BBA - Molecular Basis of Disease 1866 (2020) 165689

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Chagas disease: Historic perspective☆

Chen Chao (M.D.)[a,b], José L. Leone (M.D.)[c,d], Carlos A. Vigliano (M.D.)[a,e,*]

[a] Servicio de Anatomía Patológica, Hospital Universitario de la Fundación Favaloro, Av. Belgrano 1746, C1093AAS Buenos Aires, Argentina
[b] Director de Acuchina, Av Rivadavia 5126 7th floor, "3", C1424CET Buenos Aires, Argentina
[c] Comité de Docencia e Investigación, Sanatorio Clínica Modelo de Morón, República Oriental del Uruguay 234, C1015ABF, Morón, Buenos Aires. Argentina
[d] Dirección Médica, Clínica Bessone, Paunero 1668, B1663GJL, San Miguel, Buenos Aires. Argentina
[e] Instituto de Medicina Traslacional, Trasplante y Bioingeniería (IMeTTyB), Universidad Favaloro-CONICET, Solís 453, C1078AAI Buenos Aires, Argentina.

ARTICLE INFO

Keywords:
Chagas disease - *Trypanosoma cruzi*
History
Epidemiology
Pathogenesis
Treatment

ABSTRACT

This review is a perspective on the history of Chagas disease, and it adopts a novel approach from literary studies, historical documents and the science and epidemiology of the nature of the disease. From this analysis, comes the review's working definition of the **Contact Zone (CZ)**: "the space in which geographically and historically separated people come into contact with each other and establish long-lasting relationships, which usually involve coercive conditions, radical inequality and intolerable conflict."

In the **Patient-Physician CZ,** we verified the triple transition phenomena: the American trypanosomiasis shifted from a rural, acute, and vectorial transmitted disease to an urban, chronic and non-vectorial disease.

In the **Academic CZ,** we describe the original disagreements which denied the existence of the disease and the current controversies about pathogenic mechanisms and etiological treatment.

From the *News from Latin America*, and in the **Original CZ,** we will review the evolution of different forms of transmission.

As in any good story, research across broad disciplines is necessary to reveal historical perspectives, scientific approaches, and the epidemiology of the disease, which has a prequel of 9000 years and an open ending: thus, we explore across the **Global CZ**, with its multiple and unexpected actors.

1. Introduction

Chagas disease has been well researched in many other works, but here, we described a historical perspective on Chagas disease, and base it on a metaphor from the field of literary studies known as the Contact Zone [2]. We will briefly explain the origin, meaning and use of this metaphor, as we have found a few academic articles which refer to this metaphor within the scope of medicine. To our knowledge, this is the first time that Contact Zone will be used to comprehensively study this disease.

Mary Louise Pratt, a Ph.D. in Comparative Literature from Stanford University, and Professor of Spanish and Portuguese Language and Literature at the New York University, in her 1991 seminal work stated that, "in order to lay out some thoughts about writing and literacy", used the term Contact Zone to refer to "social spaces where cultures meet, clash, and grapple with each other, in contexts of high asymmetrical relationships of power...", or in other words, "…the space in which geographically and historically separated people come into contact with each other and establish long-lasting relationships, which usually involve coercive conditions, radical inequality and intolerable conflict." [3] In this sense, we will apply Contact Zone term to investigate Chagas' disease.

Ironically and strangely enough, Pratt states that one of the sources that develop this metaphor was found in the reading and analysis of extensive letter signed in the year 1613, with an unmistakable Andean indigenous name: Felipe Guaman Poma de Ayala. Written in a mixture of Quechua and Spanish, the manuscript was a letter addressed to King Phillip III of Spain. It was titled "*The First New Chronicle and Good Government and Justice*". The first part "New Chronicle", is an auto-ethnographic text (i.e., "a text in which people undertake to describe themselves in ways that engage with representations that others have made of them."). The second part, ironically titled "*Good Government and Justice*", "...combines a description of colonial society in the Andean region with a passionate denunciation claim against Spanish

☆ Tribute to the memory of *Rodolfo Viotti*, clinical investigator in Chagas disease [1].

* Corresponding Author's Institution: Servicio de Anatomía Patológica, Hospital Universitario de la Fundación Favaloro. Instituto de Medicina Traslacional, Trasplante y Bioingeniería (IMeTTyB), Universidad Favaloro-CONICET.

E-mail addresses: chaochen@acuchina.org (C. Chao), leonejoseluis@gmail.com (J.L. Leone), cavigliano@ffavaloro.org (C.A. Vigliano).

https://doi.org/10.1016/j.bbadis.2020.165689
Received 31 August 2019; Received in revised form 2 January 2020; Accepted 15 January 2020
Available online 27 January 2020

exploitation and abuse".

Additionally, Pratt suggests a contrast to the idea of the Contact Zone with those of community. Specifically, the concept of "imagined communities" in the context of the construction of modern nations: limited, sovereign and fraternal, or, in other words, "closed" nations.

These concepts work well with "descriptions of interaction between people in conversation, classrooms, medical and bureaucratic settings, readily taking for granted that a situation is governed by a single set of rules or norms shared by all participants." The emphasis in our review highlights that Chagas disease research is precisely defined by multiple medical narratives built with non-shared rules by all the involved stakeholders.

Throughout this article, we will define the characteristics of each group of people who came into contact with one another, emphasizing asymmetries, but, without making value judgments, only describing those opposing traits and factors in order to provide a unique perspective to understand how these differences have helped shape the nature of the research on Chagas' disease, which had more than a century of disagreements between the investigators.

2. The prequel to the first encounter

Like a modern film saga, every encounter has a prequel that anticipates what is to come. The first ancestors, whom we will later call Native Americans, walk, enter the continent and make contact with vectors and *T. cruzi*. These actions initiated the sylvatic cycle of the illness, approximately 9000 years ago.

We have chosen an illustration of a known 'sick man', Sir Charles Darwin. On his start-up voyage around the world, he arrived by boat to America, entered the continent, and had his personal encounter with the vinchuca.

2.1. Pre-Columbus Chagas disease

Researchers established that Chagas' disease has existed as early as 7000 BCE when Aufderheide et al. in their study of exhumed mummies from archaeological sites in both Peru and Chile, revealed a carbon dating of their tissues at approximately 7000 BCE, and confirmed by polymerase chain reaction (PCR) the presence of *T. cruzi*'s kinetoplast DNA [4].

Thanks to the arid desert of that region which preserved the desiccated soft tissue, these researchers confirmed that the disease was present in Latin America, approximately 9000 years ago, where *T. cruzi* infections in humans as like many other animals, acting as hosts.

The actual theory is that humans populated the western coast of South America at an estimated 9500 years ago, and by doing so, became part of the sylvatic cycle of Chagas disease. Whereas, the domestic cycle developed much after, when civilization developed along with the foundation of urban settlement. Andean population also domesticated rodents in their home for consumption and rituals attracting hematophagous insects like *T. cruzi* vectors. The *T. infestans* species (one of the vectors) found optimum living places in wattle and daub houses, where they can feast on blood from both humans and domestic animals [5].

2.2. Chagas before the train: a young Darwin sets sail on the HMS Beagle

Charles Darwin traveled to Chile aboard the HMS *Beagle* in 1834. He became severely ill while in Valparaiso, which kept him bedridden for seven weeks. Initially accredited to typhoid disease, no other members of the crew developed the illness. In March of 1835, Darwin crossed the Andes into Argentina, where he described in his journals that he slept in the village of Luxan (today's Luján de Cuyo) in the southern district of Mendoza [6]. At night he experienced the attack of a "Benchuca", a Reduvid bug, as he described "the most disgusting to feel soft wingless insects about one inch long crawling over one's body; before sucking they are quite thin, but afterwards round and bloated with blood, and in this state they are easily squashed" [7]. It is very likely that "Benchuca" is the old name for "Vinchuca" (Reduvid bug) in modern Spanish, and based on the distribution of triatomid bugs, Darwin was describing the *Triatoma infestans*, known then as the "great black bug of the Pampas" across that region. He studied the insect for at least four months, as well as those regions which had a higher possibility for several potential contacts with *T. infestans*.

From 1835 to 1841, Darwin reported no symptoms, which could be a possible latent phase of Chagas disease. From 1841 to 1861, Darwin described palpitations, sense of extreme fatigue, trembling, flatulence, and vomiting to colleagues and physicians, but no one could really identify the cause. They even thought that Darwin was suffering from illness anxiety disorder (hypochondriasis) from his clinical presentations and family history of psychiatric tendencies [7]. At the age of thirty-three, he abandoned his work due to physical exhaustion and digestive disturbances, which can be well explained by an infection of *T. cruzi*. Darwin experienced "anginal attacks", and was finally diagnosed with "heart-failure" [8]. Darwin's disease has been of extensive speculation from the scientific community. Still, two things are clear: 1) he was exposed to Reduvid bug, and 2) his symptoms can be explained by Chagas disease.

3. Medicine in the first Contact Zone: 110 years after Lassance (1909–2019)

3.1. Discovery

The vast geographical area (an entire continent) and temporal space (9000 years) of the prequel, along with the scarce reliable data of Darwin's anecdote and the vinchuca bug, in contrast, the encounter in the first Contact Zone has very spatial and temporal precision and is well-documented: Lassance, 1908–1909.

Also, the socioeconomic, cultural context is clearly defined, witnessed by the expansion of the Industrial Revolution in Central and South America. This phenomenon had clear objectives: "Order and Progress". Latin America was to be populated with railroads carrying both raw materials and people from the production center to the ports, and from there, to the rest of the world (mainly Europe).

The groups in the Contact Zone are clearly defined. On the one hand, patients, represented by Berenice, José, Joaquina, and their families, were characterized by the following descriptions: rural population, poverty, analphabetism, and disease. On the other hand, physicians represented by Dr. Carlos Chagas and Dr. Belisário Penna, and the Manguinhos team, lead by their mentor Dr. Oswaldo Cruz, were identified by these characteristics: urban population, satisfying basic needs, and university education.

In particular, Berenice, the first diagnosed patient, concentrated almost all the characteristics of marginalization and social exclusion that defined this kind of patient for decades: gender (women), age (childhood), economic condition (poverty), and health (sick).

The story is well-known: at the beginning of the 20th century, the construction of Brazil Central Railroad in the state of Minas Gerais bridged Belo Horizonte (capital of the state) to Rio de Janeiro. Stations were added sequentially from one city to another: Curvelo in 1904, Corinto in 1906, Lassance in 1908, and Pirapora in 1910. However, when an outbreak of malaria in the region delayed all the efforts of railroad construction, the current model in the vector combat era was applied, thus, eradicating the vector, and the outbreak ended. It was the tropical medicine model, also known as colonial or imperial medicine, led by Ross and Masson, who clarified the role of mosquitoes as disease vectors.

Thus, the Health Minister Calmon requested Dr. Osvaldo Cruz, director of the National Institute of Serum Therapy in Rio, to send a professional to investigate the problem. Young Dr. Carlos Chagas, along with Dr. Belisário Penna responded to investigate this case.

They used a wagon train as the central command of operations,

Fig. 1. Dr. Carlos Chagas in Lassance, Minas Gerais, Brazil, together with a young female patient.

moving from one city to another. In one of the towns, engineer Cantarino Motta told Dr. Chagas about an hematophagous insect with a nocturnal habit called “Barbeiros”. These insects had a flagellated parasite similar to one that Chagas once described in monkeys that he named *Trypanosoma minensis*. Chagas sent samples of “Barbeiros” to the National Institute of Serum Therapy where Dr. Cruz inoculated monkeys. After 30 days, when Chagas examined the blood of lab monkeys, he noticed the parasites were different from *T. minensis*. *Trypanosoma cruzi* was the name he later gave to this new parasite, to honor his mentor.

Looking for other human hosts, he found a girl named Berenice. She had fever, facial edema and hepatic-splenic-lymph node syndrome. The girl who was only two years old, was evaluated by Dr. Chagas, who had found the parasite in her blood. In one of the few sets of circumstances, Dr. Chagas performed the so-called “reverse triple discovery”: first discovering the vector, then the parasite, and finally the disease in a young girl (Fig. 1).

He presented this new disease to the public in 1909 [9] which would later become known by his own name. Along with his colleagues they defined all the clinical aspects of the disease between 1909 and 1917. However, he would soon find out that his research was overlooked by the Eurocentric world.

Although the next section will refer in further detail to the academic contact area, the extensive original Chagas' article was in a Portuguese-German bilingual publication. Researchers from peripheral countries must use the “dominant” scientific language of their time to communicate their findings. Still, scientists and physicians were not paying attention to poor underdeveloped countries' diseases, because of World War I beginning, and the focus was placed elsewhere. Positivist of the undefined progress trickles down, ironically called “The War to End All Wars”, leaded to starvation, famine, epidemic typhus and pandemic flu, causing millions of deaths in the aftermath. Clearly, the European world was not ready for American trypanosomiasis.

Berenice, diagnosed with Chagas disease, was re-examined, together with her family when she was 53 years old [10]. She showed no typical manifestations of the disease, although the complement fixation of Machado Guerreiro and the xenodiagnosis were all reactive. At that time, a strain was isolated, which was later named after her: Be-62 and then another, sixteen years later, Be-78. Finally, the researchers commented that she had “*neurotic* manifestations regarding the disease that made her famous by fantasizing resentments against the barbeiro”.

In 2002, J.C·P. Dias et al. reported that Lassance is now free of Chagas disease transmission, even though the municipality still remains infested by *Triatoma sordida* in low densities and high dispersion, where none are infected by *T. cruzi* and are restricted to peridomestic foci. The general prevalence is about 5.03% with no infected individuals found under 20 years of age. Girls like Berenice are now free of Chagas disease [11].

Fig. 2. Dr. Salvador Mazza, at MEPRA, studying the disease.

3.2. Rediscovery

The rediscovery of Chagas disease had moved to a new geographic area, from Brazil to the northern Argentine Republic. The protagonists of the Contact Zone were the same: poor, rural, marginalized patients, and urban and academic physicians, working in a Mission. In 1926, Dr. Salvador Mazza from the Misión de Estudios de Patología Regional Argentina (MEPRA), described the same disease as his colleague in Brazil. Established in a railway car similar to Dr. Chagas, Dr. Mazza assumed the studies on trypanosomiasis in Jujuy (north of Argentina), publishing routine reports, traveling one this mobile laboratory from one village to another, educating the population, and controlling the vector as much as possible. After several years of study, he described the new trypanosomiasis found in rural areas, to his fellow scientific community. He explained the reality of the situation, finally confirming the existence of *T. cruzi* in Argentina [12]. However, the reality was a harsh one: the vector triatomine bug hides in the wattle and daub housing, and emerged during the night when the inhabitants were sleeping. The poor hygiene and social-economic conditions were part of the Chagas disease cycle, and these points became a major emphasis for Dr. Mazza everywhere he went (Fig. 2).

Another contribution from MEPRA, was a semiological value that facilitated the clinical diagnosis of the disease's acute period, and which became the description of the conjunctival syndrome, better known as “sign of Romaña” [13]. The unilateral presence of palpebral edema, conjunctival hyperemia and regional lymphadenopathy allowed the disease to be identified in hundreds of children. Interestingly, this sign is seen in many photographs of patients, including Berenice, but until the time of its description it went unnoticed and undiagnosed. The publication of this finding and its dissemination accelerated the timeframe for the meeting between patients and doctors in rural Contact Zones. And, in the academic Contact Zone this contributed to the end of the controversy over the association between goiter and cretinism endemic with trypanosomiasis, which had generated so many doubts about the existence of the disease. Unlike the Minas Gerais region in Brazil or the Andean area of Argentina, in the Chaco santafecino, the goitrogenic endemic was not as common, and this epidemiological difference helped define the nosological autonomy of the disease.

4. The academic Contact Zone: initial battles and deception

Contact zone allows us to understand another conflict which described a new asymmetry. In this case, the confrontation that took place within a seemingly homogenous sociocultural group: the scientific community, which we will herein name as the “Academy”.

The confronted sectors are university professionals, on the one side, physicians represented by Chagas and their group: field clinical researchers, young people - the vast majority of them Brazilians -, as they are the “discoverers” of a “truly American” disease.

Fig. 3. Carlos Chagas presenting the disease at the Brazilian Academy of Medicine in August 1911.

On the other hand, the academics, represented in Buenos Aires by Dr. Kraus, in Rio de Janeiro by the anti-Chagas groups and in Stockholm by the members of the Nobel Committee: senior researchers, "city" physicians, non-Americans or academics who only recognize the knowledge from major European cities (Fig. 3).

4.1. Buenos Aires: conference in a foreign country

In his first trip abroad, Carlos Chagas was invited to Buenos Aires, where he set forth his knowledge in a conference, professionally describing the principal manifestations of the disease [14]. However, one of the findings was the association of goiter with American trypanosomiasis, in which Dr. Chagas' own word "was still debatable". Dr. Chagas noticed the presence of goiter associated with the social condition related to Chagas disease [15]. Different authors could not confirm such association. His detractors took advantage of this, to further slander Dr. Chagas name. Dr. Kraus et al. stated that there were places in Argentina with triatomines infected with *T. cruzi*, but no patient with Chagas disease and goiter was found, because Dr. Kraus could not find the parasite in their bloodstream [16].

4.2. Rio de Janeiro: the inner enemy

As with every paradigm shift, any fundamental new change in science means initial criticism and doubt. In medicine, this is especially true when the struggle for power and authority takes place [17]. Since the discovery of Chagas disease by Dr. Carlos Chagas in 1909, several important figures inside Oswaldo Cruz Institute, like Figueiredo de Vasconcellos, Henrique da Rocha Lima and Butantan Institute's Arthur Neiva, demonstrated their clear motivations of an anti-Chagas group, each with their own reasons, since Dr. Chagas was appointed as the Director of Oswaldo Cruz, and in June 1919 as General Director of Public Health by the Brazilian government. The power struggle between different characters would discredit Dr. Chagas' role in the discovery of the disease and any other debates related to his findings.

4.3. Stockholm: recognition and the failure to receive the Nobel Prize

In 1912, Chagas received the prestigious Schaudinn Prize for best work in parasitology, the same work suitable for a Nobel Prize. He was nominated for the Nobel Prize in 1921, but none was awarded that year. Intrigue seemed to be part of an obscure reason why Dr. Chagas did not receive the Nobel Prize [18]. During Johansson's chairmanship of the Nobel Committee, one prize was given to his close friend, one to scientists without any discovery, one to unnominated scientists, and all this while Johansson was the principal evaluator. The Nobel Committee decided not to give a prize in 1921 and the official reason was "to use the money for investments in science" at the Nobel Institute that Johansson himself created.

Another member of the Committee in 1921 was Frithiof Lennmalm, a supporter of the eugenics movement. He even proposed to create the Eugenic Nobel Institute in 1919 and was supported by the members of the Committee, but was later rejected by the Karolinska Institute. Dr. Chagas' nomination was also discarded by evaluator Gunnar Hedrén at the Nobel Committee on April 1921. Hedrén was required to submit a written report about his evaluation, but no related document has been found in the Committee Archives. By 1920, Dr. Chagas had been nominated twice for the Nobel Prize, and, no Euro-American scientist's work was deemed nonessential, despite the fact that Dr. Chagas work had and still has a direct socioeconomic impact affecting the lives of millions.

5. Urban hospitals as type of Contact Zone

5.1. The chronic forms of the disease (1940–1970)

Between 1909 and 1940, the encounter between chagasic patients and doctors occurred mostly in rural areas. In the mid 20th century, the contact area moved to large urban centers since industrialization of the countryside and social changes in cities, stimulating internal migration within all Latin American countries.

The Industrial Revolution, with the railroad in the lead, had penetrated in the interior of the regions, along with the incipient non-stop roads that move people to the cities. At first, the inhabitants migrated from the center to the periphery, and over time, from the provincial periphery to the center of big cities.

They brought their illnesses, among them: Chagas disease, malaria, leishmaniasis, etc. The sedentary lifestyle of the metropolis would be responsible for adding hypertension, diabetes, obesity, etc. However, in the contemptuous local language of Buenos Aires, these migrants were known as the "black heads," provincial inhabitants that could also live in the big cities, have political, labor, and labor union rights.

In the description made by Taquini et al. [19], in a twelve-case report with chronic chagasic heart disease, "after 1946, more common observations appear in hospital settings in Buenos Aires, as a result of exodus to the capital from endemic areas".

A similar situation was described in Rio de Janeiro. Benchimol [20] pointed out that "with increasing rural migration to large urban centers with better living conditions, more patients with Chagas heart disease were found in the large cities and capitals of most States of the Federation". He reported 51 cases of chronic chagasic heart disease observed in that metropolis, "this capital, being a point of convergence where individuals from the most diverse corners of the country flow." Most of the patients came from endemic areas, raising the possibility of urban transmission in those who had never left the cities.

If a pediatric patient with the acute form were diagnosed in areas of endemic contact, the adult chronic cases now will be detected in urban centers with cardiac [21], digestive [22] and neurological forms [23]. In the first two decades of the twentieth century, doctors, microscopes in hand, looked for patients with obvious clinical manifestations. In the fourth and fifth decades of their age, they will carry the electrocardiograph and test tubes, recognizing cardiac alterations without major clinical manifestations. Additionally, in the urban hospitals' settings, patients will be given serologies, ECG and chest radiographs, to determine a better understanding of the chronic cardiac form. Studies of the digestive tract allow doctors to recognize the esophageal and colonic problems, the mega syndromes related to the disease, and the ones related to the autonomic nervous system.

Acute central nervous system involvement was initially diagnosed in the first descriptive articles of the disease. Nervous system disease

would be another object of controversy. In hospitals studies, patients with reactive serologies, and the use of electromyogram, permitted the recognition of chronic peripheral nervous system involvement [24]. Changes in medical care would be forever changed, facilitating the understanding of other biological phenomena linked to chagasic infection.

The Contact Zone has changed throughout the 20th century. The groups changed as the patients moved, from the “inner” territories, to the “big cities”. Their skin and their way of speaking identified them. Doctors began to look for the chronic forms of the disease, but the prejudices of the sick people from the provinces continued. There was a severe asymmetry between doctor-patient relationship - among city doctors and the “chagasics” of the “interior”.

Just as some patients modified their geographical locations with migrations from the countryside to the city, so had the healthcare practices. New ways of transmitting the disease were discovered. As for the acquisition of the disease, during the first half of the 20th century, the reliable route of transmission was still the vectorial one.

Although some of the non-vector routes of transmission were suspected or described in a few cases, it was the changes in the healthcare environment that resulted from the greater access of the population to hospitals and the “medication life”, which allowed the detection and improvement in infection control.

Large number of trauma patients (and complex surgeries they received) had more risk to be transfused, therefore, potentially be in contact with the parasite that came in blood bags [25].

Similarly, when treating and controlling pregnancy in urban hospitals, mothers are detected in an indeterminate or chronic phase of the disease that would later transmit trypanosomiasis to their offspring. The existence of congenital Chagas is thus confirmed [26].

Even though laboratory accidents are few, they still exist. It should be a warning to everyone that the history of the young Argentinian physician, Dr. Mario Fatala Chabén, should never be repeated, as *T.cruzi* infected him in his lab by accident. [27].

5.2. Chagas in immunosuppressed and transplant patients (1970–2019)

A new and very interesting aspect of the patient care in modern urban hospitals, is the modification of the disease. Urban hospitals then become an additional Contact Zone, beginning a new chapter for Chagas' disease research.

Immunosuppression has become an increasingly frequent condition that may modify the natural history of *T. cruzi* infection [28]. Between the 1970s and 1980s, infected individuals with serious impairment of the immune system, such as oncological, autoimmune diseases and transplant recipients, were at risk of severe forms of Chagas disease reactivation [29–31].

The first reports of *T. cruzi* infection in patients with HIV, were published between 1988–1992. Approximately 20% of HIV-*T. cruzi* infected patients experienced reactivation with meningoencephalitis and/or myocarditis [32]. In the central nervous system (CNS), two forms were observed: meningoencephalitis with trypomastigotes in cerebrospinal fluid or pseudo-tumoral formation (chagoma) with brain images indistinguishable from other opportunistic infections such as toxoplasmosis and primary CNS lymphoma. CNS chagoma is associated with high mortality, and to further define the diagnosis, a stereotactic biopsy needs to be performed. The histopathological findings consist of extensive uni or multifocal encephalitis, necrohemorrhagic tissue, mononuclear infiltrate with predominantly perivascular distribution, and amastigote nests inside macrophages, glia or endothelial cells.

Reactivations of *T. cruzi* infection are dependent on the severity of the immune deficiency, as they have been described more often with a CD4+ T-cell count < 200/mm3, and are associated with a high level of parasitemia. Therefore, quantification of parasitic load with molecular strategies would help to characterize the reactivation, and would allow for early treatment [33]. The HIV-*T. cruzi* coinfection made it necessary to include Chagas disease as an AIDS-defining illness.

Transmission of infection from infected organ donors to naïve recipients was also further researched. In the early 1980s, transmission of *T. cruzi* from known infected donors to negative recipients was reported in kidney transplant recipients [31]. Approximately 20 years later, the first cases of accidental transmission from unscreened donors were also reported in the USA [34].

Organ transplantation in patients with chronic Chagas' disease and the use of organs from infected donors has been a matter of debate for many years [35]. The growing number of infected individuals now living in non endemic regions has increased the possibility that they might become transplant candidates or organ donors [36]. In Argentina, data from Instituto Nacional Central Único Coordinador de Ablación e Implante (INCUCAI) showed that 7% of all patients on the waiting list were infected, including 6% of heart candidates [37].

Most of the published cases of transplanted *T. cruzi*–infected patients are related to kidney transplantation [38]. Reactivation has shown to occur mainly within the first post transplant year with an incidence of 15% to 35%. Favorable responses to benznidazole treatment have been described with adequate graft and patient survivals on long-term follow-up.

Heart transplantation is now accepted as a safe and effective intervention for progressive Chagas cardiomyopathy [39]. The first cardiac transplant for a recipient with Chagas cardiomyopathy was performed in 1985 in Brazil [40]. This condition has become, over time, the third leading cause of heart transplantation in Brazil and Argentina [41,42]. Chronic Chagas disease infection used to be considered a potential contraindication for transplantation due to the risk of potential reactivation with immunosuppression. Reactivation has been reported to occur in 23% to 75% of patients [43].

Reactivation can be completely asymptomatic, and only parasitemia will show the recurrence of the infection. When clinical manifestations appear, signs of subcutaneous involvement (reminiscent of erythema nodosum or panniculitis) with tenderness and characteristic limb involvement. Skin and subcutaneous tissue biopsies will show nonspecific inflammatory infiltrate and numerous amastigote nests. Myocardial reactivation may correspond to a focal or diffuse location. Acute myocarditis is characterized by an intense inflammatory infiltrate consisting of mononuclear and polymorphonuclear cells, edema and numerous amastigote nests in cardiomyocytes.

A good response to 30–60 days of benznidazole treatment, with adequate graft and patient survival after long-term follow-up, has been reported. Mortality related to Chagas disease reactivation has been reported to be 0.3%, and the survival rates are no different from those of other heart transplant recipients [44].

Monitoring for *T. cruzi* reactivation is recommended, as treatment can be initiated before the development of clinically significant disease. PCR from blood and tissue fragments has become a decisive tool to detect early infection as it shows positive results days to weeks before circulating trypomastigotes detected by Strout method and blood smear preparations [45,46].

In recent decades, the development of biological therapies has led to an advance in the treatment of autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, spondyloarthropathy, and inflammatory bowel disease, among others. Numerous agents with different immune mechanisms are available, including anti-tumor necrosis factor, anti-interleukin 1, anti-interleukin 6, anti-CD28, anti-CD20, and anti-interleukin 12/23. These therapies, which are involved in immune response modifications, can change multiple immunological pathways, inducing an incremental risk for certain infectious diseases reactivation, such as Chagas disease [47].

The approach of medicine in the Contact Zone, illustrates that the evolution of medical care, and the increase in complexity across the infected patients' care access, begins to erode the distinctive characteristics of the groups. When non-vector transmission pathways are diagnosed, physicians now can and should suspect the disease in other

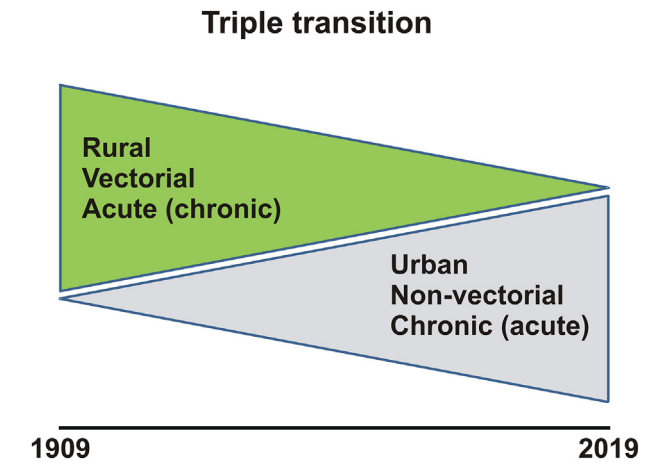

Fig. 4. A "triple transition," which conceptually reflects changes in the modality of Chagas disease of > 100 years. (Modified from Viotti-Vigliano "Enfermedad de Chagas", Editorial Médica Panamericana, 2015. Reproduced with authorization from Editorial Médica Panamericana Médica - Prohibited any use without the express consent of Editorial Médica Panamericana).

risk groups (Fig. 4).

6. News from the original Contact Zone: the Latin America endemic areas of today

6.1. Control or persistence of vector, transfusional and congenital transmission

With the second decade of the 21st century, comes a time of paradoxes, even though the exodus from the countryside to the city persists, the endemic areas (Original Contact Zone), remain a stable population that continues to get sick.

Chagas' disease is a parasitic zoonosis which constitutes a severe public health problem, and is endemic in 21 Latin America's countries.

The American trypanosomiasis has expanded from rural to urban areas [20], and from endemic to non-endemic regions [48]. It is estimated that between six and eight million people are infected with *T. cruzi*, with an additional 65 million at risk of acquiring the disease by vector-borne transmission, blood or congenital transmission, or food-borne transmission [49].

Control and elimination of Chagas disease are achievable. The incidence of Chagas disease in the Americas has been substantially reduced through efforts in vector control and systematic blood screening. The estimated number of new cases has declined by 32%, from 41,000 in 2006 to 28,000 in 2010, and the mortality from 45,000 deaths per year to the current 12,000 [49].

There are 130 triatomine species that contribute to maintaining *T. cruzi* transmission among mammals in almost every terrestrial ecoregion of the Americas [50]. This means that Chagas disease will never be eradicated and undermine the fact that effective disease prevention will require stronger, long-term vector control-surveillance systems.

The campaigns to eradicate the vectors emerge, with notable successes in some regions and disappointing results in others, due to the presence of multiple interests found, and with a lack of persistence in field actions. From the desks of the ministries are born projects that stumble amid the true realities. It will be the inhabitants of the endemic regions themselves and the health agents in intimate contact with them who will produce the best results.

Vector control measures began when a small branch of the Oswaldo Cruz Institute was established in Bambuí (Brazil) by Emmanuel Dias in the early 1940s. In his early attempts, Dias tried everything possible to eradicate triatomines from human dwellings, but positive results were better obtained with organochlorine, gammahexachlorocyclohexane (HCH, Gammexane), used successfully in both, 1948 by Dias and Pellegrino, in Brazil [51], and by Romaña and Abalos, in Argentina [52]. HCH (and/or dieldrin) remained the most widely used compound against domestic *Triatominae* until the late 1970s, when it was replaced with synthetic pyrethroids. The results from these types of campaigns have been very satisfactory in Brazil, Uruguay, Chile, in large regions of Argentina and Venezuela, and parts of Bolivia and Paraguay [53].

Suspected in the 1930s by Mazza [12], transfusion-based transmission of Chagas disease was first recognized in Brazil and other countries in the 1940s and early 1950s [25,54].

In the absence of the vector, one of the potential modes of transmission of Chagas disease in non-endemic regions is through blood and blood products. While many blood components can transmit the infection, platelets are the most frequent cause of transfusion-related transmission. As most patients with Chagas disease are asymptomatic and unaware of their condition, in the case of blood donation, they can inadvertently represent a serious threat to the safety of the blood supply in non-endemic areas [55].

Since the 1980s, screening of the blood supply has become accepted as an important pillar of the four sub-regional Chagas disease control initiatives. In Brazil, Chagas' Disease Control Programme was fully implemented in the 1980s, when it reached practically all the endemic areas, and in 1991, the Southern Cone Initiative was created, aiming to control the disease transmission through eliminating the *Triatoma infestans* and controlling blood banks. As a result, the prevalence of chagasic donors in blood banks reduced from 4.4% in the 1980s to 0.2% in 2005 [56].

With the control of vectorial and transfusional routes of infection with *T. cruzi*, congenital transmission has become an important source of new cases. The prevention of congenital Chagas' disease remains of substantial importance in endemic and nonendemic regions.

Maternal-fetal transmission occurs in approximately 5% of the newborns from infected mothers, although this rate varies between countries, ranging from 1.0% to 12%. The risk of transmission is influenced by several factors, such as maternal parasitemia levels, age, anti-*T. cruzi* immune response and parasite strain [57].

In Argentina, around 1500 children are born each year with *T. cruzi* infection. The prevalence of maternal infection has dropped from 9.0% to 2.6%. The rate of congenital infection had an irregular evolution and its national average fluctuated between 1.9 and 8.2% [58].

The first case of congenital chagasic infection was reported by Dao in Venezuela, in 1949 [26], and in Argentina the first case was described by Jörg in 1953 [59].

Congenital Chagas' disease may cause spontaneous abortion, premature birth, intrauterine growth retardation, and stillbirth. Infected children may or may not have clinical signs of disease at birth. The clinical spectrum of congenital infection with *T. cruzi* varies from severe compromise to the presence of a few mild symptoms. Cases of congenital *T. cruzi* infection should be treated as soon as the diagnosis has been confirmed [57]. Treatment with benznidazole in women of childbearing age significantly reduces the parasitemia, and was effective in preventing the congenital transmission of *T. cruzi* to their children. It also had a protective effect on the women's clinical evolution and an observed 32% to 64% conversion rate to negative serology in benznidazole-treated women after long-term follow up [60–62].

6.2. Sexual transmission

Early studies [9,63], suggested that *T. cruzi* can spread via sexual transmission. Experimental studies in laboratory animals revealed the presence of *T. cruzi* amastigote nests in the reproductive system of acutely infected mice, and sexual transmission of the parasites from *T. cruzi*-infected mice to naïve recipients were also observed.

Araujo et al. hypothesized that endemicity of Chagas infection in urban areas of Latin America and in non-endemic countries can be transmitted sexually, when in the absence of insect vectors and other

modes of the infection. They showed clinical, parasitological and nucleic acid data that *T. cruzi* footprint nuclear DNA are presented in human male ejaculates, in which injected to mice, they can detect *T. cruzi* amastigote nests in heart, and afterwards, in skeletal muscles [64].

Evidence that Chagas disease can be transmitted sexually, coupled with the migration of individuals with Chagas disease to previously non-endemic countries and increased travel to endemic countries, is a potential threat to public health worldwide.

6.3. Oral transmission

Initially in endemic rural regions, and then in food and beverage stalls along the roads, and in the growing suburbs that expand in areas with vectors parasitized by *T. cruzi*, people can ingest the parasites, producing foci of disease. This event had called to the attention of health authorities and researchers.

The most notorious outbreaks involved pediatric patients. In school situations, they were given juices to drink which were contaminated with vector feces containing parasites. On other occasions, the infected triatomines will be directly blended together with the fruits to make the juices. These cases were initially studied for prolonged febrile syndrome, until the serological and parasitic finding was confirmed [65].

It seems that, from the point of view of biology and metaphors, Chagas disease was tenaciously associated with the idea of edge, periphery, margin and contact; and the usual affected group are children of school age, low or middle class, and sometimes urban. There is another group, an “invisible group”: municipal, provincial or national entities in charge of bromatological controls, making sure infected juices are not present in children's table. Although the Contact Zone approach initially is not apparent, it can be seen between the interaction of same old patient groups and the National States that fail to avoid this new form of epidemic.

7. The academic Contact Zone again: paradigm changes and clashes

Thomas Kuhn in his work, now a classic [66], redefined the term paradigm applied to the scientific community. In this sense, a paradigm can be defined as a set of interrelated theoretical concepts that allow an approximation to reality, based on scientific evidence.

The confronted sectors are determined by the historical moments in which the interpretation of reality changes. Paradigm shifting goes through the following stages. Whatever subject is studied, at first, there is an established paradigm that constitutes the accepted science of that time. It may seem monolithic and undisputed unit, that paradigm always contains unresolved issues. When these various aspects are studied, the crisis of the established paradigm emerges. Usually, those who challenge the *status quo* are young researchers from Institutions or peripheral countries who propose a new approach, and who produce a scientific revolution. This establishes a “new” paradigm. Over time, both young researchers and the dominant paradigms “age”, other young people appear with their novel concepts that explain the “gaps” of the previous researchers, and thus, ad infinitum, the cycle is restarted. The **Academic CZ** comes to a boil.

7.1. The evolution of the interpretation of pathogenic mechanisms

In terms of the modification of the paradigms of pathogenic interpretation, it followed a relatively orderly pattern, and according to the stages proposed and suggested by Khun: one concept gradually replaces the other with the approval of the scientific community as a whole.

In order to understand the historical interpretation of Chagas' disease pathogenesis, it is necessary to remember the moments when the seminal findings of the 20th century occurred, which changed our view of biology and disease. (Reviewed in Laguens et al., [67]).

The antibodies and the complement system were discovered in the first decade of the 20th century, when Carlos Chagas described the disease. The role of lymphocyte as a key cell of the immune response was established in the 1960s. Clonal theory of immunity and molecular characterization of antibodies were from the same period. Recognition of DNA as the molecular basis of genes dated back to 1953, but molecular biology, as we understand it today, began to develop in the late 1970s. With the introduction of PCR, a key tool for genetic research; and in the 1990s, the monoclonal antibody industry began to develop.

Three epochs can be distinguished on this chronological basis:

7.1.1. 1909–1960 period

The first case description of human trypanosomiasis by Carlos Chagas was Berenice's case, a two-year-old girl, who presented with fever of 39.4 °C, palpebral edema, adenomegaly, hepatomegaly and presence of *T. cruzi* in peripheral blood, with subsequent remission of the signs and symptoms [68].

The characteristic lesions are: bi-palpebral edema or unilateral (Romaña sign), with or without conjunctivitis, adenomegalies and cutaneous lesions at the site of inoculation (chagoma), which can occur more frequently as nodules and/or erythema. The histological appearance reveals numerous amastigote nests in the basal layer of the epidermis, in the dermis and hypodermis, and within macrophages with an inflammatory infiltrate consisting of mononuclear and polymorphonuclear cells.

The acute phase usually affects children, and main manifestations are acute chagasic myocarditis and meningoencephalitis, which if not adequately treated, can cause a mortality of approximately 5 to 10% [69]. After a few months, symptoms disappear and the disease remains silent, with difficult detection of the parasite in blood, for which the diagnosis is made by titration of anti-*T. cruzi* antibodies. The so-called “indeterminate stage” attempts to define an asymptomatic period presenting without signs of the disease. It follows the acute stage and can last the entire life of the patient. The indeterminate phase of Chagas' disease is characterized by positive serology in the absence of clinical manifestations including cardiac, digestive and nervous system.

In 1911, Carlos Chagas differentiated between acute infection (with or without meningoencephalitis) and chronic infection, where he described the cardiac disease with numerous cases of heart rhythm alterations (bradycardia and heart block), along with frequent occurrence of heart failure. He described “the chronic myocarditis” as a histopathological substrate for the arrhythmic forms of adults [70].

Gaspar Vianna began pathological studies of this new entity, finding forms of amastigotes within muscle cells, intense inflammatory reaction of interstitial tissue, pericarditis, zones of inflammatory infiltration without the presence of parasites, and parasitic fibers without pericellular inflammatory reaction [63]. A last observation led to the postulation of indirect mechanisms, independent of the parasite, as responsible for the production of cardiac damage [71]. According to the terminology of that era, an “allergic” mechanism was involved in the production of tissue damage. In 1929, Magarinos Torres argued that chronic chagasic heart disease is the result of active and progressive myocarditis, due to the continuous action of the parasite associated with an “allergic” state of the host [72].

A new pathogenic hypothesis of chronic Chagas disease was proposed in the 1950s by Fritz Köberle. He proposed dysautonomia (denervation of the parasympathetic autonomic nervous system neurons) as a cause of digestive tract dilations (Chagasic megaesophagus and megacolon) and heart illness (chagasic heart disease) [73]. It is well known that, in Chagas' disease, there is a loss of autonomous system neurons, which is involved in the pathogenesis of megaviscera, as well as motor neurons presenting with subclinical manifestations. However, the role of the alterations on the autonomous system that plays over the heart is still controversial [74]. The possibility that autonomic disturbance of the nervous system disturbances plays a pathogenic role in the development of chagasic heart disease seems unlikely, especially after thousands of denervated heart transplants experiences.

A third pathogenic hypothesis, based on both pathological observations of human hearts and experimental studies, postulated that cardiac damage would be a consequence of vasculopathy, with arteritis and loss of cardiac microcirculation components. This would lead to loss of contractile units by ischemic necrosis, together with inflammation and reparative fibrosis [75], (Reviewed in Rossi M et al. [76]).

7.1.2. 1960–1993 period

In a span of 25 years, from 1957 to 1983, there was an explosion in the research and development of immunology. In the following decade, those developments built the foundation of the 21st century's immunology. This progress was seen at the beginning of the 60s, when previous work hypothesized that immune mechanisms played a key role in the myocardial damage.

Bases of autoimmunity were established at the same time when Witebsky and Rose defined the criteria necessary to diagnose an autoimmune disease [77]. It would almost be inexorable if attempts were made to explain the discrepancy between the presence of lesions and the absence of the parasite. These are the consequence of the development of immune mechanisms awareness of cardiac tissues triggered by *T. cruzi* infection, in which once established, the presence of the parasite was no longer a condition necessary for the persistence and aggravation of myocarditis [78].

In addition, experimental models of chronic infection were developed at the same time, making it possible to investigate the involvement of autoimmune mechanisms in the production of cardiac damage. During this period most studies showed:

- Presence of similar antigens between parasite and mammalian tissues (molecular mimicry).
- Activation of autoreactive clones during acute phase infection with persistence during the chronic phase.
- Cardiac tissue antigens not accessible to immunological recognition (sequestered antigens) and modification of molecular structure of normal antigens induced by the destruction of parasitic cardiac myocytes during the early phase of infection.

7.1.3. 1993–2019 period

Towards the end of 1993 and the beginning of 1994, two studies published almost simultaneously, initiated a change in the conception of pathogenesis and clinical treatment of chronic Chagas' disease. The first was the discovery of the DNA of *T. cruzi* in the myocardium of patients with chronic chagasic myocarditis [79], and the second was a non-randomized clinical study, which showed improvement of clinical and serological evolution in patients treated with benznidazole [80].

Use of highly sensitive parasite detection techniques, such as PCR, has demonstrated that *T. cruzi*, or the parasite fragments persist in the target organs, frequently as a stimulus for the observed chronic inflammatory response producing tissue damage [81,82]. That fact replaces the previous emphasis on the immune approach, focusing the greatest efforts on investigating the mechanisms by which small quantities of parasite can trigger severe damage [83].

Treatment with tripanocid drugs during the undetermined phase prevents the development of cardiomyopathy, in addition to negativizing the specific serological reactions anti-*T. cruzi* in a significant proportion of patients [80]. This supports the role of parasitic presence in chagasic myocarditis. In addition, there is an association between the areas of myocarditis, or severe fibrosis, with the discovery of amplification of the DNA of *T. cruzi* in chronic chagasic hearts [84]. Also, parasitic traces are absent in areas without injury, which supports the interpretation that the persistence of the parasite is decisive for the development of cardiac lesions [85].

However, the fact that it is necessary to resort to ultrasensitive techniques to detect *T. cruzi* in tissue lesions makes it almost impossible for the parasite to produce a direct injury, raising the question of the existence of damage amplification mechanism. Accumulated evidence about the existence of cross antigens between *T. cruzi* and mammalian tissues, and presence of humoral and cellular immune self-activity (both humans and infected animals), were initial signs supporting autoimmune hypothesis as the main reason for the production of lesions, if, on the contrary, they are the expression of an epiphenomenon resulting from tissue damage, without pathogenic liability [86].

At present, immunological mechanisms responsible for chronic cardiac inflammation seem to be the most important one. The identification of cell populations that make up the inflammatory infiltrate of chronic chagasic heart disease, with preponderance of T-lymphocytes and macrophages, show markers of participation of immune system [87], and the detection of most cytokines and chemokines described in chronic inflammation [88]. Regardless of their origin, they may be responsible for cell damage, but they do not clarify any contribution to the primary mechanisms that lead to the appearance of the inflammatory infiltrate. Chagas heart disease is an inflammatory cardiomyopathy that develops in approximately one-third of people infected with the protozoan parasite *T. cruzi,* and is characterized by an inflammatory infiltrate with predominance of mononuclear cells (lymphocytes and macrophages) and fibrosis, of moderate to intense grade, with slow and progressive evolution leading to ventricular dilation, complicated with alterations in electrical conduction (complex ventricular arrhythmias), and heart failure.

Historically, several hypotheses were raised on the pathogenesis of chronic Chagas disease: direct action of the parasite, immunological mechanisms of damage, dysautonomia, and pathology of microcirculation. Pathogenic interpretation based on autoimmunity, which prevailed until the last 25 years, was not only crucial from a speculative point of view, but had practical consequences, such as abandoning the use of trypanocidal drugs during the chronic phase of infection. The use of highly sensitive techniques for the detection of the parasite, such as PCR, has demonstrated that *T. cruzi*, or fragments thereof, persist in the target organs of the disease and would stimulate the observed chronic inflammatory response, which produces tissue damage.

Chronic Chagas' heart disease may represent a unique example of co-infectious autoimmunity, different from viral autoimmune myocarditis that would represent post-infectious autoimmunity, or from Crohn's disease caused by loss of digestive tolerance to intestinal bacterial antigens. Chagas' heart disease represents a different model of cardiac remodeling than other human diseases, where the presence of a causal infectious agent is observed in the lesions, and the persistence for years of an inflammatory cardiac infiltrate. They lead to cardiac remodeling and heart failure, with the histopathological substrate of cell death, fibrosis and hypertrophy, all which characterize chronic chagasic cardiomyopathy [67] (Fig. 5).

Even if mechanisms of probable dysregulation of the immune or autoimmune response in chronic Chagas heart disease are demonstrated, the fact that parasitic persistence is necessary to trigger the inflammatory response itself indicates the need for etiological treatment.

7.2. The etiologic treatment revisited

In the case of etiological treatment, the paradigm conflict in the Academic Contact Zone still persists. The change in pathogenic interpretation seems to have followed a relatively calm path as the issue of etiological treatment of chronic patients seems to have not yet reached its stage of equilibrium or widespread acceptance by researchers. In a previous work [89], we established that the existing body of knowledge until 1993 can be considered as the “old paradigm”, and towards the end of that year and early 1994, two studies were apparently published almost simultaneously that began in parallel to address the change in the pathogenic conception and clinical treatment of chronic Chagas disease. This latter is the new paradigm that “fights” with the previous one, following Kuhn's postulates.

Etiologic treatment of Chagas' disease aims at eliminating *T. cruzi*

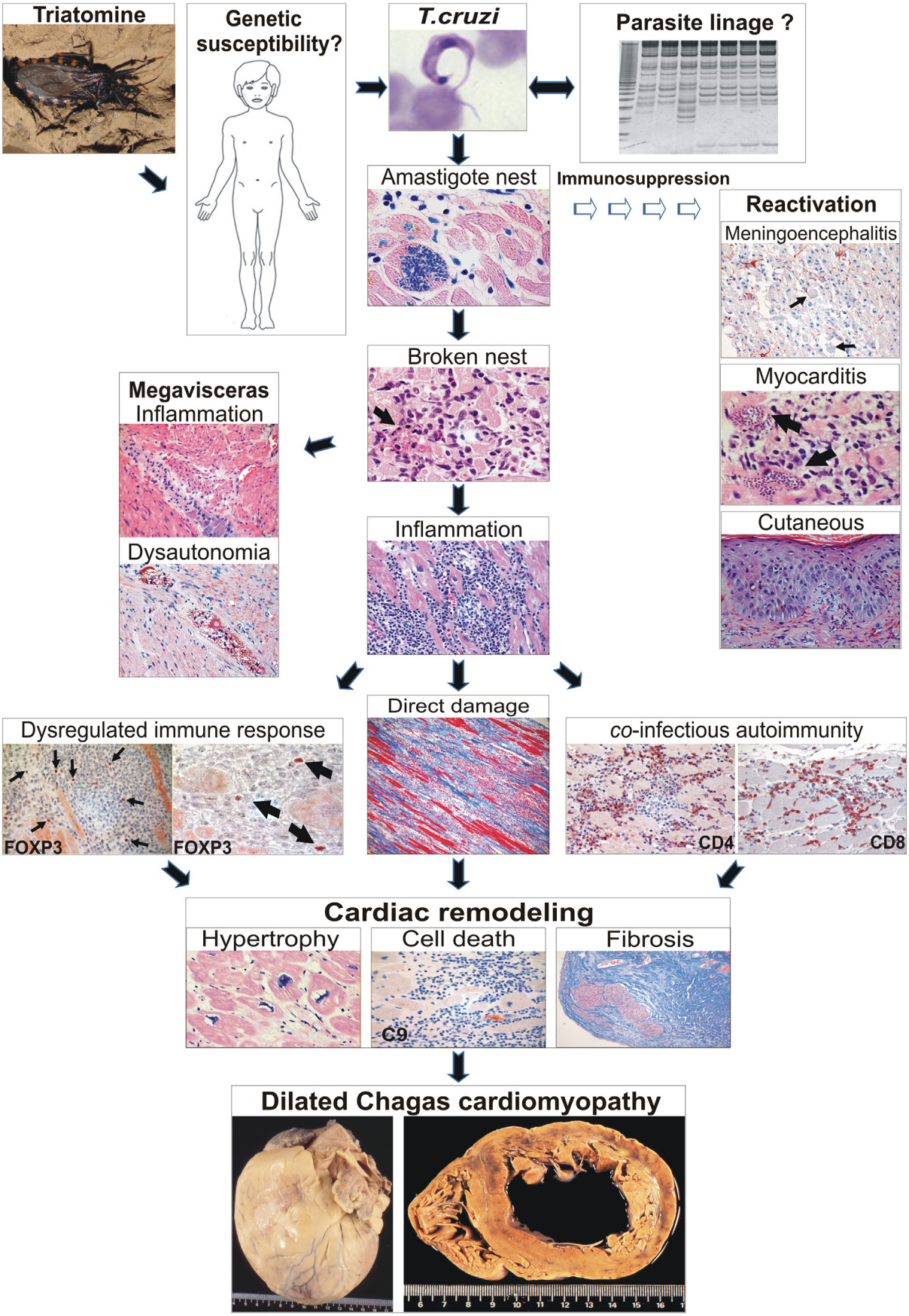

Fig. 5. Pathogenic mechanisms of chronic chagasic cardiomyopathy. (Modified from Viotti-Vigliano "Enfermedad de Chagas", Editorial Médica Panamericana, 2015. Reproduced with authorization from Editorial Médica Panamericana - Prohibited any use without the express consent of Editorial Médica Panamericana).

infection through agents capable of destroying the parasite in the host. In 1936, Mazza et al. detected the trypanocidal effect of a quinolone derivative (Bayer 7602) when using it for the first time in humans in the treatment of an acute case [90]. Based on the knowledge that 5-nitrofuran compounds were active against the circulating form of *T. cruzi* [91], Brener, in 1961, suggested their use in long-term schedules to interrupt the parasite's cycle within the host [92]. Later, in vivo investigations in mice indicated that certain compounds such as nitrofurazone, nifurtimox, and benznidazole are also active against the tissue forms of the parasite, which had been previously shown in tissue cultures [93]. The first plan for the therapeutic evaluation of Chagas' disease was proposed at a meeting held in March 1962 in Rio de Janeiro, Brazil. Experiments with benznidazole (N-benzyl-2-nitroimidazole acetamide) began in 1967 [94]. Benznidazole was launched in the 1970s and rapidly showed its efficacy in the treatment of the acute phase of the disease. First results indicate that benznidazole is effective in inducing a marked and sustained reduction in the circulating parasites' level in the majority of chronic chagasic patients, but adverse effects can lead to treatment discontinuation in 10–20% of cases [95,96].

The mechanism of action of nifurtimox and benznidazole is by direct toxic inhibition of the DNA synthesis of the parasite or indirect interactions of nitroreduction intermediates with parasite components, acting either on the intracellular forms (amastigotes) or extracellular, circulating forms or trypomastigotes [97,98]. Main side effects are related to the enzymatic activity of nitro-reduction and the generation of free radicals. This enzymatic activity is very low in children and young adults, which would explain the minor incidence of side effects in those age groups.

Since the 1970s, different therapeutic experiences were conducted in acute and chronic cases of Chagas disease using Nifurtimox and Benznidazole, comparing the effectiveness and tolerance of both drugs inside groups of patients, in which therapeutic schemes, follow-up periods and cure were all evaluated. The results showed high variability, with excellent results for acute phase and recent infection cases (reviewed in Coura JR and Castro SL [97]).

In 1994, Viotti et al. showed improved clinical and serological evolution in chronic chagasic patients treated with benznidazole, compared to non-treated patients [80]. These data support the presupposition of classical pioneer teams in the treatment of Chagas' disease who advocated antiparasitic treatment for chronically infected persons as a strategy for possibly eliminating the parasite, thus preventing or minimizing the clinical evolution of the disease [99].

Since then, much more clinical, experimental, immunopathological and parasitological evidence has sustained the use of an anti parasite treatment for adult patients with indeterminate Chagas' disease, or for those with initial stages of Chronic Chagas cardiomyopathy [83,100].

Randomized-control trial showed that a short course of benznidazole treatment significantly reduced the detection of circulating parasites, but did not reduce cardiac clinical progression through five years of follow-up in patients with advanced Chagas' cardiomyopathy [101]. The lack of correlation between the trypanocidal effect of benznidazole and the clinical evolution of the disease may be related to limited drug access or activity in the inflammatory and fibrotic foci of Chagas' cardiomyopathy, a lack of reversibility of these lesions, or both [102]. However, all components of the primary endpoint were, although not statistically significant, less frequent in the benznidazole group than in the placebo group, and patients receiving benznidazole had significantly fewer admissions to hospital for cardiovascular causes than those receiving placebo. According to the results of the BENEFIT trial in Brazil, the relative risk reduction of the primary endpoint by 15%, compared with placebo, suggests a complementary role in the comprehensive palliative therapy of chronic Chagas cardiomyopathy [103].

The set of scientific results of the last 20 years has led to a review of the parasite's role as a trigger and sustainer of tissue damage, and therefore, to a reconsideration of antiparasitic treatment. The presence of *T. cruzi* is now accepted as a trigger for the pathophysiological phenomenon of the chronic infection, as well as a key factor for its magnitude and persistence [74,85].

As previously stated, a recent change in the scientific *paradigm* on the pathogenesis of chronic Chagas disease has led to a consensus that all *T. cruzi*-seropositive patients should receive etiological treatment [104]. This important scientific advance has spurred the rigorous evaluation of the safety and efficacy of currently available drugs (benznidazole and nifurtimox), as well as novel anti-*T. cruzi* drug candidates in chronic patients [105].

Ergosterol biosynthesis inhibitors, such as posaconazole and ravuconazole, are better tolerated, but their efficacy, at the doses and treatment duration used in the initial studies, was significantly lower than with benznidazole treatment. Such results are more related to suboptimal exposure and/or treatment duration. Combination therapies are a promising perspective, but the lack of validated biomarkers of response to etiological treatment and eventual parasitological cures in chronic patients remains a serious challenge [106,107].

The current criterion for cure in the chronic phase of the disease is the negativization of at least two serological tests, such as enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay, and indirect hemagglutination assay. The serological evolution of treated subjects with chronic *T. cruzi* infection is variable. The rate of seronegativization after treatment is about 60–70% in children who have been treated before fifteen years of age, and 30–50% in adults after fifteen to twenty years of follow-up [108].

Treatment failure is indicated by a positive parasitological and/or molecular test (persistence of parasitemia). Although specific, xenodiagnosis have low sensitivity (20–50%) during chronic phase compared to PCR (30–80%) [109]. The level of susceptibility of different lineages and how this factor may interfere with treatment response are unknown, although some results suggest there is an impact [110].

From this standpoint, a trypanocidal effect is relevant for the cure of subjects [111], the potential impact on decreased morbidity and mortality [112,113] and the prevention of vertical transmission of Chagas disease [60–62]. In this framework, the PAHO recommends to offer trypanocidal drugs to all subjects with chronic *T. cruzi* infection [49].

8. The global Contact Zone in the digital communication era

The original Contact Zone is a specific space-time point, which we summarize in the expression: Lassance, 1909. In this circumstance, only two well-defined groups interact: patients and physicians.

One hundred and twenty years later, the current Contact Zone is global, i.e. the spatial variant is multidimensional, *T. cruzi* infection ceased to be American to spread across the globe. And, the initial dyad, patient-doctor, has multiplied in these various stakeholders of non-governmental organizations of patients and physicians, government agencies (Ministry of Health, etc.), supra-government entities (WHO, etc.), public and private health care systems, the pharmaceutical industry, etc.

Furthermore, the dynamics of multiple interactions have multiplied and accelerated due to the numerous means available in the digital communication era. Both the media and the flow of information online and in real time, have revolutionized the way they learn, treat and reflect on Chagas disease. Currently we don't think about isolated points of information. In the original Contact Zone, there was only one emitter (physicians) and a single receiver (patients), and in the original academic Contact Zone, there was an emitting group (scientists who “know”) and a receiving group (the practical physicians who “learn”). Now, we conceive the flow of information in true networks of reciprocal learning and mutual interaction (Fig. 6).

8.1. Open-access publications and dissemination of information

There was a time were researchers spent long hours in libraries

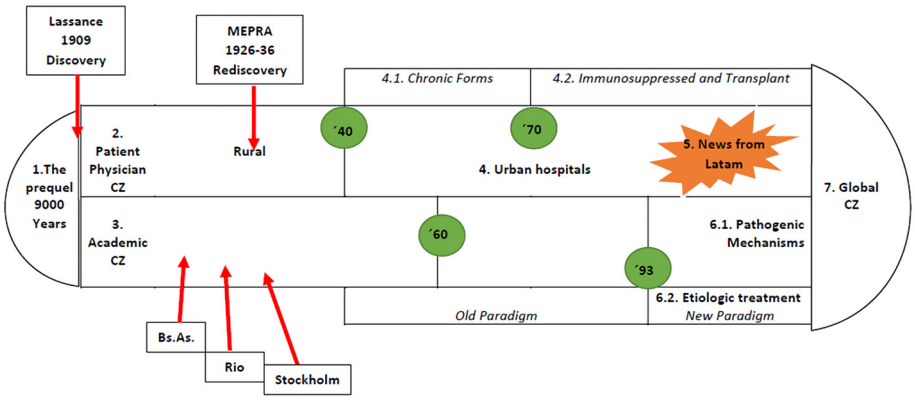

Fig. 6. Summary of the history of Chagas disease from the perspective of Contact Zone. (Modified from Viotti-Vigliano "Enfermedad de Chagas", Editorial Médica Panamericana, 2015. Reproduced with authorization from Editorial Médica Panamericana - Prohibited any use without the express consent of Editorial Médica Panamericana).

pouring through bulks of academic journals and reports. Those publications have been the basis of our citations. At the end of the 21st century, with the emergence and growth of the internet, researchers began to shift their preference to online databases. These catalogues were paid subscriptions or Open-access modality where end-users can access and download materials free-of-charge (generally through public funding, private funding, donations, or university funding). The whole idea behind Open-access is to democratize information. There are pros and cons in this new modality, but it has permitted the Chagas disease's knowledge to be spread to the rest of the world.

One example is PLOS, where in the last 10 years, it has published an elevated percentage of Chagas related articles (in this review [33,61,76,87,88,108,113,117,119,121]).

8.2. The impact of patient and medical organizations

Since information is diffused faster, physicians now know the existence of Chagas' disease and it's many narratives. Those patients are no longer "invisible", and doctors are now accessing more information, and are aware of the characteristics of identification, diagnosis, treatment and epidemiology of the disease.

Initially, each Latin American country had non-governmental organization (NGO) for educational or financial fund-seeking purposes to help patients. As an example, in Argentina, we mention ALCHA (Asociación Lucha contra el Mal de Chagas). Subsequently, true mixed networks have emerged, including Mundo Sano and Médecins sans frontières, and the NGOs that promote and investigate various diseases, and some specific ones, like NHePaCha (Nuevas Herramientas para la Enfermedad de Chagas).

8.3. Chagas disease in popular culture

The early history of the spread of this disease, especially the "rediscovery" of Mazza, in the Northern provinces of Argentina, was documented in the film "Casas de fuego", a quite reliable production with historical facts and with wide broadcasting to the general public, which constitutes the current and global Contact Zone.

And, since this work is a tribute to Rodolfo Viotti, we cannot fail to comment on a mention that our remembered "Lolo", Rodolfo said "if Chagas disease had reached the television series, Dr House (Season 4, episode 13), all physicians (Latin Americans, Northern "gringos", European, Asian, etc.) should be able to diagnose and treat trypanosomiasis, because there are no longer national or continental borders that stop their spread."

8.4. The indifference of the pharmaceutical industry

Another component of the Chagas disease continuum is the pharmaceutical industry. In short, we still only have two drugs to treat this pathology. It is remarkable that infectious diseases that appear later, such as HIV, have dozens of drugs for their control and cure.

Large pharmaceutical companies won't see any profit in developing orphan drugs for neglected diseases where production costs and massive market distribution are problematic for them. Decades have passed and we still use the same remedies for Chagas disease. Millions of patients are still waiting for a definitive cure and physicians are still discussing the effectiveness of present medications [114]. We have no doubt that if an expensive biological drug was available, the pharmaceutical industry would put formidable pressure to convince the medical community to treat all patients at all periods of the disease, through multiple actions of influence in patient organizations and in payers-financing, whether public or private. In the meantime we are still waiting.

8.5. Modern obstacles in healthcare systems

Modern healthcare requires massive investment of capital, which poses a problem for nonprofit institutions. Because of this, medical-industrial complexes are the new modality [115]. These are vast networks of investor-owned businesses supplying healthcare for profit. The system, in theory, is better than the nonprofit counterpart, where the free market should operate to improve the quality and efficiency of health-related management, whereas competition should respond by offering better and more varied products and services, at lower costs. But medical-industrial complexes create problems that influence the health policy of a country's overuse of health-care, fragmentation of services, super-specialization of disease, overemphasis on technology and "cream-skimming" practice (choosing patients for characteristic(s) other than their need for care, enhancing the profitability of the provider) [116].

Because patients with Chagas disease generally come from low socio-economic strata, it is apparent why there are so few hospital services dedicated to the care and monitoring of these patients in a comprehensive way.

8.6. The World Health Organization (WHO) and the London declaration

The WHO classified Chagas as a Neglected Tropical Disease, a group of infections in underdeveloped regions typical in tropical and subtropical conditions [117].

Based on the history of Chagas disease, the triatome vector has been able to adapt to new environments and new hosts, further spreading the disease worldwide. Human economic activities changed the surrounding ecosystem, in which deforestation, mining, lumbering, and urbanization are all connected to this increasing dissemination of Chagas disease [118].

Generally, populations with this disease live in poverty, without basic sanitation and in close contact to vectors or infected hosts. And as time goes by, Chagas disease is no longer confined to Latin America, spreading worldwide, affecting between six and eight million people

(with 65 million at risk) [49], and with easy flights available in every big city, the endemic population can go from their countries, to others where the disease is not widely known. (I.e. a major reason why the United States and Europe are getting Chagas disease diagnosis more than ever).

8.7. Goals of Chagas disease control

Chagas disease has an impact in upper-middle income countries, including the United States, with > 300.000 cases, and Europe, estimated to have between 68.000 and 122.000 cases. Underreporting is a significant part of a problem [118,119].

Finally, but not least, on the centenary of the disease in 2009, a roadmap was proposed to try to facilitate the dispersed efforts and thus direct the different initiatives in the global contact area [120,121].

Goals to better control are summarized in the following points.

8.7.1. Evaluate the extension of Chagas disease in the Americas

We still don't know the full extension of the disease. We need to develop diagnostic tests that are dependable, inexpensive and can be used for screening in all patient groups. PCR as a diagnostic tool in Chagas is debated, as it is expensive and extremely sensitive, with the possibility to give false positives (DNA without infection with live parasite has been observed during congenital infection in mouse models), complicating interpretation of results and management. New biological markers for identification of disease progression or cure are also desirable to know the patient's whole picture [109].

8.7.2. Decrease in transmission

Current controls of Chagas disease are mainly on vector control through indoor spraying of pyrenthoids and housing improvement. Vector control is still the main preventive intervention against the disease in endemic countries. As oral, congenital, transfusion and transplant are part of the transmission risk, control programs and screening should be developed with their independent assessment of efficacy [53].

8.7.3. Increase access to treatment

Treatment options are also challenging because of the limited efficacy and side effects of two available drugs for chronic chagasic cardiomyopathy and digestive forms of the disease. Priority should be focused on clinical trials of new drug candidates, strategies and policies for access to treatment, and strengthening of vaccine development. The last improvement we have, is the Benznidazole's pediatric formulation, making drug administration to children easier. New medications are progressing slowly, and there are few candidates. However, medications like Posaconazole failed to provide sustained reduction in circulating parasites in clinical trials, and other triazoles are not superior to benznidazole.

The prevalence of Chagas disease is expected to decrease progressively over the next 3 decades, including a reduction in both incidence and mortality. Morbidity has also been decreasing due to improved medical care and the specific treatment in chronic individuals. At this point, the next step is the tremendous challenge of using a universal, specific treatment to manage the illness of the millions of individuals with Chagas disease [122].

8.7.4. Interest in the development of a vaccine

As it may lead to an additional instrument for Chagas disease control [121].

8.7.5. Creating a monitoring database

The development of documented, accessible, accurate, and supervised database for diagnosis, vector control and treatment program would help enormously the health care team of each country.

8.7.6. Continuous education in all countries

Workshops, lectures, and courses are part of a physician continuous education program where the main objectives are to achieve better patient-care and update new medical resources.

There are still several challenges to be addressed to reach the goals of the London declaration on Neglected Tropical Disease, which aims to eliminate this disease (among others) as a public health concern [117].

Disclosures

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We want to thank Mrs. Jare Schneider of the University of Miami for her contributions in the language editing for comments that significantly improved our manuscript.

References

[1] J.L. Leone, [Rodolfo Viotti: clinical investigator in Chagas disease (1959–2017)], Medicina. 77 (2017) 443.
[2] J.L. Leone, R. Viotti, Perspectiva histórica, in: R. Viotti, C. Vigliano (Eds.), Enfermedad de Chagas, Un enfoque práctico basado en la investigación médica, Panamericana, Buenos Aires, 2015, pp. 3–16.
[3] M.L. Pratt, Arts of the contact zone. Profession. 1991, pp 33–40.
[4] A.C. Aufderheide, W. Salo, M. Madden, J. Streitz, J. Buikstra, F. Guhl, B. Arriaza, C. Renier, L.E. Wittmers Jr., G. Fornaciari, M. Allison, A 9,000-year record of Chagas' disease, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 2034–2039, https://doi.org/10.1073/pnas.0307312101.
[5] A. Araújo, A.M. Jansen, K. Reinhard, L.F. Ferreira, Paleoparasitology of Chagas disease - A Review, Mem. Inst. Oswaldo Cruz 104 (Suppl. 1) (2009) 9–16, https://doi.org/10.1590/s0074-02762009000900004.
[6] C. Darwin, The Voyage of the Beagle, P.F. Collier & Son Company (Eds.), New York, 1909.
[7] S. Adler, Darwin's illness, Nature 184 (1959) 1102–1103, https://doi.org/10.1038/1841102a0.
[8] R. Colp, Darwin's illness, R. Colp (Eds.) University Press of Florida, Gainesville, 2008.
[9] C. Chagas, Nova tripanozomiaze humana: estudos sobre a morfolojia e o ciclo evolutivo do *Schizotrypanum cruzi* n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem, Mem. Inst. Oswaldo Cruz 1 (1909) 159–218, https://doi.org/10.1590/S0074-02761909000200008.
[10] J.A. Salgado, P.N. Garcez, C. de Oliveria, J. Galizzi. [Current clinical review of the 1st described human case of Chagas' disease]. Rev. Inst. Med. Trop. São Paulo 4 (1962) 330–337.
[11] J.C.P. Dias, E.M.M. Machado, E.C. Borges, E. Furtado Moreira, C. Gontijo, B. Vaz de Mello Azeredo. [Chagas' disease in Lassance, Minas Gerais State: Clinical-epidemiological re-evaluation ninety years after the discovery by Carlos Chagas]. Rev. Soc. Bras. Med.Trop. 35 (2002) 167–176.
[12] S. Mazza, Chagas disease in the Argentine Republic, Mem. Inst. Oswaldo Cruz 47 (1949) 289–302, https://doi.org/10.1590/S0074-02761949000100011.
[13] C. Romaña, Acerca de un síntoma inicial de valor para el diagnóstico de forma aguda de la enfermedad de Chagas, la conjuntivitis esquizotripanósica unilateral (hipótesis sobre puerta de entrada conjuntival de la enfermedad), Misión de Estudios de Patología Regional Argentina 22 (1935) 16–28.
[14] C. Chagas, Aspectos clínicos y anatomopatológicos de la tripanosomiasis americana, Prensa Med. Argent. 3 (1916) 125–127 137–138, 153–158.
[15] R.B. Bestetti, A. Cardinalli-Neto, C.B.A. Restini, L.B. Couto, Could Carlos Chagas' assumption on the relationship between goiter and chronic Chagas heart disease be correct? A historical reappraisal, Int. J. Cardiol. 202 (2016) 410–412, https://doi.org/10.1016/j.ijcard.2015.09.052.
[16] R. Kraus, C. Maggio, F. Rosenbusch, Bocio, cretinismo y enfermedad de Chagas: segunda comunicación, Prensa Med. Argent. 3 (1916) 177–180.
[17] R.B. Bestetti, A. Cardinalli-Neto, Dissecting slander and crying for justice: Carlos

Chagas and the Nobel prize of 1921, Int. J. Cardiol. 168 (2013) 2328–2334, https://doi.org/10.1016/j.ijcard.2013.01.048.
[18] R.B. Bestetti, L.B. Couto, A. Cardinalli-Neto, When a misperception favors a tragedy: Carlos Chagas and the Nobel prize of 1921, Int. J. Cardiol. 169 (2013) 327–330, https://doi.org/10.1016/j.ijcard.2013.08.137.
[19] A.C. Taquini, B.B. Lozada, B. Furman, Chronic Chagas cardiopathy, Medicina 12 (1952) 123–148.
[20] A.B. Benchimol, Doenca de Chagas nos grandes centros urbanos, in: Anais do Congreso Internacional sôbre a Doenca de Chagas, vol. 1, Rio de Janeiro, 1961, pp. 189–203.
[21] E. Dias, F.S. Laranja, A. Miranda, G. Nobrega, Chagas' disease; a clinical, epidemiologic, and pathologic study, Circulation 14 (1956) 1035–1060, https://doi.org/10.1161/01.cir.14.6.1035.
[22] J.M. Rezende, Megaesofago por doenca de Chagas, Rev. Goiana Med. 2 (1956) 297–314.
[23] F. Köberle, Moléstia de Chagas. Enfermidade do sistema nervoso, in: Anais do Congreso Internacional sôbre a Doenca de Chagas, vol. 2, Rio de Janeiro, 1961, pp. 691–716.
[24] M.A. Pagano, G.G. Aristimuno, S. Basso, A. Colombi, R.E. Sica, [Electromyographical findings in human chronic Chagas' disease], Arq. Neuropsiquiatr. 36 (1978) 316–318.
[25] J. Pellegrino, Transmissão da doença de Chagas pela transfusão de sangue. Primeiras comprovações sorológicas em doadores e candidatos a doadores de sangue, Rev. Bras. Med. 6 (1949) 297–301.
[26] L. Dao, Otros casos de enfermedad de Chagas en el estado Guárico (Venezuela): formas agudas y crónicas: observación sobre enfermedad de Chagas congénita, Rev. Policlin. Caracas 17 (1949) 17–32.
[27] J.A. Cerisola, M. Fatala Chaben, J.O. Lazzari, [Hemagglutination test for the diagnosis of Chagas' disease], Prensa Med. Argent. 49 (1962) 1761–1767.
[28] R. Lattes, M.B. Lasala, Chagas disease in the immunosuppressed patient, Clin. Microbiol. Infect. 20 (2014) 300–309, https://doi.org/10.1111/1469-0691.12585.
[29] I. Rivero, M. Moravenik, J. Morales, M. Gomez, J.M. de Rosas, Letter: Chagas's disease–another hazard in acute leukemia, N. Engl. J. Med. 290 (1974) 285.
[30] A.P. Barousse, J.A. Costa, M. Eposto, H. Laplume, E.L. Segura, [Chagas disease and immunosuppression], Medicina, 40 Suppl 1 (1980) 17–26.
[31] P.R. Chocair, E. Sabbaga, V. Amato Neto, M. Shiroma, G.M.d. Goes, [Kidney transplantation: a new way of transmitting Chagas disease], Rev. Inst. Med. Trop. São Paulo 23 (1981) 280–282.
[32] E.A. Almeida, A.N. Ramos Junior, D. Correia, M.A. Shikanai-Yasuda, Co-infection *Trypanosoma cruzi*/HIV: systematic review (1980-2010), Rev. Soc. Bras. Med. Trop. 44 (2011) 762–770, https://doi.org/10.1590/S0037-86822011000600021.
[33] V.L. de Freitas, S.C. da Silva, A.M. Sartori, R.C. Bezerra, E.V. Westphalen, T.D. Molina, A.R. Teixeira, K.Y. Ibrahim, M.A. Shikanai-Yasuda, Real-time PCR in HIV/*Trypanosoma cruzi* coinfection with and without Chagas disease reactivation: association with HIV viral load and CD4 level, PLoS Negl. Trop. Dis. 5 (2011) e1277, , https://doi.org/10.1371/journal.pntd.0001277.
[34] Chagas disease after organ transplantation–United States, 2001, MMWR, Morb. Mortal. Wkly Rep. 51 (2002) 210–212.
[35] C.I. Cura, R. Lattes, C. Nagel, M.J. Gimenez, M. Blanes, E. Calabuig, A. Iranzo, L.A. Barcan, M. Anders, A.G. Schijman, Early molecular diagnosis of acute Chagas disease after transplantation with organs from *Trypanosoma cruzi*-infected donors, Am. J. Transplant. 13 (2013) 3253–3261, https://doi.org/10.1111/ajt.12487.
[36] F. Salvador, A. Sanchez-Montalva, E. Sulleiro, F. Moreso, C. Berastegui, M. Caralt, M.J. Pinazo, Z. Moure, I. Los-Arcos, O. Len, J. Gavalda, I. Molina, Prevalence of Chagas disease among solid organ-transplanted patients in a nonendemic country, Am. J. Trop. Med. Hyg. 98 (2018) 742–746, https://doi.org/10.4269/ajtmh.17-0735.
[37] D. Casadei, Chagas' Disease Argentine Collaborative Transplant Consortium, Chagas' disease and solid organ transplantation, Transplant. Proc. 42 (2010) 3354–3359, https://doi.org/10.1016/j.transproceed.2010.09.019.
[38] A. Riarte, C. Luna, R. Sabatiello, A. Sinagra, R. Schiavelli, A. De Rissio, E. Maiolo, M.M. Garcia, N. Jacob, M. Pattin, M. Lauricella, E.L. Segura, M. Vazquez, Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996, Clin. Infect. Dis. 29 (1999) 561–567, https://doi.org/10.1086/598634.
[39] E.A. Bocchi, R.B. Bestetti, M.I. Scanavacca, E. Cunha Neto, V.S. Issa, Chronic Chagas heart disease management: from etiology to cardiomyopathy treatment, J. Am. Coll. Cardiol. 70 (2017) 1510–1524, https://doi.org/10.1016/j.jacc.2017.08.004.
[40] N.A. Stolf, L. Higushi, E. Bocchi, G. Bellotti, J.O. Auler, D. Uip, V. Amato Neto, F. Pileggi, A.D. Jatene, Heart transplantation in patients with Chagas' disease cardiomyopathy, J. Heart Transplant. 6 (1987) 307–312.
[41] R.D. Benatti, G.H. Oliveira, F. Bacal, Heart transplantation for Chagas cardiomyopathy, J. Heart Lung Transplant. 36 (2017) 597–603, https://doi.org/10.1016/j.healun.2017.02.006.
[42] M.A. Peradejordi Lastras, L.E. Favaloro, C. Vigliano, M.F. Renedo, L. Martínez, S.E. Moscoloni, J. Abud, D.O. Absi, R.R. Favaloro, A.M. Bertolotti, Outcomes of heart transplantation based on recipient's clinical profile: 21-year experience, Rev. Argent. Cardiol. 84 (2016) 236–242.
[43] R.B. Bestetti, T.A. Theodoropoulos, A systematic review of studies on heart transplantation for patients with end-stage Chagas' heart disease, J. Card. Fail. 15 (2009) 249–255, https://doi.org/10.1016/j.cardfail.2008.10.023.
[44] A.I. Fiorelli, N.A. Stolf, R. Honorato, E. Bocchi, F. Bacal, D. Uip, T. Strabelli, V. Issa, V.A. Amato, L.R. Fiorelli, S.A. Oliveira, Later evolution after cardiac transplantation in Chagas' disease, Transplant. Proc. 37 (2005) 2793–2798, https://doi.org/10.1016/j.transproceed.2005.05.038.
[45] M. Diez, L. Favaloro, A. Bertolotti, J.M. Burgos, C. Vigliano, M.P. Lastra, M.J. Levin, A. Arnedo, C. Nagel, A.G. Schijman, R.R. Favaloro, Usefulness of PCR strategies for early diagnosis of Chagas' disease reactivation and treatment follow-up in heart transplantation, Am. J. Transplant. 7 (2007) 1633–1640, https://doi.org/10.1111/j.1600-6143.2007.01820.x.
[46] J.M. Burgos, M. Diez, C. Vigliano, M. Bisio, M. Risso, T. Duffy, C. Cura, B. Brusses, L. Favaloro, M.S. Leguizamon, R.H. Lucero, R. Laguens, M.J. Levin, R. Favaloro, A.G. Schijman, Molecular identification of *Trypanosoma cruzi* discrete typing units in end-stage chronic Chagas heart disease and reactivation after heart transplantation, Clin. Infect. Dis. 51 (2010) 485–495, https://doi.org/10.1086/655680.
[47] C.E. Perez-Diaz, E. Uribe-Pardo, O.J. Calixto, A.A. Faccini-Martinez, A.J. Rodriguez-Morales, Infections with biological therapy: strategies for risk minimization in tropical and developing countries, J. Infect. Dev. Ctries. 10 (2016) 1278–1285, https://doi.org/10.3855/jidc.8222.
[48] J. Gascon, C. Bern, M.J. Pinazo, Chagas disease in Spain, the United States and other non-endemic countries, Acta Trop. 115 (2010) 22–27, https://doi.org/10.1016/j.actatropica.2009.07.019.
[49] Pan American Health Organization, Guidelines for the Diagnosis and Treatment of Chagas Disease, PAHO, Washington, D.C., 2019.
[50] F.A. Monteiro, C. Weirauch, M. Felix, C. Lazoski, F. Abad-Franch, Evolution, systematics, and biogeography of the Triatominae, vectors of Chagas disease, Adv. Parasitol. 99 (2018) 265–344, https://doi.org/10.1016/bs.apar.2017.12.002.
[51] E. Dias, J. Pellegrino, Alguns ensaios com o gammexane no combate aos transmissores da doença de Chagas, Bras. Med. 18 (1948) 19.
[52] C. Romaña, J. Abalos, Acción del Gammexane sobre los triatomideos: control domiciliario, An. Inst. Med. Reg. Tucumán 2 (1948) 95–106.
[53] J.C. Dias, Evolution of Chagas disease screening programs and control programs: historical perspective, Glob. Heart 10 (2015) 193–202, https://doi.org/10.1016/j.gheart.2015.06.003.
[54] J. Freitas, V. Amato, R. Sonntag, First verifications of accidental transmission of Chagas disease to humans by blood transfusion, Rev. Paul. Med. 40 (1952) 36–40.
[55] A. Angheben, L. Boix, D. Buonfrate, F. Gobbi, Z. Bisoffi, S. Pupella, G. Gandini, G. Aprili, Chagas disease and transfusion medicine: a perspective from non-endemic countries, Blood Transfus. 13 (2015) 540–550, https://doi.org/10.2450/2015.0040-15.
[56] R. Bello Corassa, C. Aceijas, P.A.B Alves, H. Garelick, Evolution of Chagas' disease in Brazil. Epidemiological perspective and challenges for the future: a critical review, Perspect. Public Health 137 (2017) 289–295, https://doi.org/10.1177/1757913916671160.
[57] F. Torrico, Chagas congénito, in: R. Viotti, C. Vigliano (Eds.), Enfermedad de Chagas, Un enfoque práctico basado en la investigación médica, Panamericana, Buenos Aires, 2015, pp. 117–128.
[58] E. Danesi, M.O. Codebo, S. Sosa-Estani, Congenital transmission of *Trypanosoma cruzi*. Argentina 2002-2014, Medicina 79 (2019) 81–89.
[59] M. Jörg, *Trypanosomiasis cruzi* congénita mortal en un lactante de 17 días, in: Primera Conferencia Nacional de Enfermedad de Chagas, vol. 205, Buenos Aires, 1953.
[60] S. Sosa-Estani, E. Cura, E. Velazquez, C. Yampotis, E.L. Segura, Etiological treatment of young women infected with *Trypanosoma cruzi*, and prevention of congenital transmission, Rev. Soc. Bras. Med. Trop. 42 (2009) 484–487.
[61] D.L. Fabbro, E. Danesi, V. Olivera, M.O. Codebo, S. Denner, C. Heredia, M. Streiger, S. Sosa-Estani, Trypanocide treatment of women infected with *Trypanosoma cruzi* and its effect on preventing congenital Chagas, PLoS Negl. Trop. Dis. 8 (2014) e3312, , https://doi.org/10.1371/journal.pntd.0003312.
[62] M.G. Alvarez, C. Vigliano, B. Lococo, G. Bertocchi, R. Viotti, Prevention of congenital Chagas disease by benznidazole treatment in reproductive-age women. An observational study, Acta Trop 174 (2017) 149–152, https://doi.org/10.1016/j.actatropica.2017.07.004.
[63] G. Vianna, Contribuição para o estudo da anatomia patolojica da "Molestia de Carlos Chagas": (Esquizotripanoze humana ou tireoidite parazitaria), Mem. Inst. Oswaldo Cruz 3 (1911) 276–294, https://doi.org/10.1590/S0074-02761911000200004.
[64] P. Araujo, A. Almeida, C. Pimentel, A. Silva, A. Sousa, S.A. Valente, V.C. Valente, M.M. Britto, A.C. Rosa, R.M. Alves, L. Hagström, A.R. Teixeira, Sexual transmission of American trypanosomiasis in humans: a new potential pandemic route for Chagas parasites, Mem. Inst. Oswaldo Cruz 112 (2017) 437–446, https://doi.org/10.1590/0074-02760160538.
[65] B. Alarcon de Noya, Z. Diaz-Bello, C. Colmenares, R. Ruiz-Guevara, L. Mauriello, R. Zavala-Jaspe, J.A. Suarez, T. Abate, L. Naranjo, M. Paiva, L. Rivas, J. Castro, J. Marques, I. Mendoza, H. Acquatella, J. Torres, O. Noya, Large urban outbreak of orally acquired acute Chagas disease at a school in Caracas, Venezuela, J. Infect. Dis. 201 (2010) 1308–1315, https://doi.org/10.1086/651608.
[66] T.S. Kuhn, La estructura de las revoluciones científicas, Fondo de Cultura Económica de México (1971) 1–319.
[67] R.P. Laguens, M.P. Cabeza, C. Vigliano, Patogenia, in: R. Viotti, C. Vigliano (Eds.), Enfermedad de Chagas, Un enfoque práctico basado en la investigación médica, Panamericana, Buenos Aires, 2015, pp. 81–102.
[68] C. Chagas, Tripanosomiase Americana, Forma Aguda Da Molestia. Mem. Inst. Oswaldo Cruz 8 (1916) 37–60, https://doi.org/10.1590/S0074-02761916000200003.
[69] A. Prata, Clinical and epidemiological aspects of Chagas disease, Lancet Infect. Dis. 1 (2001) 92–100, https://doi.org/10.1016/s1473-3099(01)00065-2.
[70] C. Chagas, Nova entidade morbida do homem, Rezumo Geral de Estudos Etiolojicos E Clínicos. Mem. Inst. Oswaldo Cruz 3 (1911) 219–275.
[71] C. Chagas, Processos patogênicos da tripanossomíase Americana, Mem. Inst. Oswaldo Cruz 8 (1916) 5–9.

[72] C. Torres, Patogenia de la miocarditis crónica en la "enfermedad de Chagas", Reunión Soc. Argent. Patol. Region. Norte 2 (1929) 902–916.
[73] F. Köberle, Cardiopatia chagasica, Hospital (Rio de Janeiro) 53 (1958) 311–346.
[74] M.C.P Nunes, H. Acquatella, A. Beaton, C. Bern, A.F. Bolger, L.E Echeverría, W.O. Dutra, J. Gascon, C.A Morillo, J. Oliveira-Filho, A.L.P Ribeiro, J.A Marin-Neto, American Heart Association Rheumatic Fever; Endocarditis and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Stroke Council, Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association, Circulation 138 (2018) e169–e209, https://doi.org/10.1161/CIR.0000000000000599.
[75] Z.A. Andrade, S.G. Andrade, A patogenia da miocardite crônica chagásica: a importância das lesões isquêmicas, Arq. Bras. Med. 45 (1955) 279–288.
[76] M.A. Rossi, H.B Tanowitz, L.M. Malvestio, M.R Celes, E.C. Campos, V. Blefari, C.M Prado, Coronary microvascular disease in chronic Chagas cardiomyopathy including an overview on history, pathology, and other proposed pathogenic mechanisms, PLoS Negl. Trop. Dis. 4 (2010), https://doi.org/10.1371/journal.pntd.0000674.
[77] E. Witebsky, N.R. Rose, K. Terplan, J.R. Paine, R.W. Egan, Chronic thyroiditis and autoimmunization, J. Am. Med. Assoc. 164 (1957) 1439–1447, https://doi.org/10.1001/jama.1957.02980130015004.
[78] F. Kierszenbaum, Autoimmunity in Chagas' disease, J. Parasitol. 72 (1986) 201–211.
[79] E.M. Jones, D.G. Colley, S. Tostes, E.R. Lopes, C.L. Vnencak-Jones, T.L. McCurley, Amplification of a *Trypanosoma cruzi* DNA sequence from inflammatory lesions in human chagasic cardiomyopathy, Am. J. Trop. Med. Hyg. 48 (1993) 348–357, https://doi.org/10.4269/ajtmh.1993.48.348.
[80] R. Viotti, C. Vigliano, H. Armenti, E. Segura, Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up, Am. Heart J. 127 (1994) 151–162, https://doi.org/10.1016/0002-8703(94)90521-5.
[81] S. Brandariz, A. Schijman, C. Vigliano, P. Arteman, R. Viotti, C. Beldjord, M.J. Levin, Detection of parasite DNA in Chagas' heart disease, Lancet 346 (1995) 1370–1371, https://doi.org/10.1016/s0140-6736(95)92388-8.
[82] A.R. Vago, A.M. Macedo, S.J. Adad, D.D. Reis, R. Correa-Oliveira, PCR detection of *Trypanosoma cruzi* DNA in oesophageal tissues of patients with chronic digestive Chagas' disease, Lancet 348 (1996) 891–892, https://doi.org/10.1016/s0140-6736(05)64761-7.
[83] R. Viotti, C. Vigliano, Etiological treatment of chronic Chagas disease: neglected 'evidence' by evidence-based medicine, Expert Rev. Anti-Infect. Ther. 5 (2007) 717–726, https://doi.org/10.1586/14787210.5.4.717.
[84] A.G. Schijman, C.A. Vigliano, R.J. Viotti, J.M. Burgos, S. Brandariz, B.E. Lococo, M.I. Leze, H.A. Armenti, M.J. Levin, *Trypanosoma cruzi* DNA in cardiac lesions of Argentinean patients with end-stage chronic Chagas heart disease, Am. J. Trop. Med. Hyg. 70 (2004) 210–220, https://doi.org/10.4269/ajtmh.2004.70.210.
[85] L. Zhang, R.L. Tarleton, Parasite persistence correlates with disease severity and localization in chronic Chagas' disease, J. Infect. Dis. 180 (1999) 480–486, https://doi.org/10.1086/314889.
[86] K.M. Bonney, D.M. Engman, Autoimmune pathogenesis of Chagas heart disease: looking back, looking ahead, Am. J. Pathol. 185 (2015) 1537–1547, https://doi.org/10.1016/j.ajpath.2014.12.023.
[87] R.J. Argüello, C. Vigliano, P. Cabeza-Meckert, R. Viotti, F. Garelli, L.E. Favaloro, R.R. Favaloro, R. Laguens, S.A. Laucella, Presence of antigen-experienced T cells with low grade of differentiation and proliferative potential in chronic Chagas disease myocarditis, PLoS Negl. Trop. Dis. 8 (2014) e2989, , https://doi.org/10.1371/journal.pntd.0002989.
[88] L.G. Nogueira, R.H. Santos, B.M. Ianni, A.I. Fiorelli, E.C. Mairena, L.A. Benvenuti, A. Frade, E. Donadi, F. Dias, B. Saba, H.T. Wang, A. Fragata, M. Sampaio, M.H. Hirata, P. Buck, C. Mady, E.A. Bocchi, N.A. Stolf, J. Kalil, E. Cunha-Neto, Myocardial chemokine expression and intensity of myocarditis in Chagas cardiomyopathy are controlled by polymorphisms in CXCL9 and CXCL10, PLoS Negl. Trop. Dis. 6 (2012) e1867, , https://doi.org/10.1371/journal.pntd.0001867.
[89] R.J. Viotti, C.A. Vigliano, Tratamiento etiológico, in: R. Viotti, C. Vigliano (Eds.), Enfermedad de Chagas, Un enfoque práctico basado en la investigación médica, Panamericana, Buenos Aires, 2015, pp. 254–255.
[90] S. Mazza, R. Cossio, E. Zucardi, Primer caso agudo de enfermedad de Chagas comprobado en Tucumán y su tratamiento con Bayer 7602, Misión de Estudios de Patología Regional Argentina 32 (1937) 3–18.
[91] A. Packchanian, Chemotherapy of experimental Chagas' disease with nitrofuran compounds, Antibiot. Chemother. (Northfield) 7 (1957) 13–23.
[92] Z. Brener, Atividade terapêutica do 5-nitro-furaldeído-semicarbazona (nitrofurazona) em esquemas de duração prolongada na infecção experimental do camundongo pelo *Trypanosoma cruzi*, Rev. Inst. Med. Trop. Sao Paulo 3 (1961) 43–49.
[93] Z.A. Andrade, Z. Brener, Ação da nitrofurazona (5-nitro-2-furaldeído-semicarbazona) sôbre as formas intracelulares do *Trypanosoma cruzi* na doença de Chagas experimental, Rev. Inst. Med. Trop. Sao Paulo 11 (1969) 222–228.
[94] E. Grunberg, G. Beskid, R. Cleeland, W.F. DeLorenzo, E. Titsworth, H.J. Scholer, R. Richle, Z. Brener, Antiprotozoan and antibacterial activity of 2-nitroimidazole derivatives, Antimicrob Agents Chemother (Bethesda) 7 (1967) 513–519.
[95] C.A. Barclay, J.A. Cerisola, H. Lugones, O. Ledesma, J. Lopez Silva, G. Mouzo, Aspectos farmacológicos y resultados terapéuticos del benznidazol en el tratamiento de la infección chagásica, Prensa Med. Argent. 65 (1978) 239–244.
[96] R. Viotti, C. Vigliano, B. Lococo, M.G. Alvarez, M. Petti, G. Bertocchi, A. Armenti, Side effects of benznidazole as treatment in chronic Chagas disease: fears and realities, Expert Rev. Anti-Infect. Ther. 7 (2009) 157–163, https://doi.org/10.1586/14787210.7.2.157.
[97] J.R. Coura, S.L. Castro, A critical review on Chagas disease chemotherapy, Mem. Inst. Oswaldo Cruz 97 (2002) 3–24, https://doi.org/10.1590/S0074-02762002000100001.
[98] J.D. Maya, B.K. Cassels, P. Iturriaga-Vasquez, J. Ferreira, M. Faundez, N. Galanti, A. Ferreira, A. Morello, Mode of action of natural and synthetic drugs against *Trypanosoma cruzi* and their interaction with the mammalian host, Comp. Biochem. Physiol. A Mol. Integr. Physiol. 146 (2007) 601–620, https://doi.org/10.1016/j.cbpa.2006.03.004.
[99] J.R. Cançado, Z. Brener, Terapêutica, in: Z. Brener, Z. Andrade (Eds.), *Trypanosoma cruzi* e Doença de Chagas, Guanabara Koogan, Rio de Janeiro, 1979, pp. 362–424.
[100] P.A. Sales Junior, I. Molina, S.M. Fonseca Murta, A. Sánchez-Montalvá, F. Salvador, R. Corrêa-Oliveira, C.M. Carneiro, Experimental and clinical treatment of Chagas disease: a review, Am. J. Trop. Med. Hyg. 97 (2017) 1289–1303.
[101] C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, S. Yusuf, Randomized trial of benznidazole for chronic Chagas' cardiomyopathy, N. Engl. J. Med. 373 (2015) 1295–1306, https://doi.org/10.1056/NEJMoa1507574.
[102] J.A. Urbina, J. Gascon, I. Ribeiro, Benznidazole for chronic Chagas' cardiomyopathy, N. Engl. J. Med. 374 (2016) 189, https://doi.org/10.1056/NEJMc1514453.
[103] A. Rassi Jr., J.A.N. Marin, A. Rassi, Chronic Chagas cardiomyopathy: a review of the main pathogenic mechanisms and the efficacy of aetiological treatment following the BENznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial, Mem. Inst. Oswaldo Cruz 112 (2017) 224–235, https://doi.org/10.1590/0074-02760160334.
[104] R. Viotti, B. Alarcon de Noya, T. Araujo-Jorge, M.J. Grijalva, F. Guhl, M.C. Lopez, J.M. Ramsey, I. Ribeiro, A.G. Schijman, S. Sosa-Estani, F. Torrico, J. Gascon, Towards a paradigm shift in the treatment of chronic Chagas disease, Antimicrob. Agents Chemother. 58 (2014) 635–639, https://doi.org/10.1128/aac.01662-13.
[105] J.A. Urbina, Recent clinical trials for the etiological treatment of chronic chagas disease: advances, challenges and perspectives, J. Eukaryot. Microbiol. 62 (2015) 149–156, https://doi.org/10.1111/jeu.12184.
[106] C.A. Morillo, H. Waskin, S. Sosa-Estani, M. Del Carmen Bangher, C. Cuneo, R. Milesi, M. Mallagray, W. Apt, J. Beloscar, J. Gascon, I. Molina, L.E Echeverria, H. Colombo, J.A Perez-Molina, F. Wyss, B. Meeks, L.R Bonilla, P. Gao, B. Wei, M. McCarthy, S. Yusuf, Benznidazole and Posaconazole in eliminating parasites in asymptomatic T. cruzi carriers: the STOP-CHAGAS trial, J. Am. Coll. Cardiol. 69 (2017) 939–947, https://doi.org/10.1016/j.jacc.2016.12.023.
[107] F. Torrico, J. Gascon, L. Ortiz, C. Alonso-Vega, M.J. Pinazo, A. Schijman, I.C. Almeida, F. Alves, N. Strub-Wourgaft, I. Ribeiro, Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial, Lancet Infect. Dis. 18 (2018) 419–430, https://doi.org/10.1016/s1473-3099(17)30538-8.
[108] Y. Sguassero, C.B. Cuesta, K.N. Roberts, E. Hicks, D. Comande, A. Ciapponi, S. Sosa-Estani, Course of chronic *Trypanosoma cruzi* infection after treatment based on parasitological and serological tests: a systematic review of follow-up studies, PLoS One 10 (2015) e0139363, , https://doi.org/10.1371/journal.pone.0139363.
[109] M.J. Pinazo, M.C. Thomas, J. Bua, A. Perrone, A.G. Schijman, R.J. Viotti, J.M. Ramsey, I. Ribeiro, S. Sosa-Estani, M.C. Lopez, J. Gascon, Biological markers for evaluating therapeutic efficacy in Chagas disease, a systematic review, Expert Rev. Anti-Infect. Ther. 12 (2014) 479–496, https://doi.org/10.1586/14787210.2014.899150.
[110] B. Zingales, M.A. Miles, C.B. Moraes, A. Luquetti, F. Guhl, A.G. Schijman, I. Ribeiro, Drug discovery for Chagas disease should consider *Trypanosoma cruzi* strain diversity, Mem. Inst. Oswaldo Cruz 109 (2014) 828–833, https://doi.org/10.1590/0074-0276140156.
[111] G.L. Bertocchi, C.A. Vigliano, B.G. Lococo, M.A. Petti, R.J. Viotti, Clinical characteristics and outcome of 107 adult patients with chronic Chagas disease and parasitological cure criteria, Trans. R. Soc. Trop. Med. Hyg. 107 (2013) 372–376, https://doi.org/10.1093/trstmh/trt029.
[112] R. Viotti, C. Vigliano, B. Lococo, G. Bertocchi, M. Petti, M.G. Alvarez, M. Postan, A. Armenti, Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial, Ann. Intern. Med. 144 (2006) 724–734, https://doi.org/10.7326/0003-4819-144-10-200605160-00006.
[113] C.S. Cardoso, A.L.P. Ribeiro, C.D.L. Oliveira, L.C. Oliveira, A.M. Ferreira, A.L. Bierrenbach, J.L.P. Silva, E.A. Colosimo, J.E. Ferreira, T.H. Lee, M.P. Busch, A.L. Reingold, E.C. Sabino, Beneficial effects of benznidazole in Chagas disease: NIH SaMi-Trop cohort study, PLoS Negl Trop Dis. 12 (2018) e0006814, , https://doi.org/10.1371/journal.pntd.0006814 eCollection 2018 Nov.
[114] P. Trouiller, P Olliaro, E Torreele, J Orbinski, R Laing, N Ford. Drug development for neglected diseases: a deficient market and a public-health policy failure. Lancet 359 (2002) 2188-84, https://doi.org/10.1016/S0140-6736(02)09096-7.
[115] A.S. Relman, The new medical-industrial complex, N. Engl. J. Med. 303 (1980) 963–970, https://doi.org/10.1056/nejm198010233031703.
[116] D.L. Friesner, R. Rosenman, Do hospitals practice cream skimming? Health Serv. Manag. Res. 22 (2009) 39–49, https://doi.org/10.1258/hsmr.2008.008003.
[117] R.L. Tarleton, R.E. Gürtler, J.A. Urbina, J. Ramsey, R. Viotti, Chagas disease and the London declaration on neglected tropical diseases, PLoS Negl. Trop. Dis. 8 (2014) e3219, , https://doi.org/10.1371/journal.pntd.0003219.
[118] D. Steverding, The history of Chagas disease, Parasites Vectors 7 (2014) 317, https://doi.org/10.1186/1756-3305-7-317.
[119] A. Requena-Méndez, E. Aldasoro, E. de Lazzari, E. Sicuri, M. Brown, D.A.J. Moore, J. Gascon, J. Muñoz, Prevalence of Chagas disease in Latin-American migrants

living in Europe: a systematic review and meta-analysis, PLoS Negl. Trop. Dis. 9 (2015) e0003540, , https://doi.org/10.1371/journal.pntd.0003540.
[120] R. Reithinger, RL Tarleton, JA Urbina, U Kitron, RE Gürtler, Eliminating Chagas disease: challenges and a roadmap, BMJ 338 (2009) b1283, https://doi.org/10.1136/bmj.b1283.
[121] E. Dumonteil, C. Herrera, Ten years of Chagas disease research: looking back to achievements, looking ahead to challenges, PLoS Negl. Trop. Dis. 11 (2017) e0005422, , https://doi.org/10.1371/journal.pntd.0005422.
[122] J. Alonso-Padilla, N. Cortés-Serra, M.J. Pinazo, M.E. Bottazzi, M. Abril, F. Barreira, S. Sosa-Estani, P.J. Hotez, J. Gascón, Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America, Expert Rev. Anti-Infect. Ther. 17 (2019) 145–157, https://doi.org/10.1080/14787210.2019.1577731.