium* (cysticercosis) cause lesions in the myocardium whereas the nematode *Trichinella* causes a myocarditis. While unusual causes of cardiac disease, parasites should be considered in the differential diagnosis of myocardial and pericardial disease.

12. REFERENCES

1. Kean B.H. & R.C. Breslau: *Parasites of the Human Heart.* New York, Grune and Stratton (1964)

2. Tanowitz H.B., S.A. Morris, S.M. Factor, L.M. Weiss & M. Wittner: Parasitic diseases of the heart I: Acute and chronic Chagas' disease. *Cardiovascular Pathol* 1, 7-15 (1992)

3. Tanowitz H.B., L.M. Weiss, K.H. van Hoeven, S. Kellie & M. Wittner: Parasitic Diseases of the heart II: Toxoplasmosis and other protozoan and helminthic diseases. *Cardiovascular Pathol* 1, 97-106 (1992)

4. Bruneel F., L. Hocqueloux, C. Alberti M. Wolff, S. Chevret, J.P. Bedos, R. Durand, J. Le Bras, B. Regnier & F. Vachon: The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. *Am J Respir Crit Care Med* 167, 684-689 (2003)

5. Morris W. & C.M. Knauer: Cardiopulmonary manifestations of schistosomiasis. *Semin Respir Infect* 12, 159-170 (1997)

6. Leiby D.A., B.A. Lenes, M.A. Tibbals & M.T. Tames-Olmedo: Prospective evaluation of a patient with *Trypanosoma cruzi* infection transmitted by transfusion. *N Engl J Med* 341, 1237-1239 (1999)

7. Schmunis G.A: Prevention of transfusional *Trypanosoma cruzi* infection in Latin America. *Mem Inst Oswaldo Cruz* 94, 93-101 (1999)

8. Kirchhoff L.V., P. Paredes, A. Lomeli-Guerrero, M. Paredes-Espinoza, C. Ron-Guerrero, M. Delgado-Mejia. & J.G. Pena-Munoz: Transfusion-associated Chagas' disease (American trypanosomiasis) in Mexico: Implications for transfusion medicine in the United States. In Press

9. Herwaldt B.L: Laboratory-acquired parasitic diseases. *Clin Microbiol Rev* 14, 659-688 (2000)

10. Gurtler R.E., E.L. Segura, & J.E. Cohen: Congenital transmission of *Trypanosoma cruzi* infection in Argentina. *Emerging Infect Dis* 9, 29-32 (2003)

11. Rassi A., A. Rassi Junior, & G.G. Rassi: Acute Chagas disease, in *Trypanosoma cruzi e Doença de Chagas*. eds. Brener,Z., Andrade Z.A., & M. Barral-Netto: 231-245 (Guanabara Koogan, Rio de Janeiro; 2000)

12. Laranja F.S., E. Dias, G. Nobrega & A. Miranda: Chagas' disease: A clinical, epidemiologic, and pathologic study. *Circulation* 14, 1035-1060 (1956)

13. Och D.E., V. Hnilica, D.R. Moser, J.H. Smith & L.V. Kirchhoff: Postmortem diagnosis of autochthonous acute chagasic myocarditis by polymerase chain reaction amplification of a species-specific DNA sequence of *Trypanosoma cruzi. Am J Trop Med Hyg* 34, 526-529 (1996)

14. Hoff R., R.S. Teixeira, J.S. Carvalho & K.E. Mott: *Trypanosoma cruzi* in the cerebrospinal fluid during the acute stage of Chagas' disease. *N Engl J Med* 298, 604-606 (1978)

15. Villanueva M.S: Trypanosomiasis of the central nervous system. *Semin Neurol* 13, 209-218 (1993)

16. Jones E.M., D.G. Colley, S. Tostes, E.R. Lopes, C.L. Vnencak-Jones & T.L. McCurley: Amplification of a *Trypanosoma cruzi* DNA sequence from inflammatory lesions in human Chagasic cardiomyopathy. *Am J Trop Med Hyg.* 48, 348-357 (1993)

17. Zhang L. & R.L. Tarleton: Parasite persistence correlates with disease severity and localization in chronic Chagas' disease. *J Infect Dis* 180, 480-486 (1999)

18. Anez N., H. Carrasco, H. Parada, G. Crisante, A. Rojas, C. Fuenmayor, N. Gonzalez, G. Percoco, R. Borges, P. Guevara & J.L. Ramirez: Myocardial parasite

persistence in chronic chagasic patients. *Am J Trop Med Hyg* 60, 726-732 (1999)

19. Bustamante JM, H.W. Rivarola, A.R. Fernandes, J.E. Engers, R. Fretes, J.A. Palma, & P.A. Paglini-Oliva: Indeterminate Chagas' disease: *Trypanosoma cruzi* strain and re-infection are factors involved in the progression of cardiopathy. *Clin Sci* 104, 415-420 (2003)

20. Hagar J.M. & S.H. Rahimtoola: Chagas' heart disease in the United States. *N Engl J Med* 325, 763-768 (1991)

21. Marin-Neto JA, M.V. Simoes & A.V.L. Sarabanda: Chronic cardiac Chagas disease, in *Trypanosoma cruzi e Doença de Chagas*, Eds. 2. eds. Brener Z., Z.A. Andrade Z.A. & M. Barral-Netto: 266-296 (Guanabara Koogan, Rio de Janeiro; 2000)

22. Kirchhoff L.V. & F.A. Neva: Chagas' disease in Latin American immigrants. *JAMA* 254, 3058-3060 (1985)

23. Kirchhoff L.V: American trypanosomiasis (Chagas' disease). *Gastroenterol Clinics N America* 25, 517-533 (1996)

24. de Oliveira R.B., Troncon,L.E., Dantas,R.O., & Menghelli,U.G. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroentero.* 93, 884-889 (1998)

25. Kobayasi S., E.F. Mendes, M.A.M. Rodrigues & M.F. Franco: Toxic dilatation of the colon in Chagas' disease. *Br J Surg* 79, 1202-1203 (1992)

26. Leiguarda R., A. Roncoroni, A.L. Taratuto, L. Jost, M. Berthier, M. Nogues & H. Freilij: Acute CNS infection by *Trypanosoma cruzi* (Chagas' disease) in immunosuppressed patients. *Neurol* 40, 850-851 (1990)

27. Riarte A., C. Luna, R. Sabatiello, A. Sinagra, R. Schiavelli, A. De Rissio, E. Maiolo, M.M. Garcia, N. Jacob, M. Pattin, M. Lauricella, E.L. Segura & M. Vazquez: Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis* 29, 561-567 (1999).

28. La Forgia M.P., G. Pellerano, P.M. las Mercedes, M.C. Kien & E.N. Chouela: Cutaneous manifestation of reactivation of Chagas' disease in a renal transplant patient: long-term follow-up. *Arch Dermatol* 139, 104-105 (2003)

29. Kirchhoff L.V: American trypanosomiasis (Chagas' disease) -- A tropical disease now in the United States. *N Engl J Med* 329, 639-644 (1993)

30. Bocchi E.A. & A. Fiorelli: The paradox of survival results after heart transplantation for cardiomyopathy caused by *Trypanosoma cruzi.* First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. *Ann Thor Surg* 71, 1833-1838 (2001)

31. Libow L.F., V.P. Beltrani D.N. Silvers & M.E. Grossman: Post-cardiac transplant reactivation of Chagas' disease diagnosed by skin biopsy. *Cutis* 48, 37-40 (1991)

32. Rocha A., A.C. Oliveira de Meneses, A.M. da Silva, M.S. Ferreira, S.A. Nishioka, M.K.N. Burgarelli, E. Almeida, G. Turcato Jr., K. Metze & E.T. Lopes: Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg* 50, 261-268 (1994)

33. Sartori A.M., M.A. Shikanai-Yasuda, V. Mato Neto & M.H. Lopes: Follow-up of 18 patients with human immunodeficiency virus infection and chronic Chagas' disease, with reactivation of Chagas' disease causing cardiac disease in three patients. *Clin Inf Dis* 26, 177-179 (1998)

34. Sartori A.M., H.H. Caiaffa-Filho, R.C. Bezerra,, C. dos Guilherme, M.H. Lopes & M.A. Shikanai-Yasuda:. Exacerbation of HIV viral load simultaneous with asymptomatic reactivation of chronic Chagas' disease. *Am J Trop Med Hyg* 67, 521-523 (2002)

35. Ferreira M.S., S.A. Nishioka, M.T.A. Silvestre, A.S. Borges, F.R.F. Nunes-Araujo & A. Rocha: Reactivation of Chagas' disease in patients with AIDS: report of three cases and review of the literature. *Clin. Infect. Dis.* 25, 1397-1400 (1997)

36. Freilij H. & J. Altcheh: Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis* 21, 551-555 (1995)

37. Moya P., E. Moretti, R. Paolasso, B. Basso, S. Blanco, C. Sanmartino & C. Soich: Neonatal Chagas disease: laboratory diagnosis during the first year of life. *Medicina* 49, 595-599 (1989)

38. Russomando G., M.M. de Tomassone, I. de Guillen N. Acosta, N. Vera, M. Almiron, N. Candia, M.F. Calcena & A. Figueredo: Treatment of congenital Chagas' disease diagnosed and followed up by the polymerase chain reaction. *Am. J Trop Med Hyg* 59, 487-491 (1998)

39. Kirchoff L.V., C. Bacchi, M. Wittner & H.B. Tanowitz: American Trypanosomiasis (Chagas' Disease). *Curr Treat Options in Infectious Diseases* 2:59-65, 2000

40. Schmunis G.A: American trypanosomiasis and its impact on public health in the Americas, in *Trypanosoma Cruzi e Doença de Chagas*, Edn. 2. eds. Brener Z., Z. A. Andrade & M. Barral-Netto: 1-20 (Guanabara Koogan, Rio de Janeiro; 2000)

41. Dias J.C., A.C. Silveira & C.J. Schofield: The impact of Chagas disease control in Latin America: a review. *Mem Inst. Oswaldo Cruz* 97, 603-612 (2002)

42. Segura E.L., E.N. Cura,, S.A. Estani, J. Andrade, J.C. Lansetti, A.M. de Rissio, A. Campanini, S.B. Blanco, R.E. Gurtler & M. Alvarez: Long-term effects of a nationwide

control program on the seropositivity for *Trypanosoma cruz*i infection in young men from Argentina. *Am. J. Trop. Med. Hyg* 62, 353-362 (2000)

43. Guzman-Bracho C., L. Garcia-Garcia, J. Floriani-Verdugo, S. Guerrero-Martinez, M. Torres-Cosme, C. Ramirez-Melgar & O. Velasco-Castrejon: Risk of transmission of *Trypanosoma cruzi* by blood transfusion in Mexico. *Pan Am J Pub Health* 4, 94-99 (1998)

44. Bureau of Census Statistical Abstract of the United States. The National Data Book. (United States Department of Commerce, Washington, D.C. (1996)

45. Schmunis G.A: *Trypanosoma cruzi,* the etiologic agent of Chagas' disease: status in the blood supply in endemic and nonendemic countries. *Transfusion* 31, 547-557 (1991)

46. Kirchhoff L.V., A.A. Gam & F.C. Gilliam: American trypanosomiasis (Chagas' disease) in Central American immigrants. *A. J Med.* 82, 915-920 (1987)

47. Appleman M.D., I.A. Shulman, S. Saxena & L.V. Kirchhoff: Use of a questionnaire to identify potential donors at risk for infection with *Trypanosoma cruzi. Transfusion* 33, 61-64 (1993)

48. Shulman I.A., M.D. Appleman, S. Saxena,, A.L. Hiti & L.V. Kirchhoff: Specific antibodies to *Trypanosoma cruzi* among blood donors in Los Angeles, California. *Transfusion* 37, 727-731 (1997)

49. Leiby D.A., E.J. Read, B.A. Lenes, A.J. Yund, R.J. Stumpf, L.V. Kirchhoff & R.Y, Dodd: Seroepidemiology of *Trypanosoma cruzi*, etiologic agent of Chagas' disease, in U.S. blood donors. *J Infect Dis* 176, 1047-1052 (1997)

50. Nickerson P., P. Orr, M-L. Schroeder, L. Sekla, & J.B. Johnston: Transfusion-associated *Trypanosoma cruzi* infection in a non-endemic area. *Ann Intern Med* 111, 851-853 (1989)

51. Grant I.H., J.W.M. Gold, M. Wittner, H.B. Tanowitz, C. Nathan, K. Mayer, L. Reich, N. Wollner, L. Steinherz, F. Ghavimi, R.J. O'Reilly & D. Armstrong: Transfusion-associated acute Chagas' disease acquired in the United States. *Ann Intern Med* 111, 849-851 (1989)

52. Cimo P.L., W.E. Luper & M.A. Scouros: Transfusion-associated Chagas' disease in Texas: report of a case. *Texas Med* 89, 48-50 (1993)

53. Villalba R., G. Fornes, M.A. Alvarez, J. Roman, V. Rubio, M. Fernandez, J.M. Garcia, M. Vinals, & A. Torres: Acute Chagas' disease in a recipient of a bone marrow transplant in Spain: case report. *Clin. Infect. Dis.* 14, 594-595 (1992)

54. Zayas C..F., C. Perlino, A. Caliendo, D. Jackson, E.J. Martinez, P. Tso, T.G. Heffron, J.L. Logan, B.L. Herwaldt B.L., A.C. Moore, F.J. Steurer, C. Bern & J.H. Maguire: Chagas' disease after organ transplantation -- United States, 2001. *MMWR.* 51, 210-212 (2002)

55. Cross G.A: Antigenic variation in trypanosomes: secrets surface slowly. *Bio Essays* 18, 283-291 (1996)

56. Borst P., G. Rudenko, P.A. Blundell, F. van Leeuwen, G.A. Cross, R. McCulloch, H. Gerrits & I.M. Chaves: Mechanisms of antigenic variation in African trypanosomes. *Behring Inst Mitt* 99, 1-15 (1997)

57. Donelson J.E., K.L. Hill & N.M.A. El-Sayed: Multiple mechanisms of immune evasion by African trypanosomes. *Mol Biochem Parasitol* 91, 51-66 (1998)

58. Stich A., P.M. Abel & S. Krishna: Human African trypanosomiasis. *BMJ* 325, 203-206 (2002)

59. Hutchinson O.C., E.M. Fevre, M. Carrington & S.C. Welburn: Lessons learned from the emergence of a new *Trypanosoma brucei rhodesiense* sleeping sickness focus in Uganda. *Lancet Infect. Dis* 3, 42-45 (2003)

60. Sinha A., C. Grace, W.K. Alston, F. Westenfeld & J.H. Maguire: African trypanosomiasis in two travelers from the United States. *Clin Infect Dis* 29, 840-844 (1999)

61. Jelinek T., Z. Bisoffi, L. Bonazzi, P. van Thiel, U. Bronner, A. de Frey, S.G. Gundersen, P. McWhinney, D. Ripamonti, & European Network on Imported Infectious Disease Surveillance: Cluster of African trypanosomiasis in travelers to Tanzanian national parks. *Emerging Infect Dis* 8, 634-635 (2002)

62. Jones I.G., M.N. Lowenthal & H. Buyst: Electrocardiographic changes in African trypanosomiasis caused by *Trypanosoma brucei rhodesiense. Trans R Soc Trop Med Hyg* 69, 388-395 (1975)

63. Poltera A.A., J.N. Cox & R. Owor: Pancarditis involving the conducting system and all valves in human African trypanosomiasis. *Br Heart J* 38, 827-837 (1976)

64. Poltera A.A. & J.N. Cox: Pancarditis with valvulitis in endomyocardial fibrosis and in human African trypanosomiasis. A comparative histological study of four Ugandan cases. *Virchows Arch A Pathol Anat Histol* 375, 53-70 (1977)

65. Hunter C.A. & P.G: Kennedy: Immunopathology in central nervous system human African trypanosomiasis. *J Neuroimmunol* 36, 91-95 (1992)

66. Pentreath V.W: Trypanosomiasis and the nervous system. Pathology and immunology. *Trans R Soc Trop Med Hyg* 89, 9-15 (1995)

67. Bailey J.W. & D.H. Smith: The use of the acridine orange QBC technique in the diagnosis of African trypanosomiasis. *Trans R Soc Trop Med Hyg* 86, 630 (1992)

68. Truc P., V. Jamonneau, P. N'Guessan, P.B. Diallo & A. Garcia: Parasitological diagnosis of human African trypanosomiasis: a comparison of the QBC® and miniature anion-exchange centrifugation techniques. *Trans R. Soc Trop Med Hyg* 92, 288-289 (1998)

69. Chappuis F., A. Pittet, P.A. Bovier, K. Adams, V. Godineau, S.Y. Hwang, E. Magnus & P. Buscher: Field evaluation of the CATT/*Trypanosoma brucei gambiense* on blood-impregnated filter papers for diagnosis of human African trypanosomiasis in southern Sudan. *Trop Med Int Health* 7, 942-948 (2002)

70. Truc P., V. Lejon, E. Magnus, V. Jamonneau, A. Nangouma, D. Verloo, L. Penchenier & P. Buscher: Evaluation of the micro-CATT, CATT/*Trypanosoma brucei gambiense*, and LATEX/*T. b. gambiense* methods for serodiagnosis and surveillance of human African trypanosomiasis in West and Central Africa. *Bulletin of the World Health Organization* 80, 882-886 (2002)

71. Penchenier L., P. Grebaut, F. Njokou, V. Eboo & P. Buscher: Evaluation of LATEX/T.b.gambiense for mass screening of *Trypanosoma brucei gambiense* sleeping sickness in Central Africa. *Acta Tropica* **85**, 31-37 (2003)

72. Radwanska M., S. Magez, H. Perry-O'Keefe, H. Stender, J. Coull, J.M. Sternberg P. Buscher & J.J. Hyldig-Nielsen: Direct detection and identification of African trypanosomes by fluorescence in situ hybridization with peptide nucleic acid probes. *J Clin. Microbiol.* 40, 4295-4297 (2002)

73. Radwanska M., F. Claes, S. Magez, E. Magnus, D. Perez-Morga, E. Pays & P. Buscher: Novel primer sequences for polymerase chain reaction-based detection of *Trypanosoma brucei gambiense. Am J Trop Me. Hyg* 67, 289-295 (2002)

74. Burri C., S. Nkunku, A. Merolle, T. Smith, J. Blum & R. Brun,: Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense*: a randomised trial. *Lancet* 355, 1419-1425 (2000)

75. Rogers D.J. & S.E. Randolph: A response to the aim of eradicating tsetse from Africa. *Trends Parasitol* 18, 534-536 (2002)

76. Ravdin J.I:. Amebiasis. *Clin. Infect. Dis.* 20, 1453-1464 (1995)

77. Ravdin J.I.: Amebiasis, in *Principles and Practice of Infectious Diseases*, Edn. V. eds. Mandell G.L., Bennett J.E., & Dolin,R. 2798-2810 John Wiley & Sons, New York; 2000

78. Supe A.N., S.S. Sathe, R.G. Redkar, A.N. Dalvi, B.A. Kulkarni & P.P. Shah,: Amebic pericarditis following ruptured right liver lobe abscess. *Indian J Gastroenterol* 10, 111 (1991)

79. Kardaras F., D. Kardara, D. Tselikos, A. Tsoukas, N. Exadactylos, M. Anagnostopoulou, C. Lolas & L. Anthopoulos: Fifteen year surveillance of echinococcal heart disease from a referral hospital in Greece. *Eur Heart J* 17, 1265-1270 (1996)

80. Porcu A., A. Dessanti, C.F. Feo, L. Ballore, A.M. Scanu, A. Fancellu, G. Padua, & T. Gherli: Three cases of cardiac hydatidosis: diagnosis, surgical treatment, and complications. *Int Surg* 86, 127-131 (2001)

81. Lioulias A.G., J.N. Kokotsakis, C.N. Foroulis & E.T. Skouteli: Multiple cardiac hydatid cysts. Consistency of echocardiographic and surgical findings. *Tex Heart Inst J* 29,226-227 (2002)

82. Malamou-Mitsi,V., L. Pappa, T. Vougiouklakis, D. Peschos, N. Kazakos, G. Grekas, D. Sideris & N.J. Agnantis: Sudden death due to an unrecognized cardiac hydatid cyst. *J. Forensic Sci* 47, 1062-1064 (2002)

83. BeshlyagaV.M., V.B. Demyanchuk, M.D. Glagola & V.V. Lazorishinets: Echinococcus cyst of the left ventricle in 10-year-old patient. *Eur J Cardiothorac Surg* 21, 87 (2002)

84. El Fortia M., M. Bendaoud, H. Maghur, A.A. Ben Musa, A. Ettir, A. Dirar & K.H. Alzwae: Intracavitary cardiac hydatid cyst and the wall sign criteria. *Eur J Ultrasound* 8, 115-117 (1998)

85. Pinkerton H. & R.G. Henderson: Adult toxoplasmosis: a previously unrecognized disease entity simulating the typhus-spotted fever group. *JAMA* 110, 807-814 (1941)

86. Sabin A.B: Toxoplasmic encephalitis in children. *JAMA* 116, 801-807 (1941)

87. McGregor CG.A., D.G. Fleck, J. Nagington, P.G.I. Stovin, R. Cory Pearce & T. English: Disseminated toxoplasmosis in cardiac transplantation. *J Clin Path* 37, 74-77 (1984)

88. Luft B.J. & J.S. Remington: Toxoplasma encephalitis. *J Infect Dis* 157, 1-6 (1988)

89. Roldan E.O., L. Moskowitz & G.T.Hensley: Pathology of the heart in acquired immunodeficiency syndrome. *Arch Path Lab Med* 111,943-946 (1987)

90. Dubey .J.P, D.S. Lindsay & C.A. Speer: Structures of *Toxoplasma gondii* tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts. *Clin Microbiol Rev* 11, 267-299 (1998)

91. Weiss L.M. & K. Kim: The development and biology of bradyzoites of *Toxoplasma gondii*. *Frontiers Bioscience* 5, D391-405 (2000)

92. McCabe R.E., B.J. Luft & J.S. Remington: Effect of murine interferon gamma on murine toxoplasmosis. *J Infect Dis* 150, 961-962 (1984)

93. Matturi L., P. Quattrone, C. Varesi & L. Rossi: Cardiac toxoplasmosis in pathology of acquired immunodeficiency syndrome. *Panminerva Med* 32, 194-196 (1990)

94. Adair O.V., N. Randive & N. Krasnow: Isolated toxoplasma myocarditis in acquired immune deficiency syndrome. *Am Heart J* 110,856-857 (1989)

95. Grange F., E.L. Kinney, J.J. Monsuez, M. Rybojad, F. Derouin, M.A. Khuong & M. Janier: Successful therapy for *Toxoplasma gondii* myocarditis in acquired immunodeficiency syndrome. *Am Heart J* 120, 443-444 (1990)

96. Tolat D. & H.S. Kim: Toxoplasmosis of the brain and heart: autopsy report of a patient with AIDS. *Tex Med* 85, 40-42 (1989)

97. Klatt E.C. & P.R. Meyer: Pathology of the heart in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 112, 114 (1987)

98.Medlock M.D., J.T. Tilleli & G.S. Pearl: Congenital cardiac toxoplasmosis in a newborn with acquired immunodeficiency syndrome. *Pediatrc Infect Dis J* 9,129-132 (1990)

99. Herdy G.V., A.H. Herdy, P.S. Almeida, R. deCarvalho, F.B. Azevedo, K. Asevedo, M.C. Vasconcelos, R. Paiva, H.Y. Tchou, P. Mascimento, R. Cosendey, A. Ferrari & V.S. Lopes: Cardiac abnormailities in the acquired immunodeficiency syndrome. A prospective study with a clinical-pathological correlation in twenty-one adult patients. *Arq. Bras. Cardiol.* 73,281-290 (1999)

100. Hofman P., M.D. Drici, P. Gibelin, J.F. Micheils & A. Thyss: Prevalence of toxoplasma myocarditis in patients with the acquired immunodeficiency syndrome. *Br Heart J* 70,376-381 (1993)

101. Memel D.S. A.J. DeRogatis & D.C. William : Ga-67 citrate uptake in a patient with AIDS, toxoplasmosis, and myocarditis. *Clin Nucl Med* 1,315-317 (1991)

102. Albrecht H., H.J. Stellbrink, S. Fenske, H. Schafer & H. Greten: Successful treatment of *Toxoplasma gondii* myocarditis in an AIDS patient. *Eur J Clin Microbiol Infect Dis* 13,500-504 (1994)

103. Wagner F.M., H. Reichenspurner, P. Uberfuhr, M. Weiss, V. Fingerle & B. Reichart: Succesfful treatment of *Toxoplasma gondii* myocarditis in an AIDS patient. *J Heart Lung Transplant* 13, 916-918 (1994)

104. Krick J.A. & J.S. Remington: Toxoplasmosis in the adult-an overview. *New Engl J Med* 298,550-553 (1978)

105. Jehn U., M. Fink, P. Gundlach, W.D. Schwab, K. Bise, W.D. Deckstein & B. Wilske: Lethal cardiac and cerebral toxoplasmosis in a patient with acute myeloid leukemia after successful allogeneic bone marrow transplantation. *Transplantation* 38, 430-431 (1984)

106. Emerson R.G., D.S. Jardine, E.S. Milvenan, B.J. D'Souza, G.J. Elfenbein, G.W. Santos & R. Saral: Toxoplasmosis: a treatable neurologic disease in the immunologically compromised patient. *Pediatrics* 87, 653-655 (1981)

107. Lowenberg B., J.Van Gijn, E. Prins & A.M. Polderman: Fatal cerebral toxoplasmosis in a bone marrow transplant recipient with leukemia. *Transplantation* 35, 30-34 (1983)

108. Watson I.G: Problems of infection after bone marrow transplantation. J Clin Pathol 36,683-692 (1983)

109. deMedeiros B.C., C.R. deMedeiros, B. Werner, G. Loddo, R. Pasquini & L.F. Bleggi-Torres: Disseminated toxoplasmosis after bone marrow transplantation: report of 9 cases. *Transp Infect Dis* 3,24-28 (2001)

110. Perez Castrillon J.L., J.M. Cruz, V. Escudero, J.A. Benhez, A. Ostos & V. Caballero: Chronic pericardial effussion due to *Toxoplasma gondii* in a patient with myelodysplastic syndrome. *Rev Clin Esp* 18, 310-311 (1990)

111. Laske A., E. Bauer, L. con-Segesser, A. Gallino & M. Turina: Operative und perioperative probleme der Herztransplantation. *Ther-Umsch* 47, 111-121 (1990)

112. Hakim M., T.G. Wreghitt, T.A. English, P.G. Stovin, R. Cory-Pearce & J. Wallwork: Significance of donor transmitted disease in cardiac transplantation. *J Heart Transplant* 4,302-306 (1985)

113. Luft B.J., M. Billinham & J.S. Remington: Endomyocardial biopsy in the diagnosis of toxoplasmic myocarditis. *Transplant Proc* 18, 1871-1873 (1986)

114. Luft B.J., Y. Naot, F.G. Araujo, E.B. Stinson & J.S. Remington: Primary and reactivated toxoplasma infection in patients with cardiac transplant. *Ann Int Med* 99, 27-31 (1983)

115. Michaels M.G., E.R. Wald, F.J. Fricker, P.J. del Nido & J. Armitage: Toxoplasmosis in pediatric recipients of heart transplant. *Clin Infect Dis* 14,847-851 (1992)

116. Holliman R.E., J.D. Johnson, S. Adams J.R. Pepper: Toxoplasmosis and heart transplantation. *J Heart Lung Transplant* 10,608-610 (1991)

117. Ross A.G., C.J. Uys, D. Novitsky, D.K. Cooper & C.N. Barnard: Toxoplasmosis of donor and recipient hearts after heterotopic cardiac transplantation. *Arch Pathol Lab Med* 107,368-373 (1983)

118. Barcan L.A., M.L. Dallurzo, L.O. Clara, A. Valledor, S. Macias, E. Zorkin, S. Gerona & B. Liverllara: *Toxoplasma gondii* pneumonia in liver transplantation: survival after a severe case of reactivation. *Transpl Infect Dis* 4, 930-96 (2002)

119. Ruskins J. & J. S. Remington:. Toxoplasmosis in the compromised host. *Ann Intern Med* 84, 193-199 (1976)

120. Reynolds E.S., K.W. Walls & R.I. Pfeiffer: Generalized toxoplasmosis following renal transplantation. *Arch Int Med* 118:401-405 (1966)

121. Chappell L.H. & J.M. Wastling: Cyclosporin A: antiparasite drug, modulator of the host parasite relationship and immunosuppressant. *Parasitology* 105, Suppl: S25-40 (1992)

122. Conley F.K., K.A. Jenkins & J.S. Remington: *Toxoplasma gondii* infection of the central nervous system: use of the peroxidase-antiperoxidase method to demonstrate toxoplasma in formalin fixed, paraffin embedded tissue sections. *Human Pathol* 2, 690-698 (1980)

123. Hakim M., D. Esmore, J. Wallwork, T.A.H. English & T. Wreghitt: Toxoplasmosis in cardiac transplantation. *Br Med J* 292, 1108 (1986)

124. Wreghitt T.G., J.J. Gray, P. Pavel, A. Balfour, A. Fabbri, L.D. Sharples & J. Wallowrk: Efficacy of pyrimethamine for the prevention of donor-acquired *Toxoplasma gondii* infection in heart and heart-lung transplant patients. *Transpl Int* 5,197-200 (1992)

125. Keogh A., P. MacDonald, D. Richens, A. Harvison & P. Spratt: Mini-dose trimethoprim with sulphamethoxazole prevents pneumocystis and toxoplasmosis infections after heart transplantation. *Transplant Proc* 24, 2263 (1992)

126. Balden L.R., J.T. Katz, L. Franck, S. Tsang, M. Hall, R.H. Rubin & J. Jarcho: Successful toxoplasmosis prophylaxis after orthopic cardiac transplantation with trimethoprim-sulfamethoxazole. *Transplantation* 75, 339-343 (2003)

127. Ali U.S., P.M. Sheth, A. Murthy, A. Chitale, K.P. Mehta & J.K. Shah: Congenital toxoplasmosis. *Indian Ped* 22, 387-392 (1985)

128. Chandenier J., G. Jarry, D. Nassif, Y. Douadi, L. Paris, P. Thulliez, E. Bourges-Petit & C. Raccurt : Congestive heart failure and myocarditis after seroconversion for toxoplasmosis in two immunocompetent patients. *Eur J Clin Microbiol Infect Dis* 19, 375-379 (2000)

129. Garcia A.G., A.C. Torres & C.S. Pegado: Congenital toxoplasmic myocarditis: case report of an unusual presentation. *Ann Trop Paediat* 5, 227-230 (1985)

130. Leak D. & M. Meghji: Toxoplasmic infection in cardiac disease. *Am J Cardiol* 43, 841-849 (1979)

131. Cunningham T. Pancarditis in acute toxoplasmosis. *Am J Clin Path* 78,403-405(1982)

132. Sagrista-Sauleda J., G. Permanyer-Miralda, C. Juste-Sanchez C, M.L. de Buen-Sanchez, R. Pujadas-Capmany, L. Arcalis-Arce & J. Soler-Soler: Huge chronic pericardial effusion caused by *Toxoplasma gondii*. *Circulation* 66, 895-897 (1982)

133. Collart F., Y. Glupzinski, E. Cogan & J. Schmerber: Acute pericarditis of toxoplasmic origin. *J Infect* 7, 82-83 (1983)

134. Mirada A., J. Rubies-Prat, E. Cerda & E. Foz: Pericarditis associated to acquired toxoplasmosis in a child. *Cardiology* 61, 303-306 (1976)

135. Najaratnam N. & S.J. Stephen: Chronic constrictive pericarditis associated with toxoplasmosis. *Br Heart J* 35,868-870 (1973)

136. Arribada A. & E. Escobar: Cardiomyopathies produced by *Toxoplasma gondii*. *Am Heart J* 76,329-339 (1968)

137. Apt W. & A. Arribada: Parasitic cardiomyopathies. *Infection* 4, 16-20 (1976)

138. Mary A.S. & M. Hamilton: Ventricular tachycardia in a patient with toxoplasmosis. *Br Heart* J 35, 3 49-352 (1973)

139. Coyle C.M., M. Wittner & H.B. Tanowitz: Cysticercosis In: Tropical Infectious Diseases. Eds Guerrant RL, Walker DH, Weller PF. Churchill Livingstone Philadelphia (1999)

140. Goldsmid J.M.: Two unusual cases of cysticercosis in a man in Rhodesia. J Helminthology 40, 331-336 (1966)

141. Ibarra-Perez C., J. Fernandez-Diez & F. Rodriguez-Trujillo: Myocardial cycticercosis: Report of two cases with coexisting heart disease. *South Med J* 65:484-486(1972)

142. Niakara A., R. Cisse, A. Traore, P.A. Niamba, F. Barro & J. Kabore: Myocardial localization of a disseminated cysticercosis. Echocardiographic diagnosis of a case. *Arch Mal Coeur Vaiss*
95, 606-6-8 (2002)

143. Lino Junior Rde S., P.M. Ribeiro, E.J. Antonelli, A.C. Faleiros, S.A. Terra, M.A. dos Reiss & P. Teixeira Vde. Developmental characteristics of Cysticercus cellulosae in the human brain and heart. *Rev Soc Bras Med Trop* 35,617-622 (2002)

144. Roy S.L., A.S. Lopez & P.M. Schantz: Trichinellosis Surveillance-United States, 1997-2001. In *Surveillance Summaries*. *MMWR* 52, No.SS-6 1-8 (2003)

145. Fourestie V., H. Douceron, P. Brugieres, T. Ancelle, J.L. Lejone & R.K. Gherardi: Neurotrichinosis . A cerebrobrovascular disease associated with myocardial injury and hypereosinophilia. *Brain* 116,603-616, (1993)

146. Compton S.J., C.L. Celum & C.Lee: Thompson D, Sumi SM, Fritsche TR, Coombs RW. Trichinosis and ventilatory failure and persistent myocarditis. *Clin Infect Dis* 16,500-504 (1993)

147. Solarz S.D: An electrocardiographic study of one hundred fourteen consecutive cases of trichinosis. *Am Heart J* 34, 230-240 (1947)

148. Metzler M.H., K.K. Dashga, G.S. Wolff: Second degree atrioventricular block in acute trichinosis. *Am J Dis Child* 124,598-601 (1972)

149. Kirshberg G.J: Trichinosis presenting as acute myocardial infarction. *Can Med Assn J* 106, 898-901 (1972)

150. Bessoudo R., Marrie T.J. & E.R. Smith: Cardiac involvement in trichinosis. *Chest* 79:698-699 (1982)

151. Markowitz S.M., A.J. Martinez, R.J. Duma & F.O. Shiel: Myocarditis associated with primary amebic (Naegleria) meningoencephalitis *Am J Clin Pathol* 62,619-628 (1974)

152. Shaper A.G: Cardiovascular diseases in the tropics. II. Endomyocardial fibrosis. *Br Med J*. 3,743-746 (1972)

153. Andy J.J: Aetiology of endomyocardial fibrosis (EMF). *West Afr J Med* 20,199-207 (2001)

154. Andy J.J., P.O. Ogunowo, N.A. Akpan, C.O. Odigwe, I.A. Ekanem & R.A. Esin: Helminth associated hypereosinophilia and tropical endomyocardial fibrosis (EMF) in Nigeria. *Acta Trop* 69,127-140 (1998)

155. Andy J.J., F.F. Bishara, O.O. Soyinka & W.O. Odesanmi: Loasis as a possible trigger of African endomyocardial fibrosis: a case report from Nigeria. *Acta Trop* 38, 179-186 (1981)

156. Silva J.S., F.S. Machado & G.A. Martins: The role of nitric oxide in the pathogenesis of Chagas disease. *Front Biosci* 8, s314-325 (2003)

157. Mukherjee S., H. Huang, L.M. Weiss, S. Costa, J. Scharfstein & H.B. Tanowitz: Role of vasoactive mediators in the pathogenesis of Chagas' disease. *Front Biosci* 8, e410-419 (2003)

158. Shirani J., A. Ilercil, M. Chandra, L.A. Jelicks & H.B. Tanowitz: Cardiovascular imaging in clinical and experimental acute infectious myocarditis. *Front Biosci* 8, e323-336 (2003)

159. Williams-Blangero S., J.L. VandeBerg, J. Blangero & R. Correa-Oliveira: Genetic epidemiology of *Trypanosoma cruzi* infection and Chagas' disease. *Front Biosci* 8, e337-345 (2003)

160. Leon J.S. & D.M. Engman: The significance of autoimmunity in the pathogenesis of Chagas heart disease. *Front Biosci* 8, e315-322 (2003)

161. Rocha M.O., A.L. Ribeiro. & M.M. Teixeira: Clinical management of chronic chagas cardiomyopathy. *Front Biosci* 8, e44-54 (2003)

162. Gao W. A., O. Luquetti & M.A. Preira: Immunological tolerance and its breakdown in Chagas' heart disease: role of parasitokines. *Front Biosci* 8, e218-227 (2003)

163. Rossi M.A., S.G. Ramos, R.B. Bestetti: Chagas' heart disease: clinical-pathological correlation. *Front Biosci* 8, e94-109 (2003)

Key Words: Parasites, Myocarditis, Cardiomyopathy, Chagas' disease, Toxoplasmosis, Trichinosis, Amebiasis, Echinococcus, Cysticercosis, Endocardial fibroelastosis, Review

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