A prior publication from our group reported the fact that Chagas disease is underdiagnosed. This review will summarize several aspects of Chagas disease in the United States including modes of transmission, which will demonstrate that clinicians should be more aware of the disease and its consequences.

Trypanosoma cruzi is present in many animal species spread throughout most of the United States. Chagas disease also reaches the North American continent through immigration, making it more frequent than expected. Apart from immigration, non-endemic countries should be aware of transmissions through blood transfusions, organ transplantations, or mother-to-child infections.

In conclusion, it is possible that many chagasic cardiomyopathies are being misdiagnosed as “primary dilated idiopathic cardiomyopathies.” Recognizing that there is an evident threat of Chagas disease present in the United States will allow an increase of clinician’s awareness and hence will permit to correctly diagnose and treat this cardiomyopathy. Health authorities should guarantee a generalized screening of T cruzi of blood donors, before organ donations, and of pregnant women who were born or have lived in endemic areas. (Am Heart J 2009;157:22-9.)
only in very severe cases presents enlargement of further chambers. Secondly, biventricular hypertrophy is seen in 90% of the DCM and only in 40% of the ChrChC. Thirdly, radiologic signs present in the lungs that suggest congestive heart failure are more frequent and appear earlier in the DCM than in the ChrChC. Finally, the mean age in which radiologic alterations are found is lower in the DCM than in the ChrChC.\textsuperscript{5}

**Treatment**

Nifurtimox and benznidazole are the currently available chemotherapy against *Trypanosoma cruzi*. They are highly effective in treating the acute stage of the disease; nevertheless, their use in the chronic stage is controversial.\textsuperscript{5,11-18} In the United States, these drugs are not approved by the Food and Drug Administration and are available only from CDC under investigational new drug protocols.\textsuperscript{8} Questions regarding treatment in the United States should be directed to the Division of Parasitic Diseases.\textsuperscript{8}

Heart transplantation is a useful therapy for end-stage ChrChC\textsuperscript{19}; however, Chagas reactivation occurs in up to 20% and accounts for 4.2% of the deaths of post-heart transplant chagasic patients.\textsuperscript{20}

Given the fact that the epitopes of antibodies against *Trypanosoma cruzi* bare great similarity with $\beta_1$-adrenergic receptors,\textsuperscript{21} a new field for future treatment arises.

**Modes of transmission in the United States**

The vectorial transmission of the disease is the most common form in endemic regions. A bug from the Triatominae subfamily, commonly known as the kissing bug for their preference to feed on people’s faces, becomes infected by biting an infected animal or a person. These vectors are found in precarious homes built with materials such as mud, adobe, or straw.\textsuperscript{5}

Black et al\textsuperscript{22} found that compared with cement walls, cane and adobe walls were associated with an increased risk of *Trypanosoma cruzi* seropositivity. These walls are prone to cracking or presenting openings that provide hiding places and breeding sites for triatomines insects.\textsuperscript{22}

At night, the triatomines emerge from the wall fissures and may eventually fall on top of a sleeping inhabitant and transmit the parasite by defecating on their skin. The person may scratch and favor the penetration of the parasite.\textsuperscript{5}

Non-endemic regions should bear in mind that the disease is also transmitted through blood transfusions, organ transplantations, and mother-to-child transmission.\textsuperscript{5} On the other hand, immigration rates help explain why Chagas disease can be found worldwide.

**T cruzi infection in reservoirs**

Analyzing the number of infected animals and the presence of the vector in the United States is important to

### Table I. Differential diagnosis between chronic chagasic cardiomyopathy and primary idiopathic dilated cardiomyopathy according to studies >560 patients

<table>
<thead>
<tr>
<th>Clinical studies</th>
<th>ChrChC</th>
<th>Primary idiopathic dilated cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology for T cruzi</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Mean age</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class II</td>
<td>26%</td>
<td>60%</td>
</tr>
<tr>
<td>Symptom that predominates</td>
<td>Dyspnea 89%</td>
<td>Dyspnea 100%</td>
</tr>
<tr>
<td>ECG findings</td>
<td>RBBB + LAFB</td>
<td>LBBB or incomplete</td>
</tr>
<tr>
<td>Afib or Aflutter</td>
<td>2%</td>
<td>26%</td>
</tr>
<tr>
<td>Chest x-ray with cardiomegaly</td>
<td>Extreme 16%</td>
<td>Extreme: 53%</td>
</tr>
<tr>
<td>Holter monitoring</td>
<td>PVC: 48%</td>
<td>PVC: 50%</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>High-pitched holosystolic</td>
<td>High-pitched holosystolic</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Gamma camera</td>
<td>Regional</td>
<td>Global hypokinesia</td>
</tr>
<tr>
<td>Need of pacemaker</td>
<td>13% for trifascicular block</td>
<td>13% for 3° AV</td>
</tr>
<tr>
<td>Annual Mortality</td>
<td>5.2% (17% for 5-y mortality)</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Differential diagnosis**

The main differential diagnosis of ChrChC is primary dilated idiopathic cardiomyopathy (DCM). Studies performed by Milei and Storino\textsuperscript{4,9,10} in >560 patients revealed clinical differences in between these 2 pathologies (Table I).

Concerning electrocardiographic differences,\textsuperscript{5} left ventricular hypertrophy, biventricular hypertrophy and anomalous P waves will prevail in the DCM whereas conduction alterations will predominate in the ChrChC. The left bundle-branch block is more frequent in the DCM than the right bundle-branch block. Complete AV blocks have a very low prevalence in the DCM. The most frequent arrhythmias present in the DCM are premature ventricular complexes, atrial flutter, and atrial fibrillation.\textsuperscript{5}

Although a differential diagnosis of cardiomyopathies cannot be made with a chest x-ray, the DCM has some radiologic characteristics that are not frequently seen in the ChrChC.\textsuperscript{5} Firstly, the DCM usually presents an enlargement of the 4 heart chambers, whereas the ChrChC only presents left ventricular hypertrophy and...
assess the risk that American citizens have of becoming infected. In fact, it is believed that Chagas disease was first transmitted to humans after the Incas brought infected wild animals to be raised near their homes.23

Raccoons are frequently exposed to *Trypanosoma cruzi* in the United States. In an urban area of northern Virginia, outside Washington, DC, it was seen that 33% of these animals were infected.23 The prevalence of infected raccoons in other States were of 50% to 59% in Georgia, 1% in Maryland, 15% in North Carolina, 63% in Oklahoma, 40% in South Carolina, 67% in Tennessee, 24% in Texas, and 1% to 12% in Florida.24

In a series of studies performed in the state of Louisiana, the parasite was found in 1.1% to 28.8% of armadillos, 35.7% of opossums, and 4.7% of rural dogs.25 In St Catherine’s, a barrier island off the coast of Georgia, 50% of the lemurs were seropositive for *T cruzi*.26 In the Cameron county of Texas, a study performed by Beard et al27 in 2003 revealed that 7.5% of stray dogs were seropositive for *T cruzi*. On the other hand, a more recent study performed in the state of Texas in the period 2000 to 2006 revealed that 20.3% of the states’ dogs were seropositive for *T cruzi*.28 From the histopathologically confirmed cases, 97.9% presented myocarditis and 42% died of acute death. These numbers underestimate the true prevalence of infected dogs in Texas, given that it is probable that many cases were missed because they were never brought to a veterinary clinic for diagnostic testing.28 Hanford et al29 considered that the State of Texas is endemic to *T cruzi*.

The above studies show that the parasite responsible of Chagas disease is found in many US states. These rates of infection among animals are extremely high, particularly if we compare these results with what is occurring in endemic countries. Whereas in Louisiana, 35.7%25 of opossums were seropositive for *T cruzi*, in Santiago del Estero (Argentina), 32%30 to 35%31 of the opossums were infected. Accordingly, 20.3%28 of Texas’ dogs are infected, whereas in Santiago del Estero in 1996 the incidence was of 15%.32 These data suggest that those regions of the United States have a greater pool of infected animals than most endemic regions of Argentina, where according to a military service census performed in 1981, the incidence of Chagas disease among young adults was 23.7%.33

According to Gürtler et al,34 the presence of infected dogs in the household was significantly associated with the human prevalence and incidence of *T cruzi*. For this reason, the *T cruzi* should not be restricted to Latin America, as some regions in the United States have a higher incidence of infected animals than the most endemic areas of South America.

Autochthonous transmission of *Trypanosoma cruzi*

A total of 6 cases of autochthonous transmission of *T cruzi* have been reported25,35-38 to occur in the United States. The first indigenous case occurred in Texas in 1955.36 The patient was a 10-month-old female infant who presented fever, listlessness, macular rash, and peri-orbital edema of 36 hours duration. The mother and child were born and had live continually in the United States, and the child had not been out of the state. The first tentative diagnosis was a viral infection of unknown type. The second suspected diagnosis was leukemia due to the finding of Gumprecht’s shadows on a blood smear. The final diagnosis was Chagas disease as a more detailed analysis of the smear revealed typical examples of *T cruzi*.36

The third case occurred in California in 1982.35 A 56-year-old woman was admitted to the hospital for presenting fever and erythematous irregular macules of the neck, thorax abdomen, and extremities. To rule out lupus erythematosus, peripheral blood was stained with Wright’s solution. As a result, *T cruzi* was identified and Chagas diagnosis was established. The illness improved after nifurtimox therapy was implemented.35

The fifth case occurred in Tennessee in an 18-month-old boy.37 The case would have been missed if the vector would have not been found by his mother in the child’s crib. In the surroundings of the patients’ house, 2 infected raccoons and a seropositive dog were also found.

A possible explanation of why there is such a difference in between the presence of the parasite in the United States and the number of autochthonous infected Americans relies on the vector that transmits the disease from infected animals to human beings. As mentioned, the way in which the parasite accidentally infects a human being is through an insect from the family of the triatomines. In the Eastern United States, the vector is the *Triatoma sanguisuga*, in Texas and New Mexico *Triatoma gerstaeckeri*, and in Arizona and California *Triatoma rubida* and *Triatoma protracta*.27 Beard et al27 collected 31 live triatomines, and 24 of them contained *T cruzi* parasites in their hindgut. Perhaps the reason why the disease is not frequently transmitted to human beings is that the vector develops in houses commonly found in underdeveloped areas, which are not present in the United States.

According to the 2001 census, a total of 314,953 houses of Argentina are made of materials such as straw or adobe. This means that 3% of the total housing of the country is precarious enough to provide hiding places for the *Triatoma infestans*. Accordingly, in rural areas of La Rioja, an argentine province, a total of 4,062 houses where inspected, of which 46.8% where found to be infested by *T infestans*.39 Poverty leads to the construction of precarious houses built with materials that allow the breeding of the vector. In other words, poverty may be the missing link that prevents the south of the United States to be as endemic as regions of South America. For this reason, there is no apparent risk for of becoming infected with Chagas disease as long as individuals do not
stay in precarious conditions that would allow the vector to cohabit with them.

Changes in the ecosystem

Changes in the ecosystem could favor the transmission of the disease. In the Yucatan peninsula, there have been reports of increased number of triatomines 6 months after hurricane Isidore. Almost 2 months after this recommendation was published, hurricane Katrina passed through New Orleans where, 9 months later, an American citizen became infected with Trypanosoma cruzi. It was the last case of autochthonous transmission of T cruzi that occurred in a 74-year-old woman who had been repeatedly bitten by bugs from the triatomines species. The woman was positive for T cruzi antigens, and 56% of the 20 triatomines found on her home were infected as well. Given the fact that the armadillo population increased substantially in the months after hurricane Katrina, it has been hypothesized that these hosts supported a larger bug population, which later sought other blood-meal sources as the armadillo population returned to prestorm levels.

Blood transfusions

A report from the American Red Cross Blood Services of Los Angeles, CA, revealed that of 3.1 million donors, 8.3% were Hispanic. This 10-year database showed that the highest percentage of group O was found in Hispanic donors (56.5%) in contrast to white non-Hispanic donors (45.2%). As a result, blood centers initiated blood donor recruitment targeting the Hispanic population. In Rhode Island, recruitment efforts included translating the donor registration record and predonation brochure into Spanish, and hiring Spanish-speaking personnel among other things.

Five cases of transfusion-transmitted T cruzi have been unequivocally reported in the United States in the last 20 years. In the first case, fatal myocarditis developed in a 17-year-old boy who received a blood transfusion from his father, an immigrant from southeast Mexico; this patient had also traveled to endemic areas. The last case occurred in Rhode Island in a 3 1/2-year-old girl with stage 4 neuroblastoma. The patient completed 5 courses of nonmyeloablative chemotherapy that had required platelet support. A total of 78 U of leukoreduced and irradiated platelets concentrates and red cells from 78 donors had been transfused to this patient. A routine blood smear of the child revealed parasites identified as Trypanosoma cruzi. The patient was treated with nifurtimox for >3 months. Three years after the diagnosis of Chagas disease was made, the patient died because of cancer progression. The implicated donor was 50 years old who came from Bolivia 17 years earlier. This was the first case detected in a patient whose acute phase was asymptomatic. As stated by the authors, had the patient not been neutropenic, the blood smear would not have been performed and the case may have remained undiagnosed.

In a study performed in Los Angeles in 1.1 million blood transfusions, 7.1% of the donors had a broad risk for T cruzi infection (being born or having visited for >6 months an endemic country). In the Miami area, 14.3% of the donors responded “yes” to the broad risk question. Of the donations tested, 147 from Los Angeles (0.19%) and 20 from Miami (0.08%) were confirmed as seropositive for T cruzi antibodies. It is worrying how fast the seroprevalence of T cruzi in Los Angeles blood banks is increasing in the last years. In 1996, the seroprevalence rate estimate was 1/9,850 cases, 1 year later the seroprevalence increased to 1 case every 7,200. In 1998, once again, the seroprevalence increased to 1/5,400. Centers for Disease Control and Prevention reported in 2007 a seroprevalence of 1/1,993 in Los Angeles city. Figure 1 shows a linear progression of the seropositive blood donations in Los Angeles that was calculated using Microsoft Excel, demonstrating that the seropositive blood donations in Los Angeles by the year 2012 would be expected to be of 1/1,466.

These results show an alarming increase in the seroprevalence of T cruzi in the blood donations in California. A conservative estimation has shown that annually more than 600 potentially infectious components are entering the US blood supply.

Consequently, in 2007, the organizations that are responsible for approximately 65% of United States blood supply began screening all donations for T cruzi. The Food and Drug Administration is expected to recommend implementation of the test by all blood-collection establishments. Screening blood donations for T cruzi antibodies can identify persons with previously undiagnosed Chagas disease and further enhance the safety of the US blood supply.

Considering that Mexico borders with the State of California and that 68.8% of the Hispanic blood donors are represented by Mexicans, it is worthwhile mentioning that the seroprevalence of T cruzi in 43,048 Mexican blood donations increased from a mean of 1/267 in the period 1999 to 1/163 in 2003.

Organ transplantation

By July 2006, the CDC published the fourth and fifth cases of T cruzi infection through solid organ transplantation. The first 3 cases occurred on April 2001. An immigrant from Central America infected with T cruzi was the donor of a kidney and a pancreas to a 37-year-old woman, a liver to a 32-year-old woman, and
the other kidney to a 69-year-old woman. Cultures of blood from all 3 recipients were positive for *T. cruzi*. The 3 patients were treated with nifurtimox. The 69-year-old patient remained asymptomatic. The liver recipient died of sepsis and hepatic and renal failure unrelated to the *T. cruzi* infection. The 37-year-old patient who was the most immunosuppressed experienced recurrent symptomatic parasitemia and soon after he died of acute chagasic myocarditis 2 weeks into her second course of nifurtimox therapy. The fourth case was after a 64-year-old man received a heart transplant in December 2005. He was readmitted to the hospital for presenting anorexia, fever, and diarrhea of 2 weeks duration. The peripheral blood smear, the blood cultures, and the endomyocardial biopsy showed evidence of *T. cruzi* infection. After therapy with nifurtimox, the parasitemia cleared. In April 2006, he died of complications attributed to acute rejection of the transplanted organ. The organ donor had been born in the United States but had traveled to an endemic area of Mexico. Two additional recipients of this donor had no evidence of being infected. The last case of Chagas disease after organ transplantation occurred in a 73-year-old man who received a heart transplant in January 2006. He was readmitted to the hospital in February 2006 with fever, fatigue, and abdominal rash. He was positive for *T. cruzi* in the blood smear and blood cultures, but the endomyocardial biopsy did not reveal the presence of the parasite. The patient died in June because of cardiac failure and no autopsy was performed. The donor had been born in El Salvador and the 3 other recipients still remain negative for *T. cruzi*.

Transplant recipients, as well as HIV-infected patients, between others, are immunosuppressed and have a large variety of infections, several of them due to opportunistic protozoa. Although the process is not clearly understood, there appears to be a reactivation of *T. cruzi* infection, which can lead to severe meningoencephalitis. To date, there is no United Network for Organ Sharing policy or CDC recommendation concerning serologic screening for potential organ donors for *T. cruzi* in the United States.

Nowicki et al in a study performed in a total of 404 archived serum samples from deceased organ donors, found 6 initially reactive specimens. The samples belonged to 3 Hispanic, 2 African American, and 1 white. According to these results, the authors suggested that screening donors from *T. cruzi* endemic countries for
anti-*T. cruzi* antibodies may be beneficial in areas with a high frequency of these organ donors.50

Mother-to-child infections

According to Buckens et al.,51 there are 189 infected newborns per year in the United States. These estimations were calculated taking into account that there are 944,993 live births per year from Hispanic couples living in the United States. Assuming a 0.4% seropositivity rate, there would be a total of 3,780 infected mothers per year. Considering a 5% mother-to-child transmission rate, there would be a total of 189 infected newborns per year. Mother-to-child transmission of *T. cruzi* has all the characteristics required to be a public health priority, as it is relatively frequent, severe, identifiable, and treatable.51

Immigration

As said earlier, autochthonous cases of American trypanosomiasis are rare in the United States. Nevertheless, Chagas disease reaches the North American continent through immigration making it more frequent than expected.

According to an estimation made in 1992 by Milei et al,370,000 people had *T. cruzi* infection in the United States and 75,000 of those had ChChC.3 According to the Pan American Health Organization and World Health Organization,52 around 89,221 to 693,302 infected Latin Americans migrated to the United States in the period 1981 to 2005. Mexican-infected immigrants range between 47,943 and 652,024, whereas the rest of the South American infected immigrants account for a total of 17,251 Chagas disease cases exported to the United States. These numbers are mere estimations that result from combining the prevalence rates of *T. cruzi* in blood donors in the endemic countries with the immigration rate from these countries to the United States. The author considered that the prevalence in the blood bank correlated well with the serologic surveys among the general population.52

Conclusion

The first autochthonous case was identified because a blood smear was performed to rule out leukemia.36 In the third indigenous case, the parasite was accidentally discovered during a test intended to diagnose lupus eritematosus.35 The fourth case was suspected 1 year after the child’s death and was confirmed by PCR 7 years later.38 The fifth case would not have been identified if the mother would not have recalled watching a television program about insects that prey on mammals and would not had asked an entomologist to examine the bug.37 A similar situation occurred in the last identified case: the woman observed the vector in her house and showed them to a fumigator who identified them as triatomines.25

As a result, an Internet search that showed the potential for transmission of Chagas disease was made and the woman sought help from a local health center.25

In cases transmitted by organ donations and blood transfusions, it must be said that most identified cases occurred in immunosuppressed patients often leading to readily identifiable infections. As an exception, the last case identified by blood transfusion was identified because blood smears were routinely performed to study neutropenic patients.42

Therefore, we hypothesize that other cases in immunocompetent patients have occurred but were not recognized as Chagas disease. Furthermore, it is possible that other, more clinically benign cases of induced acute Chagas disease may have occurred in the United States. Given the nonspecific symptoms and the generally self-limited course followed by the acute phase of Chagas disease in most patients, it is very unlikely that it would be recognized as such in the United States given the low levels of clinician’s awareness of the disease as stated by the CDC.5,44

In addition, based on the large gap in between the number of case reports and the estimations of Storino et al.10 and Buckens et al.,51 it may be suggested that many cases are left undiagnosed.

Finally, it is possible that many chagasic cardiomyopathies are being misdiagnosed as “primary dilated idiopathic cardiomyopathies.”

A study of Storino et al.10 revealed that infected patients with normal electrocardiogram and without evidence of myocardial damage have the same life expectancy than the general population. For this reason, patients should not be discriminated by preserving them from normal lifestyle and regular jobs.5

Recognizing that there is an evident threat of Chagas disease present in the United States will allow an increase of clinician’s awareness and hence will permit to correctly diagnose and treat this cardiomyopathy.

Health authorities should implement a generalized screening of *T. cruzi* in blood banks, organ donations, and pregnant women who were born or have lived in endemic areas. Specific research in high-risk subjects would refine estimates of the disease presented herein, and it would provide further support in defining the prognostic impact of the disease in the United States.

References


