

## Eponym

## Chagas' disease

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## Case report

A 43-year-old woman was admitted to hospital with palpitations, dizziness, weakness, fatigue, and dyspnoea on exertion. A coincidental complaint was of chronic constipation. She had been born in a rural area near Goiânia, a Brazilian region in which Chagas' disease is endemic, and reported that causative (triatomine) bugs were frequently seen in her home. She recalled no details suggestive of the acute phase of Chagas' disease. The findings on examination were primarily those of congestive cardiac failure. Chest radiographs showed cardiac enlargement, and echocardiography revealed pronounced dilatation of the right atrium, together with aneurysmal changes to the apex of the left ventricle. Echocardiogram showed ventricular premature beats, right bundle branch block, and left anterior hemiblock. She received treatment with diuretics, digoxin, and angiotensin-converting-enzyme inhibitors.

After an initial good response, she collapsed suddenly on the third day and could not be resuscitated. At necropsy, the heart was globally enlarged, the apex of the left ventricle was thin (figure 1), and there were areas of chronic fibrous inflammation throughout the myocardium. The epicardium showed areas of thickening and whitening together with small white nodules composed of fibrous tissue along the epicardial vessels. There were no thrombi present and no evidence of cerebral embolism. Histopathological examination of the heart confirmed widespread myocardial fibrosis, interspersed with hypertrophic muscle cells and some foci of mononuclear cell infiltrate. No parasites were seen. Pathological changes were also detected in rectosigmoid and descending colon which showed huge and irregular dilatation, with faeces filling the intestinal lumen. Histologically, there were chronic inflammatory changes in both the mucosa and submucosa of the bowel wall. There was degeneration of ganglion cells with mononuclear cell infiltration in the submucosal (Meissner) and myenteric (Auerbach) plexuses.



Figure 1: Fibrotic thinning of the apex of the left ventricle

## Carlos Chagas and the first case of Chagas' disease

Carlos Ribeiro Justiniano Chagas (figure 2) was born on July 9, 1879, his father died when he was only 4 years old. It was his uncle's influence which led to him entering medical school in Rio de Janeiro, Brazil, where his final year thesis was on the haematological aspects of malaria. After qualification, he was encouraged by Prof Francisco Fajardo to pursue his interest in malaria and he was introduced to Oswaldo Cruz who became his close friend. Cruz was at that time involved in attempts to eradicate malaria and yellow fever from Rio, where both diseases were rife. In 1908, Chagas was deployed to the Velhas River Valley to control an outbreak of malaria among construction workers on the new railway between Rio and the Amazon basin. Chagas and his colleague, Belisario Pena, established their headquarters in a railway carriage at Lassance where they were to remain for more than a year. It was while he was working in Lassance that a local railway engineer told Chagas about the local haematophagous bugs which dropped from the ceilings of the huts onto the faces of people while asleep. They were known as "barberios" (barbers) or "chupança" (kissing

bugs). Chagas began to speculate that these bugs might act as the host for a parasite and identified in them a flagellate organism. He went on to demonstrate that this organism could infect mammals, and that it was a previously unrecognised organism later to be named *Trypanosoma cruzi*.<sup>1,2</sup>

While in Lassance, Chagas searched for evidence of animal infection by this organism and he found it in the bloodstream of a domestic cat. Shortly afterwards he was asked to see a 2-year-old girl named Berenice who lived in the same house as the infected cat, and who fell ill with a febrile illness. He was able to demonstrate the same organism in her blood in the acute phase of the illness, but also noted that it cleared as she recovered. This led to the publication of Chagas' classical paper on "New Human Trypanosomiasis" in August, 1909. In this paper he was able to describe a new disease, a newly identified causative organism, the existence of an invertebrate vector, and experimental transmission to mammals. In the next few years he was to describe the chronic features of the disease, including the cardiac, gastrointestinal, and neurological manifestations which were endemic in the area. In 1911, he described congenital infection. He went on to receive many honours and awards for this work, including the international Schaudinn Prize and the Grand Prize of the Pasteur Centenary Commemorative Exposition in Strasbourg in 1922.

Berenice lived until 1961 when she died of apparently unrelated causes—some 46 years after the death of Chagas himself. She had no cardiac, digestive, or other clinical manifestations of the disease, and thus constitutes one of the best examples of the indeterminate form of the disease. This form is seen in about two thirds of the

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estimated 18 million people suffering with the chronic phase of Chagas' disease, most of whom live in Latin America.

The way in which the young Carlos Chagas discovered the cause, epidemiology, pathology, and clinical features of this disease was exceptionally brilliant. Progress since that time has, however, been slow. Despite considerable advances in basic understanding into the condition, major challenges still remain.

### Chagas' disease<sup>3</sup>

The acute phase begins about 1 week after initial infection, but only one in 30 patients with chronic disease recall having had relevant symptoms and signs. These include fever, lymph-node enlargement, and unilateral swelling of the eyelids (Romaña's sign)—the classic indication of the inoculation site. There may be an acute myocarditis, with intense inflammatory reaction adjacent to ruptured nests of parasites and damaged muscle cells; pseudocysts are frequently seen, with associated oedema. It is usually possible to identify parasites in the blood stream during the acute phase, and serological testing may reveal IgM antibodies to *T cruzi* (even though false-negative results are common).

### Chronic phase

The chronic phase begins about 2 months after the initial infection; parasites are no longer easily detectable in bloodstream, but serological tests become positive. The chronic phase is subdivided into indeterminate, cardiac, and digestive forms on the basis of the clinical features.

#### Indeterminate form

The indeterminate form represents one pole of Chagas' disease, and is seen in 60–70% of the chronic-phase patients. Patients with this form may be completely free from cardiac, gastrointestinal, or neurological features of the disease. However, 2% to 5% of the patients with the indeterminate form convert to cardiac or digestive forms each year, for reasons which are not yet clear.

#### Cardiac form

This form is seen during adulthood, and comprises about 30–40% of the chronic cases. Patients may present with arrhythmia, cardiac failure, or thromboembolism. ECG abnormalities include ventricular premature beats, multifocal ventricular tachycardia, atrial and ventricular fibrillation, complete right bundle branch block, anterosuperior fascicular block, ST-T wave changes, varying degrees of atrioventricular block, and ventricular hypertrophy. Cardiomyopathy (referred to as chagasic cardiomyopathy) presents also as heart failure, which may be mild, moderate, or severe.

Management involves the use of conventional antiarrhythmic agents, together with treatment of heart failure. Atrioventricular block may require pacemaker insertion. Defibrillator-cardioverter implantation may help prevent sudden death. In most cases, however, the dominant problem is one of congestive heart failure, which becomes progressively refractory to medical

treatment. Cardiomyoplasty and partial ventriculectomy have not been successful, but the prognosis following cardiac transplantation is as good as in those receiving transplants for other reasons.

#### Digestive form

This form is usually manifest as megaesophagus and megacolon, and occurs in about 10% of the cases, depending on the geographical region under study. It may or may not be associated with the cardiac form. Dysphagia, with swallowing that is often painful, is the most common symptom of megaesophagus, and occurs in 3% of cases. Regurgitation and aspiration may cause pneumonia and death. Conventional barium swallow may show the classic changes of dilated oesophagus with narrowing of the lower segment. Chronic constipation is indicative of megacolon (figure 3), which can be confirmed by contrast studies. Faecal impaction or volvulus of the sigmoid may lead to colon infarction or perforation. Management of the digestive form of the disease is surgical: endoscopic dilatation of the cardia or surgical myotomy of the lower segment of the oesophagus, and colonic resection where necessary.

#### Diagnosis

Diagnosis of the chronic phase of the disease is usually confirmed by the demonstration of IgG antibodies to *T cruzi* in serum,<sup>4</sup> with ELISA, immunofluorescence, or haemagglutination tests. False-positive reactions are often seen (especially in patients with leishmaniasis), but this can be avoided by use of *T cruzi* recombinant proteins, purified mucins, or through western-blot assay for *T cruzi* antigens (TESA-blot). Parasites are not normally

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Figure 2: Carlos Ribeiro Justiniano Chagas 1879–1934

### Chagas' disease

- Caused by infection with *Trypanosoma cruzi*, which is endemic in many parts of Southern and Central America.<sup>5</sup>
- 16–18 million people are affected by chronic disease, and there are 50 000 deaths each year.
- Acute phase apparent in only 3% but characterised by swelling of the eyelids at the inoculation site (Romaña's sign). Congenital transmission also occurs, and is a cause of miscarriage. Transmission by blood transfusion is becoming the leading source of infection in countries where natural vectors are becoming controlled (Argentina, Brazil, Chile, and Uruguay).
- 60–70% have the indeterminate form in which there may be no clinical symptoms or signs, but 2–5% of these convert to clinically significant disease each year.
- Cardiac form is characterised by myocardial fibrosis, arrhythmia, and thromboembolism; chronic congestive failure is the dominant cause of death.
- The digestive form is manifest by degeneration (with lymphocytic infiltration) of the submucosal and myenteric plexuses of the bowel wall, leading to megaesophagus and megacolon.
- Treatment is largely symptomatic: treatment of arrhythmias and heart failure, dilatation of the cardia for megaesophagus, colonic surgery. Chemotherapy is used in certain groups but its efficacy is not clearly established.

identified in the chronic phase disease, although detection is enhanced by PCR.

### Chemotherapy

Medication is not usually administered to chronic-phase patients, even after the confirmation of the diagnosis. Instead, treatment is reserved for those diagnosed in the acute phase, for accidentally infected laboratory staff, and for immunosuppressed individuals (AIDS and transplant recipients) in whom reactivation may occur. Treatment of children and young patients with indeterminate forms or incipient cardiac lesions is currently being assessed. The overall efficacy of chemotherapy (the only commercially available preparations being nitrofurantoin and nitroimidazole) is uncertain because of variations in *T. cruzi* strain susceptibility—itsself dependent on geographical factors—and unreliability of methods to determine parasite eradication. Available preparations are toxic, causing nausea and vomiting, bone marrow hypoplasia, dermatitis, and polyneuritis.

### New developments

#### Genetic characterisation of *T. cruzi*

There are two major phylogenetic lineages of this parasite, one each is highly heterogeneous. The genome of the parasite is now being analysed as a result of a collaborative network launched by the WHO (the *T. cruzi* genome project).

#### Mechanisms of cell infection and intracellular survival

Transialidase is a unique enzyme that transfers sialic acid from host sialylated molecules to mainly mucins on the parasite surface, and this renders the parasite resistant to antibody-mediated lysis in human beings. Hence, transialidases may be important for *T. cruzi* interaction with host cells and extracellular matrix proteins, and are currently under investigation.

### Immunology and immunopathology

*T. cruzi* seems to have co-evolved with its hosts, a fact consistent with host survival in the absence of disease, as manifest in several wild mammalian species. Studies have shown that parasite persistence may have been facilitated by ingestion of *T. cruzi*-induced apoptotic lymphocytes by macrophages, followed by intracellular parasite survival. Furthermore, host reaction is mediated by Th1-related cytokines, activated macrophages, and CD8 T cells, although these mechanisms are poorly defined in human beings. Interestingly, it seems that some of these cellular immune responses are responsible for the immunopathology: the glycolipid anchor fraction of

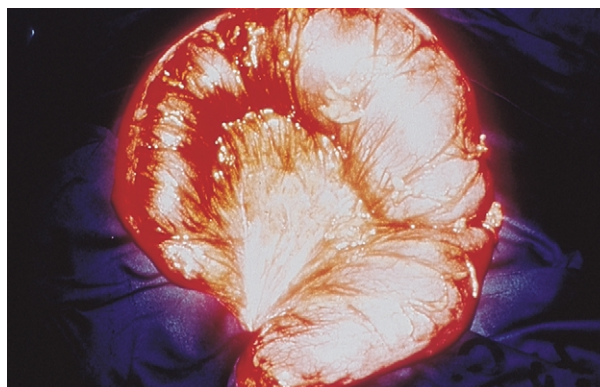


Figure 3: Megacolon caused by degeneration of Auerbach and Meissner plexuses

trypomastigote mucins are one of the most potent microbial proinflammatory molecules.

The occurrence of inflammation in the absence of obvious parasite survival in chronic-phase disease has given rise to the suggestion that autoimmune mechanisms may be involved, especially in the pathogenesis of chronic chagasic cardiomyopathy. However, recent data on the presence of *T. cruzi* DNA in heart biopsy samples by PCR, as well as the presence of *T. cruzi* antigens in T CD8 cells by immunohistochemistry, suggest that parasite persistence is the primary cause of heart damage. Moreover, chronic infection with *T. cruzi* can be particularly severe in those with immunosuppression, in whom parasitism of the central nervous system is common.

There are few studies on the immunopathological mechanisms involved in the denervation which leads to the digestive form of Chagas' disease.

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