The recovery of \textit{T. cruzi} DNA from South American human mummies shows that Chagas’ disease already afflicted mankind as early as 4000 years ago \(^1\). Charles Darwin probably contracted the disease during his expedition to South America, as suggested by his vivid description of the “benchuca” sting and the nature of his late life symptoms \(^2\). However, it was in the early twentieth century that Carlos Chagas, in a most unique accomplishment in the History of Medicine, discovered the new morbid entity that carries his name, described its pathological and clinical features, the etiologic agent and its transmission mechanism through the inoculation of infected excreta of hematophagous insects of the family \textit{Reduviidae} (subfamily \textit{Triatominae}) \(^3\).

Although the mechanism by which \textit{T. cruzi} invades mammalian cells is not completely known, experimental work suggests that an essential step involves triggering of activation of the transforming growth factor (TGF)-beta signaling pathway. Therefore, adherent parasites cannot penetrate cells lacking TGF-beta receptors and replicate within them, whereas administration of TGF-beta potentiates \textit{T. cruzi} invasion ability in experimental models \(^4\).

Virtually every organic system may be affected. Megaesophagus and megacolon occur in about 6% of the chagasic population and neurologic disorders in around 3%, but, by far, Chagas’ heart disease is the most serious complication, with clinical manifestations arising in nearly one third of Chagas infected people throughout their life span.

**Epidemiological aspects**

Conditions for vectorial transmission range between latitudes 42°N and 40°S of the American Continent, from Mexico to Argentina. On the basis of limited serological surveys, 4% to 7% of more than 200 million Latin Americans are estimated to be chagasic in extensive areas of 21 countries, and 65-90 million are at risk of becoming infected \(^5\).

Cross-sectional epidemiological studies in Brazil and Venezuela assessed the prevalence of clinical manifestations and mortality due to Chagas’ heart disease. However, no clear-cut epidemiological picture of Chagas’ heart disease is yet available, due to the lack of appropriately designed large-scale studies to address this serious public health problem in extensive areas of the Latin American subcontinent. In addition, case reporting is not reliable even in areas of high endemicity. Probably because of marked variations in the genetic background, parasite strain, climate, socioeconomic and related hygienic-alimentary conditions, and health care policies, the morbidity and mortality rates ascribed to Chagas’ disease are extremely variable even among endemic areas of each country \(^6\).

Although the true prevalence of Chagas’ heart disease is unknown, these rough estimates clearly indicate that Chagas’ myocarditis is undoubtedly the most common form of cardiomyopathy in Latin-American countries \(^7\). Also, due to migratory currents between countries and far-distant regions, Chagas’ heart disease is likely to become ubiquitous \(^7\). A reflection of this tendency is exemplified by the recent growing awareness regarding the occurrence of Chagas’ heart disease in the United States. Based on a prevalence of 4.5% of \textit{T. cruzi} serologically detected infection in 205 Latin American immigrants to the USA, and on estimates of the number of such immigrants, approximately half a million infected people are believed to exist now in that country \(^8\). Moreover, rural-urban migration from endemic areas in Brazil is believed to have brought to large cities half a million infected people in the last three decades \(^6\).

**Other mechanisms of transmission** - Infestation can also, infrequently, occur by congenital and oral routes, breast feeding, laboratory contamination, and organ transplantation. Transfusional transmission of \textit{T. cruzi} is currently under close scrutiny in most places, since a survey carried out from 1988 to 1990 in 850 counties of Brazil, revealed that serological screening for Chagas’ disease was performed in only two thirds of all blood donors \(^6\). Also, a review of serological surveys for Chagas’ infection among blood donors, conducted over the last decade in several countries, disclosed a seropositivity rate ranging from 10 to 50% in endemic areas \(^9\).

**Prevention** - Chagas’ heart disease carries a very high social impact, with over 750 thousand years of productive life probably lost annually, due to premature deaths in Latin-American countries, at a cost of about US$ 1200 million/year \(^10\).
These are figures that thoroughly substantiate the concept that elimination of Chagas’ disease vectorial (by improving the quality of housing and use of residual insecticides) and of transfusion transmission in both endemic and nonendemic areas is a highly cost-effective public health policy. Despite being hindered by financial limitations, these goals have been attained in scattered regions.

The Southern Cone Initiative program launched in 1991 has already produced impressive results at a cost of US$ 207 million that was allocated from national resources of the six countries involved. Thus, in Brazil, the 89% reduction in the number of house-infested counties was accompanied by a drop in the rate of T. cruzi infected blood donors from 6.5% to 1%, from 1982 to 1993. On the basis of such figures, interruption of transmission is expected to occur between 1998 and 2000 in Brazil, Argentina, Chile and Uruguay. However, it may be too early for such high expectations, as suggested by sporadic reports of transmission of the disease in areas previously considered under epidemiological control.

Natural history and prognostic factors

Experimental, pathological and clinical evidence substantiate the conceptual division of Chagas’ heart disease into the acute myocarditis and the chronic phase, separated by the long period - 10 to 30 years - known as the indeterminate form of the disease, that constitutes its most intriguing conundrum. Reactivation of Chagas’ disease, with proteiform clinical expression, is now often seen in chronic chagasic patients with various causes of immunodeficiency, natural or iatrogenically induced.

Several observational studies mainly conducted in endemic areas in Brazil, Argentina and Venezuela, since the early 1940s disclosed the natural history of Chagas’ heart disease.

Also, many case-series studies describe the acute phase of Chagas’ disease acquired through nonvectorial transmission, but have limited value for the knowledge of its natural history.

Natural history studies of Chagas’ heart disease derive predominantly from cross-sectional observations of infected people in rural areas of those countries. Very few studies have described case-control populations of chagasic and non-chagasic people. Other observational investigations focused on the description and follow-up of hospital-based cohorts of chagasic patients.

Both the rural and hospital-based types of studies have clear limitations for the assessment of the influence of prognostic factors in Chagas’ heart disease’s natural history. Thus, no adequate identification of cardiac involvement is usually provided in most of the rural-based studies. Conversely, in hospital-based studies the heart disease is usually well characterized, but their results cannot be extended to the whole spectrum of the chagasic population. Furthermore, because of the rather protracted course of heart involvement, from the acute myocarditis to the end-stage heart failure or malignant arrhythmia, no prospective studies encompassing the whole span of the disease in sizable populations are available.

Prognosis in the acute phase - Although cardiac myocarditis is a constant finding in biopsy specimens or at necropsy examination, case series reported in endemic areas using specific serological tests have shown that only around 10% of the acute cases have clinical manifestations consistent with a correct clinical diagnosis of Chagas’ disease. This is a major obstacle for gathering direct insight into the transition from the acute to the chronic stages of human Chagas’ disease. Nevertheless, studies in experimental models of Chagas’ disease are in general agreement with such findings.

When the clinical diagnosis was possible (in the small subset of patients), cardiac involvement occurred in around 90% of 313 successive cases; in 70-80% cardiac enlargement was seen on X-rays, contrasting with only 50% of cases showing electrocardiogram (ECG) abnormalities. The severity of myocarditis was inversely proportional to age, with signs of heart failure being twice more intense in children aged up to two years than in those between the ages of three and five years. Mortality in the acute phase of the disease, in this study, was 8.3%, a higher figure than the 3-5% reported in similar studies in other endemic areas in Brazil, Argentina and Uruguay. The ECG was normal in 63.3% of the nonfatal cases, and in only 14.3% of those who died in the acute phase of Chagas’ disease. Of all deaths, 75% occurred in children less than three years of age. Heart failure was the constant finding in all fatal cases, associated or not with encephalitis, and independent of age.

Of 172 patients whose acute phase of Chagas’ infection had been diagnosed on the basis of general clinical signs and a positive serology, followed in Bambuí (central Brazil) for up to 40 years, the development of chronic cardiac involvement - based on clinical signs, ECG and chest X-rays changes - occurred in 33.8%, 39.3% and 58.1%, respectively during follow-up periods of 10-20 years, 21-30 years and 31-40 years. In another review concerning the same endemic area, for 268 patients whose acute phase of the disease had been diagnosed in an average of 27 years before, the overall mortality in the period was 13.8%.

Survival is characterized by disappearance of symptoms and signs of heart failure within 1-3 months, and normalization of the ECG in over 90% of the cases after one year of the infection.

However, there is no evidence of spontaneous cure of the infection, as demonstrated by serial xenodiagnosis and serological tests in studies of several hundreds of chagasic patients.

Prognosis in the indeterminate phase - Although the clinical relevance of this definition could be currently disputed, the indeterminate phase of Chagas’ disease...
requires that patients have positive serology and/or a positive xenodiagnosis test, no cardiovascular or digestive symptoms, a normal resting 12-lead ECG and no abnormalities detected by radiological examination of heart, esophagus and colon. Thus, the indeterminate phase ends and the chronic cardiac or digestive forms of the disease ensue only when symptoms appear or abnormalities are shown on the ECG or by radiological cardiac or digestive scans.

The evolution potential at this stage of the disease, determined by as yet unknown factors, is shown by longitudinal cohort studies in endemic areas. A 1-3% per year rate of appearance of heart involvement has been observed in several studies.

Of 400 young adults followed for 10 years, 91 (23%) showed clinical and/or ECG or chest-X-ray markers of cardiac disease. Of note, eight deaths were recorded in that period, of which only one could be ascribed to recurrence of chagasic cardiomyopathy.

Another longitudinal study in Bambuí, central Brazil, contrasted the evolution of 885 young chagasic patients in the indeterminate phase, for 10 years, with that of 911 chagasic patients with initially abnormal ECG, in the same period. Survival after 10 years was 97.4% and 61.3%, respectively for the indeterminate group and the group with cardiac involvement.

A third longitudinal study in a rural Venezuelan community, with 47% prevalence of positive serology for Chagas’ disease, followed 364 patients for a mean period of four years. It revealed the appearance of heart disease at a rate of 1.1% per year in seropositive individuals. Mortality was 3% in the four years of follow-up and Chagas’ heart disease was the cause of death in 69% of all fatal cases.

In 1973 a longitudinal study was initiated in a rural community in northeast Brazil. In the initial cross-sectional study of 644 individuals aged >10 years, 53.7% were seropositive. The population initially described in 1973-1974 was re-examined in 1977, 1980 and 1983. The overall rate of development of abnormal ECG was 2.57% in seropositive (248) as compared to 1.25% per year in seronegative (332) individuals, a relative risk of two for the same geographical area. The age-adjusted mortality rate was higher in seropositive (8.9/1000/year of 488 patients) than in seronegative individuals (7.8/1000/year of 509 individuals). However, mortality in this study was strongly associated with ventricular conduction defects and arrhythmias.

In summary, the results of these studies indicate that, as long as the patients remain in the indeterminate phase, their prognosis is fine. It must be emphasized that these results were obtained in chagasic populations with >50% of the individuals younger than 20 years, and less indeterminate cases are found in older age groups because of the evolutional nature of the disease. It is relevant to know that after 10 years almost 80% of the patients remain in the indeterminate phase of the disease and probably 50% of the entire population will have no signs of heart disease throughout their lives. What remains elusive are those factors which determine the development of overt cardiac disease and cardiac failure in some patients who have been infected with *T. cruzi* as opposed to others with positive serology but without cardiac involvement. It is likely that the explanation will be multifactorial.

### Prognosis of chronic Chagas’ heart disease

From the studies mentioned above, analyzing prognostic factors of the indeterminate phase in rural populations in which only a superficial evaluation of the heart condition was carried out, it became apparent that the mere appearance of ECG changes entailed a bad prognosis. Also, a retrospective analysis of seropositive individuals followed over 18 years revealed that right bundle branch block was three times more common in fatal cases than in survivors.

In addition to ECG markers, the notion that the male gender is an important deleterious prognostic factor once the heart disease is manifest, is borne out from several studies carried out with long-term follow-up of hospital-based cohorts of chagasic patients and also by a case-control study. The later study also suggests possible geographical clustering and/or familial aggregation of cases of Chagas’ heart disease in endemic areas.

Few case-control follow-up studies have been reported in endemic areas. In central Brazil, two cross-sectional clinical assessments spanning 10 years (1974 to 1984) were carried out including 12-lead ECG and radiological evaluation of heart size. Serum positive patients and controls were matched by age and gender. In the first cross-sectional study, 264 pairs of subjects were evaluated, of which 110 could be recomposed and reexamined after the 10-year follow-up period, with the same clinical, ECG and chest-X-ray assessment. The incidence of clinical heart disease, as diagnosed by the development of symptoms, ECG and/or radiological changes, in previously healthy but serologically positive individuals was 38.3% in the ten-year period. In those patients with previous heart involvement a rate of 34.5% of deterioration was observed in the same period. In the chagasic population the overall mortality was 23%, compared with 10.3% in the controls. Moreover, cardiac mortality, including sudden death and death in heart failure was 17% among chagasic patients, and only 2.3% in the control population. Again, the overall mortality was much higher in chagasic males and predominated in the group aged 30 to 59 years.

The same group of investigators, applying similar methods in northeastern Brazil showed that mortality rates were 1.6% and 0% for 125 matched pairs of respectively chagasic and nonchagasic patients followed for 4.5 years. Progression of disease as assessed by ECG changes occurred in only 10.4% of patients, as compared to 4.8% of controls. The different morbidity and mortality rates between the two regions were hypothesized to mean possible differences in the pathogenicity of *T. cruzi* strains in the two geographical regions, but no direct evidence for this was provided.

There is also evidence to support the notion that
mortality associated with Chagas’ disease is strongly correlated with the severity of the myocardial dysfunction 7.

For example, survival two years after the first episode of heart failure was only 33.4% in 160 cases 38. Of note, 10% of deaths were sudden. In addition 98 deceased people were autopsied, revealing <20% of prevalence of cardiac tissular forms of T. cruzi, with a clear predominance of this finding in male patients 38.

In a study of 107 chagasic patients followed for 10 years, a significant reduction in life expectancy, as compared to that of 22 nonchagasic patients, was detected only in those with ECG and/or clinical changes. A mortality rate of 82% over the 10-year follow-up period was seen in the group of 34 patients with signs of heart failure at the beginning of the study. In contrast, a 65% 10-year survival was associated with ECG abnormalities but in absence of signs of heart failure 39.

Another study of 104 male patients admitted to the hospital with congestive heart failure revealed a mortality rate of 52% after five years. The strongest predictors of survival were left ventricular (LV) ejection fraction and maximal oxygen uptake during exercise 40.

In a series of 42 patients with Chagas’ heart disease in the USA, 11 deaths occurred during a mean follow-up of nearly five years, always in association with global or regional LV dysfunction. Established or developing heart failure was a strong predictor of mortality, but, quite surprisingly, not aborted sudden death or the presence of sustained ventricular tachycardia 8. These results conflict with the evidence that ventricular tachycardia detected during exercise testing is a marker of increased risk of sudden death in 44 chagasic patients followed for a mean period of two years 41. This discrepancy is likely related to the fact that both studies are fraught with the same limitation of small numbers and a relatively short follow-up.

In summary, there is substantial evidence that the most important prognostic factor in established Chagas’ heart disease is the degree of myocardial dysfunction. Once overt cardiac failure is manifest, the prognosis is bleak, similarly to that reported in the heart failure Framingham cohorts, with mortality rates approaching 50% in four years. It is possible - but by no means proven by good evidence - that sudden death and related ventricular arrhythmias may play a more prominent role in mortality due to Chagas’ disease than in heart failure due to other etiologies 7.

Clinical features of Chagas’ heart disease

Following inoculation by the etiologic agent, there is an incubation period of approximately 7 to 10 days. Local skin or mucosa swelling produces the typical entry lesions known as chagomas (including the nonspecific Romaña’s sign).

Cardiac abnormalities are always present in all stages of Chagas’ disease, but, characteristically, in the acute phase, there is a striking discrepancy between the severity of the myocarditis and the paucity of its clinical expression 7. Gen-

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cardia or complete AV block who have well preserved global ventricular performance (but usually regional wall motion abnormalities) 52.

Sudden unexpected death occurs with an undefined but not negligible frequency and can supervene (albeit rarely) even in patients previously asymptomatic. It is usually precipitated by physical exercise, and associated with ventricular tachycardia and fibrillation or, more rarely, with complete AV block. From autopsy studies, it is apparent that such patients have constant but variable degrees of inflammatory abnormalities and neuronal cardiac depopulation 44. In addition, necropsy and in vivo studies show that most such patients have ventricular aneurysm at one or more sites (posterior, inferolateral, or apical) 42.

Systemic and pulmonary embolism, arising from mural thrombi in cardiac chambers and from deep venous thrombosis due to low cardiac output, is a conspicuous complication of chronic Chagas’ heart disease. However, evidence from postmortem studies suggests that emboli are often overlooked. In a review of 1345 autopsy cases, the incidence of cardiac thrombus or thromboemboli was 44 percent; the right and left cardiac chambers were equally affected 50. Although thromboembolic phenomena were more common in the systemic circulation, pulmonary embolism accounted for 14 percent of deaths. Chest pain, more often atypical for myocardial ischemia, is another common symptom 8,47,54. In a small but appreciable subset of chagasic patients, it may mimic an acute coronary syndrome 55,56.

**Diagnosis laboratory methods**

It is remarkable that some chagasic patients with conspicuous ECG and ventricular regional abnormalities may be asymptomatic hard workers 7,44,47. The appropriate use of several diagnostic methods will detect the cardiovascular dysfunction in virtually all patients, and help in establishing both the diagnosis and prognosis 42.

**Serologic tests** - The etiologic diagnosis is routinely performed with methods that detect circulating antibodies that bind to parasite antigens 57. The most commonly used tests are based upon complement fixation, immunofluorescence, or ELISA assays, that, carefully standardized, achieve sensitivity and specificity rates higher than 90 percent. Chagas’ disease is diagnosed with greater sensitivity by the detection of *T. cruzi* specific sequences of DNA, using molecular biology approaches 58-60. These later techniques also have the potential for improving the diagnostic and prognostic characterization of the disease, on the basis of parasite strain identification 60.

**Electrocardiogram** - The most common alterations on the routine ECG are right bundle branch block, often associated with left anterior hemiblock, diffuse ST-T changes, ventricular premature beats that may be multifiform, and runs of nonsustained ventricular tachycardia. Other frequent findings are abnormal Q waves and various degrees of atrioventricular block and, in more advanced stages of disease, atrial fibrillation and low QRS voltage 61.

**Chest x-ray** - The most common radiographic finding is marked cardiomegaly with mild or absent pulmonary congestion 42.

**Ambulatory electrocardiographic monitoring** - Virtually all types of atrial and ventricular arrhythmias can occur including sinus node dysfunction, intermittent com-
Electrophysiologic testing does not have an important prognostic role in most patients with preserved LV function who have nonsustained ventricular tachycardia or in those without spontaneous arrhythmia. Programmed stimulation did not induce sustained ventricular tachycardia in any of 72 patients with 400 to 1200 ventricular extrasystoles/hour, of whom 35 percent had nonsustained ventricular tachycardia on Holter monitoring. The mean LV ejection fraction in this group was 60 percent. During an average follow-up of 36 months only 1 of the 72 patients had spontaneous sustained ventricular tachycardia.

Signal averaged electrocardiogram - Preliminary experience in patients not showing conduction disturbances suggests that late potentials occur more frequently with sustained ventricular tachycardia than in its absence but the significance of this finding remains to be determined. The presence of late potentials also seems to correlate with the degree of myocardial depression.

Magnetic resonance imaging - Although not yet used for clinical purposes, this method has the potential to show the underlying myocarditis and also may provide accurate anatomic and functional characterization of cardiac involvement.

Cardiac autonomic assessment - Cardiac autonomic dysfunction, mainly parasympathetic, can be shown in chagasic patients (including those with isolated digestive disease) whose heart response to several autonomic tests (including the RR variability measurement) is impaired, as compared to control subjects. However, these abnormalities are neither correlated with any symptoms, nor cause postural hypotension.

Pathological abnormalities

Necropsy findings in humans have been correlated with observations in several animal models of experimental Chagas’ disease reproducing the various stages of the disease. Endomyocardial biopsy has also been used in subsets of the chagasic population, including patients in the indeterminate phase. The main cardiac pathologic changes during the acute phase consist of four-chamber marked dilation and pericardial effusion.

Microscopic examination shows intense parasitism in virtually every organic system. The myocarditis is intense and diffuse, showing myocyte necrosis, interstitial edema, vasculitis, and mononuclear and polymorphonuclear infiltration. The inflammatory process may reach the endocardium, resulting in thrombus formation. The conduction system is also involved, as well as the intramural and extracardiac neuronal ganglia.

In chronic patients who die after the clinical onset of heart failure there is dilatation and increase of cardiac weight (usually 350 to 800g). Dilation is usually more conspicuous...
in the right chambers, and signs of systemic congestion (ascites, hepatomegaly) predominate over lung congestion. It is possible that this peculiar feature of Chagas’ heart disease could be explained by early severe damage of the right ventricle, a chamber frequently neglected in many investigations that included cardiac functional evaluation.

Intracardiac mural thrombosis in various stages of organization is found in nearly 50% of such cases; the right and left heart chambers are equally affected. The most specific cardiac anatomic lesion is the ventricular apical aneurysm which, in one series, was noted in 52 percent of 1078 autopsied chagasic patients. The lesion does not show the fibrosis usually seen in aneurysms due to myocardial infarction, and rarely undergoes rupture. There is no relation between the frequency of apical aneurysm and age or heart weight, and aneurysms have been reported even in patients who died suddenly, with no apparent previous clinical manifestations of disease. Histologic examination reveals mild chronic myocarditis, manifested by scattered mononuclear cell infiltrates with the surrounding myocytes undergoing various stages of degeneration and necrosis. These changes have been traditionally interpreted as not being related to direct parasitism of myocardial cells, since intact parasites are rarely detected in humans and in experimental models of Chagas’ disease.

Focal and diffuse fibrosis is prominent, in the myocardium and the conduction system. Preferential involvement of the right bundle branch and the left anterior fascicle of the left bundle by inflammatory and fibrotic changes correlates with the frequent occurrence of ECG block of these structures. Microvascular changes in experimental models consist of decapillarization, interstitial edema, intravascular platelet aggregation and thickening of the vascular basement membrane.

Similar findings are found on endomyocardial biopsy. Studies in patients with the indeterminate form have described changes in approximately 60 percent of patients, although the findings are less severe than those in patients with overt cardiac disease.

Striking autonomic neuronal depopulation and nerve degeneration, mostly in the cardiac, esophageal and colon tissues, is another typical feature of chronic Chagas’ disease. However, no correlation exists between the intensity of neuronal destruction and dilation of the organ or other microscopic indices of myocarditis in the chronic phase.

Pathophysiology and pathogenetic mechanisms

The clinical manifestations and organ damage occurring during the acute phase are clearly linked to parasite presence in target organs like the gastrointestinal tract, central nervous system and heart. High grade parasitemia also correlates with lymphadenopathy, liver and spleen enlargement, as markers of widespread immunologic reaction. As the parasitemia abates, and the systemic inflammatory reaction subsides, it is believed that a silent relentless focal myocarditis ensues, during the indeterminate phase. This causes cumulative destruction of cardiac fibers and marked reparative fibrosis. During this phase ventricular arrhythmias and sudden death may rarely occur as manifestations of the underlying focal inflammatory process. This is also eventually responsible for myocardial mass loss attaining critical degrees, thereby leading to cardiac dilation and setting the anatomic substrate for malignant ventricular dysrhythmia. The support for this basic concept comes from several investigations in various experimental models of Chagas’ heart disease using various animal species. Additional evidence has been provided by many studies correlating clinical and pathological findings in autopsied humans dying in all phases of the disease. All studies were observational and usually included case-series of dozens chagasic patients for the acute and indeterminate phases, and ranging from hundreds to thousands cases for the chronic phase of Chagas’ heart disease.

Complex ventricular arrhythmia constitutes one of the most important pathophysiological aspects, considering its implication on sudden death. It is believed that complex ventricular arrhythmia is more common in chagasic patients than in other dilated cardiomyopathies, but no adequate comparative study has been reported to support this general belief. As expected, there is reasonable evidence that more complex and frequent ventricular dysrhythmia parallels the worsening of ventricular function. However, complex arrhythmias including nonsustained and sustained VT may also occur in chagasic patients with preserved global LV function. There is growing evidence that the electrophysiological substrate underlying sustained ventricular tachycardia in Chagas’ heart disease is a macroreentrant circuit within akinetic or dyskinetic areas in the posterobasal and/or posterolateral regions of the LV.

Despite recent advances in the understanding of Chagas’ heart disease pathophysiology, the main challenge still consists of the identification of the pathogenetic mechanisms acting during the indeterminate phase. The widely disparate clinical and pathological manifestations of the acute and chronic phases of a disease with a common infective basis also needs elucidation. Basiclly, four main classes of mechanisms have been implied in the pathogenesis of chronic Chagas’ heart disease.

Neurogenic mechanisms - Necropsy studies in humans clearly demonstrated intense cardiac neuronal depopulation in the various Chagas’ disease stages. These findings were reproduced by investigations in animal models of the disease. The histopathologic features are foci of damaged nervous tissue arranged in a diffuse and irregular distribution. Neuronal parasitism, periganglionitis and degenerative abnormalities in Schwann cells and nervous fibers have also been observed. Not only cardiac parasym pathetic nervous structures are involved but paravertebral sympathetic ganglia destruction has also been described.

Correspondent striking abnormalities of parasym-
pathetic and, to a lesser extent, of sympathetic cardiac autonomic control have been clearly documented by extensive laboratory investigation in humans. This aspect seems to be a hallmark of this disease. In fact, less severe degrees of denervation have been found in rheumatic disease, endomycocardiofibrosis, and idiopathic dilated cardiomyopathy by direct comparative studies with Chagas’ disease.

Taking into account the early, intense, and largely predominant parasympathetic denervation in Chagas’ disease, that mostly explains the pathogenesis of chagasic megaesophagus and megacolon, a neurogenic theory of Chagas’ heart disease has been proposed: a long lasting autonomic imbalance would lead to a catecholamine-induced cardiomyopathy.

However, various lines of evidence cast doubts on the participation of neurogenic derangements as main pathogenetic mechanisms of Chagas’ heart disease. Thus, the frequency and the intensity of this abnormality are quite variable, and a mismatch between the presence of autonomic denervation and ventricular dysfunction is often seen. Differences in strain and/or regional environment are likely causes for variable neuropathology observed in several regions. More important, studies aimed at investigating the presence of autonomic dysfunction and early contractile abnormalities have failed to show any significant association.

A more appropriate insight into this aspect was obtained by recent investigations using 123I-MIBG scintigraphy for evaluation of myocardial sympathetic nerve terminals. Segmental areas of sympathetic denervation were detected in a high proportion of patients even in the indeterminate phase of Chagas’ heart disease. This is the first functional evidence of cardiac sympathetic impairment preceding left wall motion abnormalities in the indeterminate phase of chronic Chagas’ disease.

Increased 123I-MIBG washout rate was also observed in patients with normal segmental ventricular function. This could be due to early increased cardiac sympathetic activity, and lend support to the neurogenic theory as stated above. Alternatively, this abnormality could be caused by competition between the radiotracer and an endogenous substance for the neurotransmitter receptors of the sympathetic nerve terminals.

In plausible concordance with this last hypothesis, recent reports have documented in patients with Chagas’ disease the existence of circulating antibodies that bind to adrenergic and cholinergic receptors of lymphocytes and myocardium. Studies focusing on antibodies against heart adrenergic and cholinergic receptors have shown their ability to trigger physiologic, morphologic, enzymatic and molecular alterations, potentially leading to cardiac damage. Deposit of autoantibodies upon the myocardial neurotransmitter receptor could induce its desensitization or down-regulation and cause progressive denervation. Such mechanisms could represent the elusive but significant link between denervation and autoimmune aggression as pathogenetic factors in Chagas’ heart disease.

In conclusion, the neurogenic theory is still under debate. Its diagnostic meaning has never been assessed, and the hypothesis implicating autonomic impairment in triggering sudden death remains entirely speculative.

Parasite-dependent inflammation - For decades no significant pathogenetic role was attributed to T. cruzi infection in the chronic phase of the disease, on the basis of histopathological evidence of low-grade fiber parasitism and an intriguing lack of topographic correlation between inflammatory foci and amastigote T. cruzi nests. This classical view emphasized the presence of focal lymphocytic myocarditis and myocytolytic necrosis in areas where no parasite could be seen, and seemed to be supported by the finding of very low grade parasitemia that could be detected in only a minority of chronic Chagas’ disease patients.

However, more recent studies employing immunohistochemical techniques and monoclonal antibodies against T. cruzi antigens have been performed on endo-myocardial biopsy specimens retrieved from chronic Chagas’ heart patients and a relationship between parasite antigens and inflammatory foci was observed. Similar results were obtained by detection of T. cruzi genomic fragments applying the polymerase chain reaction method. In addition, molecular biology techniques now permit the detection of circulating T. cruzi antigens in a much larger contingent of chagasic patients in whom the conventional serologic methods fail for such purpose. It is plausible to speculate that even low-grade persistent parasitism may lead to a continuous antigenic feedback loop to the autoimmune system, which may constitute the main damaging mechanism in the late phase.

A direct role of parasitism in the pathogenesis of chronic Chagas’ heart disease can have relevant therapeutic implications. There is only very incipient evidence regarding the possible favorable impact of etiological treatment in the clinical outcome in the chronic phase of disease. In particular, some results have been reported on a nonrandomized, open label, placebo controlled trials of benznidazole in the clinical outcome of 131 treated and 70 nontreated chronic chagasic patients followed for eight years on average. Significant reduction in the rate of new electocardiographic abnormalities and in the incidence of clinical deterioration was observed in the treated group. Similar results were also recently obtained employing itraconazole and allopurinol. These results, if confirmed in larger adequately designed studies, would give further support to the theory of direct parasite participation in the establishment and further progression of chronic myocardial damage.
Microvascular disturbances - Various classes of evidence arising from clinical and experimental grounds suggest that transitory ischemic microvascular abnormalities occur in Chagas’ heart disease.

The first order of evidence is related to morphological features of chronic myocarditis. The focal distribution of myocytolysis and interstitial reparative fibrosis (features also observed in nonchagasic experimental models of ischemia/reperfusion) is compatible with transient ischemic involvement at the microcirculatory level of discrete groups of fibers. Also, pathological involvement of coronary vessels has been shown by necropsy studies and is reinforced by observations in murine experimental models of chronic Chagas’ disease. In the experimental setting, the detection of occlusive platelet thrombi in small epicardial and intramural coronary arteries indicates the occurrence of microcirculatory disturbances likely to produce ischemia detected by special histochemical techniques. Moreover, the administration of verapamil (a calcium blocker with prominent vasodilator and anti-platelet effects) to T. cruzi infected-mice was accompanied by significant reduction in mortality and extension of tissue damage.

On clinical grounds, myocardial perfusion abnormalities have been documented by several independent reports using various types of myocardial perfusion markers (thallium-201, 99mTc-Sestamibi, 99mTc-microspheres), during effort and at rest, in chagasic patients with angiographically normal coronary arteries. Reversible, fixed and paradoxical perfusion defects, in areas with normal contraction, were found in a large proportion of patients even in the absence of other signs of myocardial involvement. Abnormal response of coronary flow to acetylcholine administration has been reported in chronic Chagas’ heart disease patients, suggesting the occurrence of endothelial dysfunction. The demonstration of abnormal subepicardial coronary artery reactivity to hyperventilation and nitrate administration also supports the notion that functional abnormalities in myocardial flow regulation occur in chagasic patients.

Recent ultrastructural studies in canine experimental models suggest that small vessel involvement may be secondary to direct interaction of inflammatory cells and the endothelium. It is possible to speculate that substances like thromboxane A2, cytokines, and prostaglandins, produced in the inflammatory infiltrate, may have important effects on vascular reactivity. According to this hypothesis, microvascular ischemia documented in Chagas’ cardio-myopathy may be secondary to the inflammatory response. Conversely, the ischemic phenomena may represent a feedback loop that potentiates the primary damage mechanism.

It is also reasonable to assume that elucidation of the actual cause of ischemia in Chagas’ disease might improve the understanding of the precordial chest pain commonly experienced by the patients and help to establish therapeutic strategies for treatment of this symptom.

Immune mediated cardiac damage - A wide array of scientific investigations is considered to lend support to the theory of autoimmunity as the key process in the pathogenesis of chronic Chagas’ heart disease. The concept that the effector cells in the mononuclear chagasic myocarditis may damage nonparasited myocardial fibers has been suggested by histopathologic studies using light microscopy; it was recently corroborated by ultrastructural studies in animal models, and is based on the postulate of abnormal immune cross-reactivity between T. cruzi and myocardial antigens.

Antigenic mimicry shared by the T. cruzi and the myocardium has been shown for a series of cross-reactive antibodies directed against several host antigens. However, the demonstration that this biological effect could have a clinical counterpart to support the autoimmune nature of this disease required the identification of an organ-specific autoantigen whose injection into the susceptible host could reproduce the lesion. Also, the myocardial damage in such circumstances, should be induced by passive transference of lymphocytes.

This kind of definite support of the lesion mechanism ascribed to the cellular immune infiltrate has been recently obtained by identification of myosin-specific TCD4+ lymphocytes in the chronic murine Chagas’ disease model. Other evidence was obtained by abrogation of the myocardial damage subsequently to depletion of TCD4+ in chronic infected mice. In addition, myocardial damage could be reproduced in noninfected animals by passive transfer of TDC4+ lymphocytes, obtained from infected mice.

Moreover, specific epitopes associated with the host immune response and potentially able to produce myocardial damage have been recently identified. There is also evidence that persistent T. cruzi antigen presentation to macrophages could lead to cytokyne production, thus modulating the immune response and possibly causing the relative immunosuppressive state responsible for perpetuation of infection. All these findings can be combined to support the theory of chronic chagasic focal fibrotic lymphocytic myocarditis being determined by autoimmune response to epitopes within myocardial proteins. This break of immune tolerance would be due to mimicry of myocardial antigens by T. cruzi, thus inducing cross-reactive immune responses.

In essence, T. cruzi inflammatory and autoimmune aggression seem to constitute the more prominent pathogenetic mechanisms. Autonomic disturbances and microvascular ischemia appear to play an ancillary role, acting as amplification loops and contributing to expand myocardial tissue damage. A unified overall pathogenetic framework may be constructed on the basis of such notions.

Management of Chagas’ heart disease

Etiologic treatment - Nifurtimox and benznidazol have been shown to have comparable antityranosoma efficacy and also similarly high incidence of untoward side effects,
commonly responsible for discontinuation of treatment: dermatitis, polyneuritis, leukopenia, gastrointestinal intolerance. A recent report on higher incidence of cancer following antitrypanosoma therapy in heart transplanted patients is also an indication that the search for more effective and better tolerated drugs seems clearly warranted. Recent reports of allopurinol and itraconazole for treating Chagas’ disease reactivation after heart transplantation and chronic chagasic yielded intriguing results that require further serious scrutiny before any firm conclusions can be derived.

In the acute phase of Chagas’ infection, irrespective of the mechanism of transmission (vectorial, blood transfusion, laboratory accident, oral, or even reactivation of chronic disease during immunosuppressive conditions), it is virtually consensual that etiologic treatment is mandatory to control symptoms and life threatening conditions, such as myocarditis and encephalitis, and, presumably, to prevent chronic organ damage. However, the efficacy of treatment regarding this later aspect has not been proved as no controlled long-term follow-up trials have been reported. Parasitologic evaluation shows negativity of xenodiagnosis in over 90% of cases and serologic tests are negative in 80%, after adequate treatment. The prognostic meaning of conversion to a negative serology has not been established, again due to lack of appropriately designed follow-up studies focusing on this relevant aspect.

Evidence for potential benefits of specific antitrypanosoma chemotherapy in chronic Chagas’ heart disease is lacking because misleading criteria have been used to assess therapeutic efficacy and also due to the fact that only small, nonrandomized, noncontrolled trials have been carried out. Thus, conversion from a serum-positive to a serum-negative state following therapy is an unreliable marker of the impact of such treatment upon the course of Chagas’ disease, because in any event, negative serology is common in the chronic phase. Moreover, large fluctuations of parasitemia occur over time. Another negative aspect in those trials is the bias induced by selection of patients with persistent parasitemia in the pretreatment period. Furthermore, results of experimental studies have shown that in the chronic phase the parasitemia is low or not detectable at all while there is a predominant tissular parasitism by amastigote forms of T. cruzi.

Conversely, persistently positive serologic tests may merely reflect mechanisms of immunological memory, or be associated with cross-reactivity to altered host antigens. Hence, results of any of the serological criteria used to assess the therapeutic value of etiologic treatment in patients with the chronic form of Chagas’ heart disease are clearly unreliable. The reported rate of negativity of serological tests following treatment in the chronic phase is consistently very low (4-8%) in the trials suffering the epidemiological restrictions already pointed out.

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**Pathogenic mechanisms in Chronic Chagas’ Heart Disease**

![Diagram](image_url)

**Fig. 1 – Pathogenetic mechanisms in Chagas’ heart disease.**
Thus, until an adequate laboratory method is available for assessment of cure, the only acceptable criteria for any etiologic therapeutic intervention benefit must be based on the prevention of the appearance of the clinical form of disease or the arrest of progression of the damage already detected. For this, a very long follow-up period of large cohorts of chagasic patients is required to detect changes in the natural history of the disease.

No definitive recommendations are justifiable for etiologic treatment in the chronic phase of Chagas' heart disease, until large randomized controlled studies encompassing patients in different stages of disease have been performed.

**Treatment of congestive heart failure** - Since the hemodynamic derangements in chronic chagasic patients with heart failure are comparable to those reported in dilated cardiomyopathies of other etiologies, classical therapeutic interventions (sodium restriction, diuretics, digitalis, and vasodilation with nitrates and hydralazine) are usually employed for relief of congestive symptoms in chagasic patients. Several uncontrolled small studies documented short-term hemodynamic beneficial effects of these agents, and, to a lesser extent, improvement in exercise tolerance in chronic chagasic patients. However, no studies reported improvement in survival, or even in long-term outcome based on hemodynamic and symptomatic benefit.

Preliminary studies involving therapy with ACE-inhibitors, enrolling small numbers of patients, have shown promising results in heart failure complicating Chagas' disease, in regard to symptomatic control. Although no long-term prospectively controlled study has been reported assessing the impact on survival of chagasic patients treated with ACE-inhibitors or any other pharmacological interventions, there is no reason to expect that their beneficial effect would be any different from that observed in heart failure due to other etiologies. In fact, there seems to be a favorable acute neuromodulating effect of ACE-inhibition in chagasic patients.

As discussed earlier, early regional ventricular wall motion impairment and diminished contractile properties can be seen even in patients with the indeterminate form of the disease. The mild dyssynergia thus detected appears to reflect more extensive myocardial damage than the ECG changes classically interpreted as heralding more advanced cardiac involvement. Furthermore, there is recent preliminary evidence that these minor segmental wall motion abnormalities in chagasic patients may bear relevant prognostic implications. Therefore, it is reasonable to conclude that it remains to be tested if chagasic patients, similar to what has been shown in other causes of heart failure, would benefit from early medical intervention, to detain the natural history and prevent the installation of overt cardiac dysfunction.

**Surgical approaches to treatment - Heart transplantation** - As in other cardiomyopathies, heart transplantation has been performed in small groups of patients with refractory heart failure due to Chagas' disease. However, wider application of this therapy is currently hindered by socioeconomic factors in endemic areas, and by the reactivation of infective manifestations associated with immunosuppression. Acute myocarditis, with marked transitory LV systolic depression occurred in five of the first nine patients included in the largest series - 22 patients operated in a single surgical center. Although the acute reactivation was usually responsive to antiparasite therapy, the possibility of chronic damage to the allograft could not be ruled out. The results reported on the latest 13 patients of this series, using a reduced regimen of immunosuppression with cyclosporine, are promising as reactivation of disease supervened in only one patient. Also, a survival rate at 24 months posttransplantation of 80% in that later group, appears to compare favorably with those reported in clinical series. Nevertheless, the long-term impact of heart transplantation in chagasic patients remains to be determined by adequately controlled studies in large cohorts.

**Dynamic cardiomyoplasty** - Reported experience with this palliative surgical procedure in chagasic patients is quite limited. Initial results showed encouraging symptom and LV function improvement in very few patients. A recent survey of surgical centers in South America showed results pertaining to a total of 112 patients of whom 96 had heart failure due to dilated cardiomyopathy and 13 due to Chagas' heart disease. Comparative analysis disclosed survival rates of 86.1% and 49.8% for patients with dilated cardiomyopathy and 40% and 9.5% for chagasic patients, at one and five years follow-up, respectively. No clues from these data would point to any factors possibly involved in the worse prognosis thus suggested for chagasic patients. Clearly, large controlled randomized trials are necessary to define the issue of cardiomyoplasty as a temporary approach, before more radical interventions such as heart transplantation can be used in selected patients with refractory Chagas' heart disease.

**Prevention of thromboembolic events** - There is very limited clinical information concerning the risk of embolic phenomena in patients with detected mural thrombus or apical aneurysm. In 65 selected patients with apical aneurysm a follow-up study ranging from 19 to 176 months documented 17 episodes of thromboembolism occurring in 14 patients (24.5%). These patients also had congestive heart failure, and 11 died in the period of observation. In eight of those patients the cause of death was related to heart failure, and in three it was a consequence of cerebral embolism. Another small study addressed the relative contribution of Chagas’ heart disease as the underlying cause of embolism in 69 patients with embolic strokes treated in an endemic region in South America. Of 13 patients with nonischemic dilated cardiomyopathy, Chagas’ heart disease was detected in 9 (13.0%). It was the third more frequently identified cause of embolism, just after atrial...
fibrillation (29%) and rheumatic valvular heart disease (20.3%).

However, the real risk of thromboembolism in patients with Chagas’ heart disease is unknown, as no specific studies have addressed this problem. Furthermore, despite the preliminary evidence that thromboembolic events are relevant prognostic factors in the natural history of Chagas’ disease, no clinical studies focusing on adequate treatment and prevention of thromboembolism in chagasic patients have been conducted to date.

Current recommendations for anticoagulant therapy are based on information derived from other dilated cardiomyopathies. Chagasic patients presenting global LV dysfunction, atrial fibrillation, previous embolic episodes, dyskinetic areas with detected mural thrombus, are candidate to treatment with intravenous and/or oral anticoagulants. The issue is further complicated by the fact that social and economic factors limit the implementation of this strategy, even in chagasic patients with otherwise apparent clear indications for prevention of thromboembolic events.

Management of chagasic patients with precordial pain - This may be a difficult task, and is entirely empirically based. The symptom is not related to vasotonic angina and recent studies show that chagasic patients do not have augmented responses to either coronary constrictor or endothelium-independent vasodilator stimuli, suggesting that no increased baseline coronary tonus occurs. Also, therapeutic interventions aiming at the relief of symptoms as possibly derived from esophageal involvement are not usually justifiable. Although endoscopy evidence of esophagitis can be obtained in a substantial proportion of chagasic patients, their sensitivity to chemical or mechanical stimuli is typically depressed. Some patients benefit from the use of nitrates and beta-adrenergic or calcium channel blockers, but the individual response is unpredictable.

Management of rhythm disturbances - Management of symptomatic bradyarrhythmias does not differ from that recommended for other cardiomyopathies, and in most situations relies on permanent pacemaker insertion, but no sound evidence based on large randomized controlled trials is available to support any specific treatment strategy.

Main indications for pacing are atrioventricular block and sinus node dysfunction. The evidence for a beneficial effect of pacemaker implantation comes from the superior clinical outcome of patients with such rhythm disturbances in limited case-series reports, as compared with the natural history of patients in whom this treatment was not possible. Another relevant aspect is the common association of atrioventricular disturbances and ventricular complex dysrhythmia in the same patient. The acceptable management of this clinical condition requires “prophylactic” artificial pacemaker implantation associated with pharmacological antiarrhythmic therapy, even though this combined strategy is not based on adequate evidence.

For patients with asymptomatic ventricular ectopic beats or nonsustained ventricular tachycardia no definite antiarrhythmic therapy was shown to improve survival. Indeed, very scanty information has been published regarding this issue, but two moderately large randomized trials included chagasics among patients treated with amiodarone.

The GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) concluded, after two years of follow-up, that low-dose amiodarone was effective in reducing mortality and hospital admission in patients with severe heart failure, independent of the presence of complex ventricular dysrhythmia. Unfortunately, the contingent of chagasic patients was very small (48 of 516 patients), and subgroup analysis was neither provided nor would likely be useful.

An ongoing prospective multicenter randomized controlled study designed to evaluate the impact on survival of treatment of asymptomatic ventricular arrhythmia also included chagasic patients. In its pilot phase this trial enrolled 127 patients (24 with Chagas’ heart disease) with LVEF <35%, presenting frequent ventricular premature complexes and/or repetitive forms of asymptomatic ventricular arrhythmia. The preliminary results after 12 months of follow-up showed a significant reduction in the incidence of sudden death in the amiodarone group (7.0% vs 20.4%). It must be pointed out that follow-up data were obtained in only 106 patients. This was a consequence of an excessively high drop-out rate (16%) which seriously limits the appraisal of the results. Nevertheless, we should await the final results of this trial, hopefully recruiting a larger contingent of chagasic patients, before the routine use of amiodarone could be recommended for chagasic patients with asymptomatic ventricular arrhythmias.

Although no prospective controlled studies with antiarrhythmic drugs have been performed for treatment of hemodynamically tolerated sustained VT in the setting of Chagas’ heart disease, those patients are generally treated with class III anti-arrhythmic drugs, either amiodarone (1000mg/day for 10 to 14 days followed by maintenance therapy at 200 to 600mg/day) or sotalol (320mg/day) after electrophysiologic study. The efficacy of empiric treatment with amiodarone is strongly influenced by the grade of left ventricular dysfunction. This is reflected in one-year mortality rates of 0 and 40 percent and of recurrence of ventricular tachycardia of 30 and 100 percent after one year, respectively for groups of chagasics with class I-II and III-IV of the NYHA.

Patients at high risk of sudden death from lethal tachyarrhythmias would probably benefit from an implantable cardioverter-defibrillator, but its widespread use is hampered by socioeconomic limitations. Aneurysmectomy or cryosurgical ablation following electrophysiology study, have been indicated for patients with ventricular tachycardia refractory to medical treatment, particularly those in whom a structural lesion can be spotted.
Preliminary evidence shows efficacy of approximately 60 percent in such group 194.

Sustained monomorphic ventricular tachycardia (VT) may also be amenable to percutaneous ablation using catheter-delivered radiofrequency in selected patients with inducible, hemodynamically tolerated VT and identifiable sites of the reentry circuits 195-199. One of these studies reported that after endocardial radiofrequency ablation in 15 patients, only 4 (27%) patients were free of induced ventricular tachycardia 195. In 5 (33%) patients VT was favorably modified and the procedure was unsuccessful in 6 (40%) patients. Antiarrhythmic drugs were continued in 14 (93%) patients. On a 2-year follow-up, VT recurrence rate and mortality were significantly reduced in patients whose VT was suppressed or modified by endocardial radiofrequency ablation, in comparison with those patients in whom ablation was considered unsuccessful. However, another study described that after endocardial radiofrequency and/or low energy direct current ablation in 24 patients, whereas suppression or modification of VT was achieved in 19 (79%) patients, successful clinical outcome was obtained in only 4 (17%) patients on a follow-up of 26±21 months 196. Moreover, only 2 (8%) patients were off all antiarrhythmic drugs and 4 (17%) patients also required other nonpharmacological therapy.

Thus, because endocardial radiofrequency ablation could only be performed in selected patients with hemodynamically tolerated VT and more than 90 percent of patients still need antiarrhythmic drug therapy after ablation, endocardial radiofrequency ablation should still be regarded more as a potential ancillary therapy than a curative procedure for VT 197.

More recent studies suggest that progress in ablation of chagasic VT might be made with new mapping techniques of VT such as epicardial mapping through the coronary venous system 198 or nonsurgical transthoracic epicardial mapping through pericardial puncture 199. This later investigation found a high prevalence of epicardial reentrant circuits in chagasic VT, reporting that of 10 consecutive patients who underwent transthoracic epicardial mapping, VT was rendered noninducible in all six patients in whom epicardial ablation was attempted 199. In contrast, unsuccessful ablation and clinical outcome occurred in the four patients in whom epicardial-guided endocardial delivery of radiofrequency energy was performed.

Clearly, the preliminary experience with such approaches must be expanded, on an investigational basis, to define their relative value for arrhythmia control and mortality reduction.

In summary, pharmacological, surgical and device-based strategies for the treatment of ventricular dysrhythmia in chagasic patients are empirical and not supported by large randomized controlled trials 7. For chagasic patients with symptomatic bradyarrhythmias it is generally agreed that a permanent pacemaker should be inserted. For patients with unstable ventricular tachyarrhythmias an implantable cardioverter-defibrillator should be primarily considered. Catheter-based or surgical ablative therapy should be considered investigational procedures, for selected patients with good hemodynamic tolerance during ventricular tachycardia. For patients with asymptomatic ventricular premature beats or nonsustained ventricular tachycardia no antiarrhythmic therapy would generally be required 200.
34. Sargento JN, Cortez A, Barros O, Vitti PER, Cardoso J, Quintino J. Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. Int J Cardiol 1997; 60: 49-54.


