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# Assessment and management of Chagas disease: a comprehensive analysis

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**ABSTRACT**

The protozoan Trypanosoma cruzi is the cause of Chagas disease, a serious but often ignored topical illness that mostly affects people in Latin America. Triatomine bugs are the vector of transmission, and the illness can progress through acute and chronic phases, the latter of which may cause serious neurological, gastrointestinal, or cardiac problems. Chagas disease is still a major worldwide health concern despite tremendous progress in diagnosis and treatment because of poor control measures in endemic areas, lack of knowledge, and restricted access to healthcare. This review article gives a summary of what is now known about Chagas disease, including its pathogenesis, clinical presentation, epidemiology, and diagnostic methods. It also examines the current therapy choices, emphasizing the difficulties associated with pharmacological effectiveness, side effects, and the requirement for novel treatment alternatives. The essay also covers the global spread of Chagas disease and how increased travel patterns have contributed to its growth, as well as current developments in monitoring systems and vector control techniques. In order to combat the rising incidence of Chagas disease globally, the study also emphasizes current studies into new treatment drugs and vaccine development. This review article gives a summary of what is now known about Chagas disease, including its pathogenesis, clinical presentation, epidemiology, and diagnostic methods. It also examines the current therapy choices, emphasizing the difficulties associated with pharmacological effectiveness, side effects, and the requirement for novel treatment alternatives. The essay also covers the global spread of Chagas disease and how increased travel patterns have contributed to its growth, as well as current developments in monitoring systems and vector control techniques. In order to combat the rising incidence of Chagas disease globally, the study also emphasizes current studies into new treatment drugs and vaccine development.

**Keyword:** Chagas disease, protozoan Trypanosoma cruzi, Triatomine bugs, epidemiology, diagnostic methods.

## I. INTRODUCTION

The tropical parasite Trypanosoma cruzi is the cause of Chagas disease, commonly referred to as American trypanosomiasis. The majority of the insects that carry it are "kissing bugs" that belong to the Triatominae subfamily. Throughout the illness, the symptoms vary. Fever, enlarged lymph nodes, headaches, or swelling at the bite site are among the early symptoms, which are usually either nonexistent or very minor. Untreated patients go into the chronic phase of the illness after four to eight weeks, which often does not cause any further symptoms. Ten to thirty years after the first sickness, up to forty-five percent of persons with chronic infections develop heart disease, which can result in heart failure. Up to 21% of individuals may also develop digestive problems, such as an enlarged colon or esophagus, and up to 10% may sustain nerve damage.Both the kissing bug's bite wound and its contaminated excrement are frequent ways for humans and other mammals to get T. cruzi. Additionally, taking food or drink tainted with the parasites, receiving an organ donation, receiving blood transfusions, and vertical transmission—the transfer of the illness from mother to child—can all spread the disease. Early illness diagnosis involves either identifying the parasite in the blood under a microscope or detecting its DNA via a polymerase chain reaction. Finding T. cruzi antibodies in the blood helps diagnose chronic illness.

Eliminating kissing bugs and preventing their bites are the main goals of prevention. This might entail using bed nets or pesticides. Transfusion-related blood screening is one of the other prophylactic measures. If administered soon after infection, benznidazole or nifurtimox may

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typically cure early infections; however, their effectiveness decreases with the length of time a person has had Chagas disease. Medication may postpone or stop the onset of end-stage symptoms in chronic diseases.Benznidazole and nifurtimox frequently induce adverse effects, such as neurological symptoms, gastrointestinal distress, and skin diseases, which may lead to the discontinuation of therapy. Although experimental vaccinations have been tested in animal models, no human vaccine has been created, and new medications are being researched to treat Chagas disease.As of 2019, an estimated 6.5 million individuals, primarily in Mexico, Central America, and South America, suffer from Chagas disease, which causes around 9,490 fatalities annually. The majority of those who have the illness are impoverished, and the majority are unaware that they have it. Chagas disease has spread to new areas due to large-scale population migrations, including the US and several European nations. The illness affects about 150 different kinds of animals.

**Signs and symptoms**

Chagas disease has two phases: an acute stage that appears one to two weeks after the bug bite and a chronic stage that takes years to manifest. Often, there are no symptoms during the acute phase. When they do appear, the symptoms are usually mild and unrelated to any one illness. Fever, malaise, headaches, and enlargement of the liver, spleen, and lymph nodes are among the symptoms. A swelling nodule, known as "Romaña's sign" if it appears on the eyelid or "chagoma" if it appears elsewhere on the skin, can occasionally form at the site of infection. Less than 1% to 5% of infected people get severe acute illness, which can be fatal and include inflammation of the heart muscle, fluid buildup around the heart, and inflammation of the brain and surrounding organs. Without therapy, the acute phase usually ends within four to eight weeks.

People who recover from the acute phase of T. cruzi infection continue to have the infection unless they get antiparasitic medication. Indeterminate chronic Chagas disease refers to the majority of chronic infections that do not cause any symptoms. About 30 to 40 percent of patients with chronic Chagas disease, which mostly affects the heart or digestive system, experience organ failure throughout the course of the disease.

Heart disease is the most prevalent long-term symptom, occurring in 14%–45% of those with chronic Chagas disease. Due to abnormal cardiac function, people with Chagas heart disease frequently feel palpitations and even fainting. Arrhythmias are the most common ECG abnormality in patients with Chagas heart disease. With dilated cardiomyopathy, the heart's ventricles grow as the illness worsens, decreasing the heart's capacity to pump blood. Heart failure, thromboembolism, or chest discomfort linked to anomalies in the microvasculature are frequently the initial symptoms of Chagas heart disease.

Ten to twenty-one percent of persons with chronic Chagas disease also have digestive tract impairment. The most prevalent digestive problems are esophageal or colon enlargement. Acid reflux, coughing, weight loss, and discomfort (odynophagia) or difficulty swallowing (dysphagia) are common symptoms of an enlarged esophagus. Constipation is common in people with larger colons, and they may also endure severe intestinal or blood vessel obstruction. Up to 10% of people with persistent infections experience nerve injury, which can lead to numbness and changes in movement or reflexes. Less than 10% of people with Chagas disease get cardiac damage right after acute illness, although chronic disease usually takes decades to develop.

For those who get T. cruzi through less usual routes, the signs and symptoms vary. Infected individuals typically have severe symptoms, such as fever, vomiting, dyspnea, coughing, and discomfort in the muscles, chest, and abdomen, within three weeks of ingesting the parasites. Congenitally infected individuals usually have few or no symptoms, although they may have moderate, nonspecific symptoms or more serious ones,including cardiac issues, respiratory distress, and jaundice. The symptoms of vector-borne illness are often identical in those infected by organ transplantation or blood transfusion, but they may not appear for a week or five months. Chronically infected people who develop immunosuppression as a result of HIV infection may experience a very severe and unique illness, which is typically characterized by brain abscesses or inflammation in the brain and surrounding tissue. Fever, headaches, seizures, loss of feeling, and other neurological problems that point to specific areas of nervous system injury are common symptoms, however, they can vary greatly depending on the size and location of brain abscesses. On rare occasions, these people also have skin lesions, stomach, intestinal, or peritoneal diseases, and acute cardiac inflammation.

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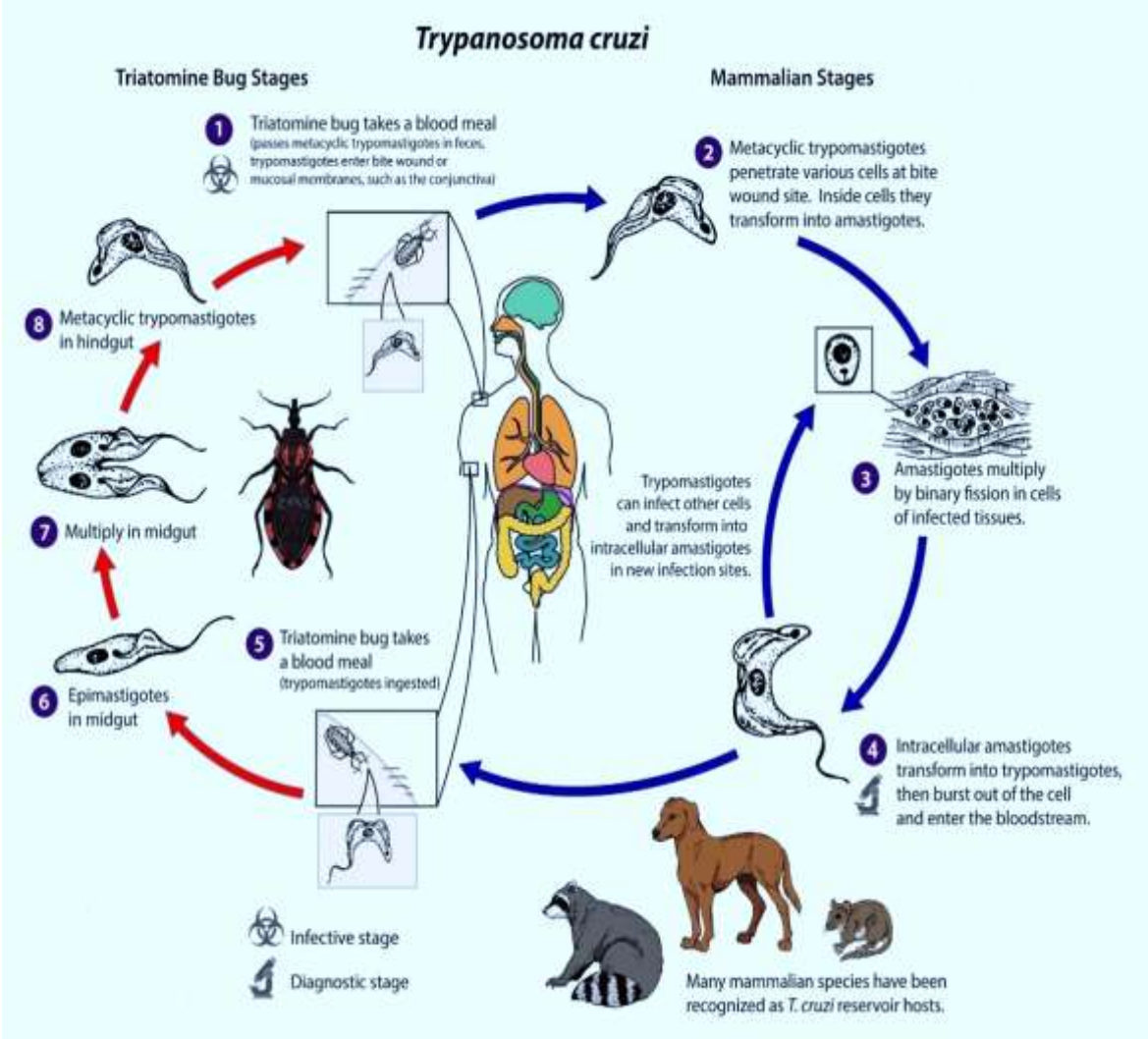
**Cause**

The protozoan parasite T. cruzi, which causes Chagas disease, is usually contracted by humans through the bite of a triatomine insect, commonly known as a "kissing bug." Trypomastigotes, which are motile T. cruzi forms, enter the circulation and infiltrate different host cells when the insect excretes at the bite site. The parasite changes into an amastigote, a replicating form that replicates several times inside a host cell. After replicating, the amastigotes change back into trypomastigotes, which rupture the host cell and enter the circulation. Trypomastigotes then spread to different parts of the body, where they infiltrate cells and multiply. These tissues, especially the heart and digestive system, can sustain significant damage over many years due to cycles of parasite multiplication and immune response.




**Transmission**

Several triatomine insects belonging to the genera Triatoma, Panstrongylus, and Rhodnius can spread T. cruzi. The triatomine insect species that live in human homes—Triatoma infestans, Rhodniusprolixus, Triatoma dimidiata, and Panstrongylusmegistus—are the main carriers of human infection. Local names for these insects include barbeiro (the barber) in Brazil, pito in Colombia, chinche in Central America, chipo in Venezuela, and vinchuca in Argentina, Bolivia, Chile, and Paraguay. The insects often feed at night and like damp areas close to the mouth or eyes. When a triatomine insect feeds on an infected host, it can contract T. cruzi. T. cruzi is excreted in the insect's feces after replicating in its digestive system. As an infected triatomine eats, it punctures its skin, consumes a blood meal, and

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simultaneously excretes to create way for the new food. Although the bite usually does not hurt, it itches. Scratching the bite causes the bite wound to become infected with T. cruzi-laden excrement.

Apart from traditional vector transmission, the ingestion of food or beverages tainted with triatomine insects or their excrement can also spread Chagas disease.The most common source of infection is beverages, particularly fruit juices, as heating or drying destroys the parasites.A single crushed triatomine in a food or beverage containing T cruzi can contain approximately 600,000 metacyclic trypomastigotes, while triatomine fecal matter contains 3,000–4,000 per μL. This oral route of transmission has been linked to multiple outbreaks where it caused abnormally severe symptoms, most likely because the infection had a higher parasite load than from the bite of a triatomine bug.

Independent of the triatomine bug, T. cruzi can spread after blood transfusions, after organ transplants, or during pregnancy through the placenta. Ten to twenty-five percent of the time, the receiver becomes infected after receiving blood transfusions from an infected donor. Many nations with endemic Chagas disease, including the United States, test blood donors for T. cruzi to avoid this. Transplanting solid organs from an infected donor might also expose the recipient to T. cruzi. This is especially true for heart transplant, which transmits T. cruzi 75–100% of the time, and less so for transplantation of the liver (0–29%) or a kidney (0–19%). An infected mother can pass T. cruzi to her child through the placenta; this occurs in up to 15% of births by infected mothers. As of 2019, 22.5% of new infections occurred through congenital transmission.

**Pathophysiology**

Large-scale cardiac structure affected by long-term Chagas disease

T. cruzi replication and the immune system's reaction to it are the direct causes of the disease's acute phase signs and symptoms.T. cruzi circulates in the blood and is present in a variety of bodily tissues during this phase.Over the first few weeks of infection, the production of antibodies and the activation of the host's inflammatory response—especially cells that target intracellular pathogens like NK cells and macrophages—driven by inflammation-signaling molecules like TNF-α and IFN-γ, control the replication of parasites.

Long-term organ damage occurs over years in chronic Chagas disease as a result of immune system damage and the parasite's ongoing proliferation. The heart's striated muscle fibers are often home to T. cruzi early in the course of the illness.The heart often enlarges as the illness worsens, with significant areas of cardiac muscle fiber gone and replaced by fat and scar tissue.The heart contains inflammatory immune cells, mostly T cells and macrophages, in each of the areas of active inflammation.The presence of parasites in the heart is uncommon in the later stages of the illness and may be quite low.

Chronic illness causes a significant loss of nerve endings in the esophagus, colon, and heart. This might be a contributing factor to cardiac dysfunction, including arrhythmias. The primary cause of organ dysfunction in the colon and esophagus is a lack of nervous system regulation. Nerve loss affects how food passes through the digestive system, which can cause obstruction of the colon or esophagus and limit the flow of blood to those areas.

The parasite can insert kinetoplast DNA into host cells, an example of horizontal gene transfer. Vertical inheritance of the inserted kDNA has been demonstrated in rabbits and birds. In chickens, offspring carrying inserted kDNA show symptoms of disease despite carrying no live trypanosomes. In 2010, integrated kDNA was found to be vertically transmitted in five human families.

**Diagnosis**

It is possible to diagnose Chagas disease by looking for T. cruzi in the blood. Fresh anticoagulated blood or its buffy coat can be examined under a microscope for motile parasites during the acute phase of infection. Alternatively, thin and thick blood smears stained with Giemsa can be prepared for direct parasite visualization.In 34–85% of instances, a blood smear test finds parasites. Using methods like microhematocrit centrifugation to concentrate the blood improves sensitivity.T. cruzi trypomastigotes are visible as S or U-shaped organisms with a flagellum attached to the body by an undulating membrane when seen under a microscope on stained blood smears.Inside the parasite's body, one can see a nucleus and a smaller component known as a kinetoplast; T. cruzi's kinetoplast is comparatively big, which helps to differentiate it from other human-infecting trypanosome species.

An alternative method for detecting T. cruzi DNA is the polymerase chain reaction (PCR). Because PCR is unaffected by the transmission of antibodies against T. cruzi from a mother to her child (passive immunity), it is more sensitive than

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microscopy in cases of acute and congenital Chagas disease and more trustworthy than antibody-based assays for the diagnosis of congenital illness.PCR also helps detect infection or reactivation early on by tracking T. cruzi levels in immunocompromised individuals and organ transplant patients.

Serological tests, which identify immunoglobulin G antibodies against T. cruzi in the blood, are often used to diagnose chronic Chagas disease since the quantity of parasites in the blood is too low to be accurately identified by microscopy or PCR.Confirmation of the diagnosis requires two positive serology results from several test modalities.It is possible to employ other testing techniques, including Western blot, if the test findings are not definitive.

There are several quick diagnostic tests for Chagas disease. People without specialized training can do these tests, and they are portable.They work well for screening a lot of people and testing those who can not go to medical institutions, but they have a poor sensitivity, therefore, it is best to employ a second approach to confirm a positive result.

It is possible to cultivate T. cruzi parasites from blood samples using xenodiagnosis, blood culture, or animal inoculation. To promote the parasite's growth, the blood culture procedure involves removing the individual's red blood cells from the plasma and adding them to a specific growing medium. The outcome may not be available for up to six months. Feeding the blood to triatomine insects and then checking their excrement 30 to 60 days later for the parasite is known as xenodiagnosis.We do not often employ these techniques since they are sluggish and insensitive.It is possible to cultivate T. cruzi parasites from blood samples using xenodiagnosis, blood culture, or animal inoculation. To promote the parasite's growth, the blood culture procedure involves removing the individual's red blood cells from the plasma and adding them to a specific growing medium. The outcome may not be available for up to six months. Feeding the blood to triatomine insects and then checking their excrement 30 to 60 days later for the parasite is known as xenodiagnosis.We do not often employ these techniques since they are sluggish and insensitive.

**Prevention**

To reduce exposure to triatomine bugs, vector management has been the main focus of efforts to prevent Chagas disease. The cornerstone of vector control has been insecticide-spraying operations, which include applying residual pesticides to dwellings and the surrounding region. Originally, carbamate, organochlorine, and organophosphate insecticides were used for this, but in the 1980s, pyrethroids replaced them.These initiatives have eradicated key vectors from some places, including Rhodniusprolixus from Central America and Triatoma infestans from Brazil, Chile, Uruguay, and portions of Peru and Paraguay. They have also significantly decreased transmission in Brazil and Chile. The emergence of pesticide resistance in triatomine bugs has made vector management more difficult in some areas. Vector control programs have responded with other insecticides (such as benitrothion and bendiocarb in Argentina and Bolivia), pesticide-impregnated paints, treatment of farmed animals (which are also consumed by triatomine bugs), and other experimental methods.In regions where triatomine bugs are present, sleeping beneath bed nets and making home renovations that keep triatomine bugs from colonizing homes can help stop the spread of T. cruzi.

Chagas disease was once most often spread by blood transfusions.T. cruzi may persist in whole blood, packed red blood cells, granulocytes, cryoprecipitate, and platelets because it can withstand freezing and thawing as well as being in refrigerated stored blood.The danger of infection during a blood transfusion has significantly decreased because of the creation and application of blood bank screening techniques.Serological tests, usually ELISAs, are used to detect antibodies against T. cruzi proteins in donor blood. Chagas screening is performed on almost all blood donations in Latin American countries. Widespread screening is also common in non-endemic countries with sizable immigrant populations from endemic areas, such as the United Kingdom (implemented in 1999), Spain (2005), the United States (2007), France and Sweden (2009), Switzerland (2012), and Belgium (2013).

Programs to prevent Chagas disease have focused on other ways of transmission. Pregnancy-related treatment for moms infected with T. cruzi lowers the chance of congenital infection transmission.The World Health Organization advises screening all children born to infected mothers to prevent congenital infection from progressing into chronic illness, and several Latin American nations have instituted routine screening for T. cruzi infection in pregnant women and babies.Many nations with endemic Chagas disease use serological testing to screen organs for

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transplantation, just like they do with blood transfusions.

A vaccination to prevent Chagas disease does not exist. Although several experimental vaccinations have been tried on T. cruzi-infected animals and have been shown to lower blood and heart parasite counts, as of 2016, no vaccine candidates had passed human clinical trials.

**Management**


A container of Nifurtimox pills

The management of Chagas disease involves the use of antiparasitic medications to eradicate T. cruzi from the body and symptomatic therapy to alleviate the infection's consequences. Although benznidazole is the sole medication accessible in the majority of Latin America, as of 2018, nifurtimox and benznidazole were the preferred antiparasitic medications for treating Chagas disease.The usual course of treatment for either medication is two to three oral doses daily for 60 to 90 days. Early in the course of infection, antiparasitic therapy is most successful; it eradicates T. cruzi from 50–80% of patients during the acute phase (WHO: "almost 100%") but only 20–60% of patients during the chronic phase. Children respond better to chronic illness treatment than adults do, and congenital disease cure rates are nearly 100% if treated within the first year of life.Additionally, antiparasitic therapy can lessen the chance of congenital transmission and decrease the disease's course.Treating chronic Chagas disease separately is necessary since eliminating T. cruzi does not repair the damage to the heart and gastrointestinal tract.People who already have dilated cardiomyopathy should not use antiparasitic medication.

Since its effectiveness is well known and its negative effects are less severe than those of nifurtimox, benzolidazole is typically regarded as the first-line therapy.The usual negative effects of nifurtimox and benznidazole might lead to the discontinuation of therapy. Skin rash, digestive issues, decreased appetite, weakness, headaches, and sleep issues are the most frequent adverse effects of benznidazole. Antihistamines and corticosteroids can occasionally be used to alleviate these adverse effects, which usually go away when therapy is stopped. However, up to 29% of instances result in the discontinuation of benznidazole. Side effects of nifurtimox are more common; up to 97.5% of patients experience them. Loss of appetite, weight loss, nausea, vomiting, and a variety of neurological conditions, such as mood swings, sleeplessness, paresthesia, and peripheral neuropathy, are the most frequent adverse effects. Up to 75% of instances result in the discontinuation of treatment. Pregnant women and anyone with liver or renal problems should not use either medication. There have been reports of resistance to these medications as of 2019.

**Complications**

Treatment for the chronic stage entails controlling the disease's clinical symptoms. Treatment for Chagas cardiomyopathy is comparable to that for other cardiac conditions. It may be necessary to prescribe beta blockers and ACE inhibitors, although some patients with Chagas disease may not be able to take the recommended dosage due to low blood pressure or a slowed heart rate.Anti-arrhythmic medications like amiodarone or pacemaker implantation are two options for treating irregular heartbeats. Using blood thinners can help avoid stroke and thromboembolism. Untreated T. cruzi infection is a prevalent cause of chronic heart disease, which frequently leads to heart transplant surgery.Transplant recipients are tracked using PCR to identify illness recurrence since they receive immunosuppressive medications to avoid organ rejection. The survival rates of heart transplant recipients with Chagas disease are greater than those of the general population.

Mild gastrointestinal disease may be treated symptomatically, such as by using laxatives for constipation or taking a prokinetic drug like metoclopramide before meals to relieve esophageal symptoms. Surgery to sever the muscles of the lower esophageal sphincter (cardiomyotomy)

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may be performed in more severe cases of esophageal disease, and surgical removal of the affected part of the organ may be required for advanced megacolon and megaesophagus.

**History**

Long before humans arrived in South America, T. cruzi was probably circulating among animals there. From a 9000-year-old Chinchorro corpse in the Atacama Desert to remains of varying ages in Minas Gerais to a 1100-year-old mummy as far north as the Chihuahuan Desert near the Rio Grande, T. cruzi has been found in ancient human remains across South America. Chagas disease symptoms are described in several early written records; Miguel Diaz Pimenta (1707), Luís Gomes Ferreira [pt] (1735), and Theodoro J. H. Langgaard (1842) are occasionally cited as the authors of these early accounts.

After evaluating a two-year-old child who had a fever, enlarged liver and spleen, and swollen lymph nodes, Carlos Chagas officially described Chagas disease in 1909. When Chagas examined her blood, he discovered trypanosomes that were the same as those he had previously discovered in the triatomine bug's hindgut and called Trypanosoma cruzi in honor of his mentor, Brazilian doctor Oswaldo Cruz. He transported infected triatomine bugs to Cruz in Rio de Janeiro, who demonstrated that marmoset monkeys could also get T. cruzi via the bite of an infected triatomine. Chagas described the disease, the organism that caused it, and the insect vector needed for infection in two years, 1908 and 1909. The illness was well known as "Chagas sickness" almost immediately after Miguel Couto, a professor at the Faculty of Medicine do Rio de Janeiro [pt], proposed the term. Chagas gained national and international recognition for his discovery, but by drawing attention to the shortcomings of the Brazilian government's response to the illness, he drew criticism against both the illness and himself. This hindered research on his discovery and probably hampered his chances of winning the Nobel Prize in 1921.

After reporting more than a thousand cases in Argentina's Chaco Province in the 1930s, Salvador Mazza reignited interest in Chagas disease research. Mal de Chagas-Mazza, named for him, is the name of the illness in Argentina. The introduction of serological testing for Chagas disease in the 1940s showed that T. cruzi infection was common across Latin America. Together with the success of using pesticides to remove the malaria vector, this led to the development of public health campaigns that aimed to eradicate triatomine bugs by treating homes with insecticides. Crystal violet was widely used in transfusion screening programs throughout Latin America after it was discovered in the 1950s that treating blood with it might eliminate the parasite. In the 1960s, extensive control initiatives started to emerge, initially in São Paulo, then in other parts of Argentina, and finally at the national level across Latin America. The development of pyrethroid insecticides in the 1980s, which were more economical and long-lasting and left no odors or stains after spraying, significantly boosted these initiatives. The Southern Cone Initiative for the Elimination of Chagas Diseases was established in 1991, followed by the Andean Initiative (1997), the Central American Initiative (1997), and the Amazonian Initiative (2004). These regional organizations were established with the assistance of the Pan American Health Organization to control Chagas disease.

**Research**

**Treatments**

In animal models, fexinidazole, an antiparasitic medication authorized for the treatment of African trypanosomiasis, has demonstrated efficacy against Chagas disease. In Spain, phase II clinical trials for persistent Chagas disease are underway as of 2019. Additional medication options include AN4169, which has shown encouraging outcomes in animal models, and GNF6702, a proteasome inhibitor that effectively treats Chagas disease in mice and is undergoing its first safety trials.

Numerous investigational vaccinations have undergone animal testing. Apart from subunit vaccines, several strategies have included immunizing against attenuated T. cruzi parasites or species like Trypanosoma rangeli or Phytomonasserpens that express some of the same antigens as T. cruzi but do not infect humans. There has also been research on DNA vaccination. As of 2019, small animal models have been the primary focus of vaccination research.

**Diagnostic tests**

As of 2018, the ability of standard diagnostic tests for Chagas disease to assess the efficacy of antiparasitic treatment was limited because PCR can produce false-negative results when the parasite concentration in the blood is low, and serological tests can continue to show positive results for years after T. cruzi has been eradicated from the body. Immunoassays against particular T.

cruzi antigens, flow cytometry testing to identify antibodies against various T. cruzi life stages, and indicators of physiological changes brought on by the parasite, such as modifications in coagulation and lipid metabolism, are some of the possible biomarkers of treatment response that are being considered.

The application of biomarkers to forecast the course of chronic illness is another field of study. There has been research on the prognosis of Chagas cardiomyopathy using serum levels of angiotensin-converting enzyme 2, brain and atrial natriuretic peptide, and tumor necrosis factor alpha. A marker of early acute and congenital infection, T. cruzi shed acute-phase antigen (SAPA) is detectable in blood by Western blot or ELISA. It has proven possible to determine congenital illness by using an assay for T. cruzi antigens in urine.

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