A recent study showed a 9000 year record of Chagas Disease (Afderheide et al. 2003)

Studied 283 mummies from the Atacama desert region of Northern Chile and Southern Peru.

<table>
<thead>
<tr>
<th>Culture</th>
<th>Time range</th>
<th>No. tested</th>
<th>Percent positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Chinchorro</td>
<td>7050–3000 BC</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td>Late Chinchorro</td>
<td>3000–1500 BC</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Early Alto Ramírez</td>
<td>1000 BC–0</td>
<td>16</td>
<td>25</td>
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<tr>
<td>Late Alto Ramírez</td>
<td>0–400 AD</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Cabuza</td>
<td>400–1050 AD</td>
<td>27</td>
<td>41</td>
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<tr>
<td>Maitas</td>
<td>1000–1250 AD</td>
<td>25</td>
<td>40</td>
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<tr>
<td>Chiribaya</td>
<td>1050–1250 AD</td>
<td>70</td>
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<td>M8 (upper Chiribaya)</td>
<td>1050–1250 AD</td>
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<td>San Miguel</td>
<td>1250–1350 AD</td>
<td>9</td>
<td>33</td>
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<td>Inca</td>
<td>1450–1550 AD</td>
<td>26</td>
<td>50</td>
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<tr>
<td>Colonial</td>
<td>1550–1850 AD</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>All cultures</td>
<td>7050 BC–1850 AD</td>
<td>283</td>
<td>40.6</td>
</tr>
</tbody>
</table>

DNA was extracted from mummy tissue and PCR performed using primers specific for the conserved regions of the kinetoplast DNA minicircles from *T. cruzi*.

Results: 115 of the 283 mummies were positive = 40.6%. No sex differences or time period differences.

In the 1970’s the *T. cruzi* infection rates in Bolivia, Peru and Venezuela were 15-60%

Possible reasons for the ancient transmission of Chagas Disease:
1. People built wattle and thatch houses until present time.
2. People kept domestic animals in houses.
In 1735 the physician Gomes Ferreira wrote: “the corruption of bicho is nothing else but an enlargement and distention of the rectum.” These descriptions suggest that patients in Brazil suffered from a disease that resulted in megaesophagus and megacolon—now recognized as a signal character of American trypanosomiasis.
Chagas was sent to Northern Brazil to try to stop a malaria epidemic. After he had been there for one year, a railroad engineer told him about blood sucking bugs in the local huts, which were called "barbeiros" or "kissing bugs" due to their behavior of biting sleeping people on the face. Chagas then became interested in seeing if this bug could be transmitting some disease to humans or animals. He examined the hindgut contents of a bloodsucking triatomine bug (*Panstrongylus megistus*), and found numerous flagellates which resembled stages of a trypanosome he has described previously from a marmoset. Chagas sent infected triatomine bugs to the Institute in Rio where they were allowed to bite monkeys and after 30 days large numbers of trypanosomes were found in the peripheral blood. Subsequently, it was found that other animals i.e. rabbits, pigs, dogs and other monkeys, could also be infected.
Kissing bugs

During the colonial and missionary period in Latin America there are descriptions in the writings from Portuguese and Spanish missionaries and historians of the conquistadors that describe attacks by bugs called vinchucas, with biting and blood-sucking habits: "Instead of ordinary bedbugs. . these are bugs bigger and more pernicious to the inhabitants.. they are as big as the tip of a little finger, long brownish and in the shape of beetles. They live in the ceiling of the houses and get out at night guided by the smell of people asleep, and getting down on the beds, bite cruelly, making a big wheal and sucking up to a half a thimble full of blood. While they suck blood they do it with such care and sweetness that it cannot be felt; but when they withdraw full they leave an unbearable pain and itching."

Triatoma infestans
Discovery of trypanosomes in blood of sick people

Though Chagas was convinced he had found the vector of a human disease he did not know what that disease was. In 1909, two or three weeks after finding triatomines and a cat infected with *T. cruzi* he was called to treat a seriously ill 2 year old child named Berenice. She was feverish, had an enlarged spleen, liver and swollen lymph nodes and her blood teemed with trypanosomes similar in morphology to those found in the marmoset. He wrote: "Examination between cover glass and slide revealed the existence of flagellates in good number and fixing and staining of blood films made it possible to characterize the parasite’s morphology and to identify it with *Schizotrypanum cruzi*".

Berenice died in 1975 (aged 69)
---not of Chagas Disease

Isolates cultured from her in 1957 and 1973 indicate that she was infected multiple times

Aged 2 (1908) with Carlos Chagas
Discovery of trypanosomes in heart muscle of sick people

In 1911 Chagas described the dividing forms in heart muscle. The connection between human disease and the blood-sucking bug had been made. In 1912 Chagas found that the armadillo was a reservoir host.

An original micrograph of T. cruzi in human blood

Drawings of the types of cells he found
At 29 years of age, Carlos Chagas had described the agent, the vectors, clinical symptoms in humans and animals, and the existence of a new disease. The species name was given to honor Oswaldo Cruz, who was the Director of the Oswaldo Cruz Institute where Chagas worked.

Unfortunately he made some enemies, including Afrânio Peixoto, a Brazilian scientist interested in eugenics, who disputed Carlos Chagas' clinical and parasitological findings and tried to transfer credit for the discovery of the trypanosome to Oswaldo Cruz. This dispute prevented Chagas from receiving the Nobel Prize in 1921. He also had some enemies in other countries, including Charles Donovan and a German microbiologist named Krause. Krause denounced Chagas' findings and for 20 years his work was forgotten.
Morphology of T. cruzi

Epimastigote

Amastigote

Trypomastigote

Flagellum
Flagellar pocket
Kinetoplast
Nucleus
trypomastigote

epimastigote
Chagas Disease

Chagas Disease is prevalent throughout South and Central America. An estimated 15-20 million people are infected and over 100 million people are at risk. In some endemic areas up to 60% of the population is serologically positive for *T. cruzi*. It was once thought to be an exotic rare disease, but with improved diagnostic methods it is now known to be one of the most widespread infectious diseases in Latin America. In one hospital in Goiania, Brasil, more than 20% of the patients had Chagas Disease. Most cases of sudden death in young adults in parts of Latin America can be attributed to chronic Chagas Disease.
Life Cycle

**Triatome Bug Stages**
1. Triatome bug takes a blood meal (passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)
2. Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
3. Amastigotes multiply by binary fission in cells of infected tissues.
4. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.
5. Triatome bug takes a blood meal (trypanastigotes ingested)
6. Epimastigotes in midgut
7. Multiply in midgut
8. Metacyclic trypomastigotes in hindgut

**Human Stages**

**CDC**

[i] = Infective Stage
[d] = Diagnostic Stage

http://www.dpd.cdc.gov/dpdx
Romana’s Sign

Hepatosplenomegaly
The ACUTE phase of *Trypanosoma cruzi* infection

1. Romaña’s Sign
2. Fever
3. Hepatosplenomegaly
4. Trypomastigotes in Blood
5. Lasts 2–8 weeks
6. 10% Mortality
The INDETERMINATE phase

1. No parasite evident in blood

2. Amastigote nests in muscle tissue

3. Anti-\textit{T. cruzi} IgG present

Normal Heart

Chagasic Heart
Trypanosoma cruzi amastigotes in heart muscle

Amastigotes in a tissue culture cell

Scanning EM of isolated amastigotes
CHRONIC phase of Chagas Disease

1. Nerve Degeneration
2. Cardiomyopathy (80%)
   Heart arrhythmia and blocks
   Heart enlargement (cardiomegaly)
   Apical aneurism
3. Megaesophagus (25%)
4. Megacolon (30%)
Chagas Disease
Right Branch-bundle Block

ECG

Some impulses cross from healthy side

Bundle-branch block
Damage to a branch of the heart’s bundle of conducting fibers impedes the passage of impulses. The rate slows if all of the branches are blocked.

Normal and V6
Cardiomegaly

Apical Aneurysm

Fig. 13.11 — A — Coração de indivíduo falecido com miocardiite chagásica crônica: notar a cardiomegalia. B — Coração de indivíduo normal. (Segundo Jairo Ramos e cols.)
Megaesophagus
Megacolon

Constipation

Negative control

Autopsy
Definitions

ANTHROPONOSIS - disease with humans as only vertebrate hosts

ZOONOSIS - disease transmitted among wild animals (reservoir hosts) and humans

RESERVOIR HOST - wild animal that maintains infection in nature
Distribution of Triatomine vectors

[Map showing distribution of Triatomine vectors]

Chagas Endemic Countries

WHO/CTD, May 1986
Fecal transmission of *T. cruzi*

There are several genera of Reduviidae that can transmit the protozoan. *Triatoma infestans*, as its name suggests, frequently invades homes (mud and stick huts) and is responsible for what is termed the domestic transmission cycle. Other reduviids, such as *Rhodnius prolixus*, reside in rural settings or forests, they are associated with the silvatic cycle of transmission, which includes many wild animals as vertebrate hosts. As mentioned above, the common reduviid vectors *R. prolixus* and *Panstrongylus megistus* defecate during the blood meal, allowing efficient infection by the parasite.
Chagas Disease as a Socio-Economic Disease

Chagas disease is mainly a disease of third world countries with substandard housing with dirt floors, mud walls and thatched roofs, that allows infestation with the reduviid vectors. Prevention involves the destruction of the vectors by spraying insecticides in houses and also by replacement of adobe houses (see below) with modern houses. The best insecticide seems to be BHC (hexochlorocyclohexane), in terms of low cost, low toxicity to humans and animals, and activity in the mud walls of houses. Most other insecticides are rapidly inactivated when sprayed on such walls. The number of applications required vary from twice per year to every month.

Habitat of *T. infestans*
Alternative Methods of Transmission

Rural migrations to urban areas in South and Central America during the 1970s and 1980s changed the traditional epidemiological pattern of Chagas disease: it became an urban disease, as unscreened blood transfusion created a second way of transmission. Between 1960 and 1989, the prevalence of infected blood in blood banks in selected cities of South America ranged from 1.7% in Sao Paulo, Brazil to 53.0% in Santa Cruz, Bolivia, a percentage far higher than that of hepatitis or HIV infection. Transmission by blood transfusion has also become a potential problem in the Los Angeles area due to immigration from Central America where the disease is endemic. In Los Angeles, 2% of the blood donors in a 1993 study were seropositive. Five cases of Chagas in the US in 1990-1993 came from blood transfusion or organ transplants.

Congenital transmission also occurs. 0.5-6.3% of infants born to Chagasic mothers are positive for T. cruzi.
“Sugar Cane Juice Causes Deadly Outbreak of Chagas in Brazil”!

Contaminated sugar cane juice is thought to be the source of a Brazilian outbreak of Chagas disease, a potentially fatal parasitic disease normally transmitted to people by insect bites. In the past few days, health officials in the state of Santa Catarina have recorded 45 cases of patients developing symptoms of Chagas disease after drinking the juice. At least five of the patients died. The patients initially reported having fever, migraine, and muscle pain, with some going on to develop jaundice, abdominal pain, internal bleeding, fluid in the lungs and heart failure. Blood tests confirmed the presence of Trypanosoma cruzi in 31 of the 45 suspected cases.

Ninety per cent of cases had consumed sugar cane juice from the Kiosk #2 along the northern beaches of Santa Catarina. It is estimated that more than 50,000 people (including international travelers) may also have been exposed.
The Southern CONE initiative

PREVALENCE OF HUMAN *Trypanosoma cruzi* INFECTION
1984

PREVALENCE OF HUMAN *Trypanosoma cruzi* INFECTION
1996

Rates x 100

- 0.0 - 1.9
- 2.0 - 3.9
- 4.0 - 6.9
- > 7.0

SOURCE: Country Reports 1986 (Countries in white = No data available)

SOURCE: Country Reports 1996 (Countries in white = No data available)
Diagnosis of Chagas Disease and detection of the parasite

Assay must be:
Specific (No False Positives or crossreactivity, e.g. *T. rangeli*)
Sensitive (Single Cell)

Indirect Assays Detect Antibody
i.e. evidence of past (present?) infection
Direct Assays Detect Parasite
Microscopy – Direct Detection Method

This is generally made directly on blood smears, or following culture in synthetic medium. When the parasite is not abundant, one can concentrate the parasites first by centrifugation; they are found in the "buffy coat" or white cell layer. The real problem is that the parasite is not abundant in the blood during the indeterminate and chronic stages. This method probably can only detect less than 1% of chronic infections.

Another problem is that *Trypanosoma rangeli* looks very much like *T. cruzi* and can lead to misdiagnosis. *T. rangeli* is a trypanosome that is infective for humans and other animals but is nonpathogeneic to humans (but detrimental to the insect!). The chief insect host is *R. prolixus*. The trypomastigotes are discharged in the saliva rather than the feces. It looks morphologically like *T. cruzi* and has an overlapping geographical distribution.
Indirect Immunofluorescence

57% of 87 raccoons in South Georgia were seropositive

Negative control. Stained with Evans blue

Flourescein conjugated anti-racoon Igg Ab’s binding to anti-T. cruzi Ab’s in the serum

From Yabsley et al (1999)
Xenodiagnosis is a method of diagnosis first described in 1877. Laboratory-reared non-infected triatomines are allowed to feed on patients suspected to have Chagas disease. The bugs are then examined 3-4 weeks later for the presence of *T. cruzi* in the hind gut/excreta; *T. rangeli* will be found in the salivary glands. Although this method is quite efficient in diagnosing the acute disease, it may be only 50% efficient in the chronic stage. Whereas 1 µl of blood can be viewed on a microscope slide, 10 bugs can sample 1 ml of blood. The efficiency of this technique is complicated by variable growth of different *T. cruzi* isolates in different genera and species of reduviids.
DNA-based assays (Direct)

There are two major criteria for successful PCR detection of a parasite (or any microorganism):

Specificity -- must detect only the *T. cruzi* parasite

and

Sensitivity -- how few parasites can the assay detect?
How do *T. cruzi* parasites enter the cell?

Metacyclic trypomastigote parasites from the feces of the infected triatomid bug enter the vertebrate host through the bite wound or the mucosal membrane. These invade cells through the formation of a membrane vacuole. This vacuole is disrupted and the trypomastigotes are released and differentiate into amastigotes. The amastigotes go through nine cycles of intracellular replication in 4-5 days, and then differentiate into trypomastigotes. The host cell ruptures and the parasites are released into the bloodstream, where they are disseminated throughout the body.

*T. cruzi* entry into cell

No engulfing pseudopodia
Resistant to Cytochalasin D
Recruitment of lysosomes to the invading parasite

(a) Phase-contrast image of a trypomastigote (arrow) in the process of entering a HeLa cell. (b) Immunofluorescence image of the same cell shown stained with antibodies against the lysosome-specific protein, Lamp-1. (c) The green line represents lysosomal membranes that are gradually incorporated into the vacuole, the small arrows indicate the direction of lysosome movement, and the large arrows indicate the direction of parasite movement.  
(Tardieux et al, 1992)
A secreted protein, TcTOX, which has antigenic relatedness with the lytic complex C9 of the complement system, lyses the vacuole, and the metacyclic trypomastigote enters the cytoplasm where it differentiates into an amastigote and divides.
Evidence for Genetic Exchange in *T. cruzi*

GAUNT ET AL. 2003).

Two clones of *T. cruzi* from the Amazon forest were transfected with plasmids containing either the Neomycin marker or the Hygromycin marker.

These were passaged either singly or together through the life cycle stages. The parasites were recovered and cultured with both drugs and cloned.

Results:

1. 50 tissue cultures infected with the mixture of strains gave populations resistant to both drugs. Six *T. cruzi* clones contained both drug resistance genes. The clones were not binucleate.

2. No double resistant populations were obtained from mixed axenic epimastigote cultures, from mixed passage through triatomids, or from mixed passage in mice.
The Case of Charles Darwin
In his own words:
"We slept in the village, which is a small place, surrounded by gardens, and forms the most southern part, that is cultivated, of the province of Mendoza; it is five leagues south of the capital. At night I experienced an attack (for it deserves no less a name) of the Benchuca (a species of Reduvius) the great black bug of the Pampas. It is most disgusting to feel soft, wingless insects, about an inch long, crawling over one's body. Before sucking, they are quite thin, but afterwards become round and bloated with blood, and in this state are easily crushed. They are also found in the northern parts of Chile and in Peru."

Darwin returned to his ship and even brought back some of these insects and fed them on the sailors.

This insect was the triatomid, *Triatoma infestans*, of which today more than 70% of the insects in that region are infected with *T. cruzi*. Also 12% of the population in Mendoza today has antibodies against *T. cruzi*. 
Darwin was at that time one of the most active members of the Beagle's crew. He often took long overland expeditions and was a mountain climber. He returned to England in 1836 and in 1838 his health suddenly became poor. His health became progressively worse and he suffered from periodic vomiting, fatigue and flatulence. After social dinners he had violent shivering and vomiting attacks, and mainly for these reasons he gave up all social interactions. His diaries are full of descriptions of his mysterious illness.

He wrote to the Botanist, Joseph Hooker, in 1845: "I believe that I have not had a whole day, or rather night, without my stomach being greatly disordered, during these last three years, and most days great prostration of strength." In 1849 he was too ill to attend his father's funeral.

He wrote:
"I was quite broken down, head swimmy, hands trembling and never a week without violent vomiting."
<table>
<thead>
<tr>
<th>Causal type</th>
<th>Specific cause</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>Darwin himself (1831–1882)</td>
<td>and <em>Diary of Health</em></td>
</tr>
<tr>
<td>Nervous indigestion</td>
<td>Obituary (1882)</td>
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<tr>
<td>Chronic from sea</td>
<td>Obituary (1882)</td>
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<tr>
<td>sickness</td>
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<tr>
<td>Chronic neurasthenia</td>
<td>Johnston, 1901</td>
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<tr>
<td>Chronic eye strain</td>
<td>Gould, 1903</td>
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<td>Aftermath of Chilean fever</td>
<td>Leonhard Huxley, 1927, see</td>
<td>Colp7</td>
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<td>Pyorrhoea</td>
<td>Leonard Darwin, 1927, see</td>
<td>Colp7</td>
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<td>Brucellosis</td>
<td>Simpson, 1958</td>
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<td>Chagas’ disease</td>
<td>Adler, 1959</td>
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<td>Metabolic disease</td>
<td>Stetten, 1959</td>
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<td>Acute intermittent porphyria</td>
<td>With, 1960, see</td>
<td>King-Hele11</td>
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<td>Diaphragmatic hernia</td>
<td>Kohn, 1963</td>
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<td>Narcolepsy (diabetes)</td>
<td>Roberts, 1966</td>
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<td>Arsenic poisoning</td>
<td>Winslow, 1971</td>
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<td>Pigeon allergy</td>
<td>Gruber and Barrett, 1974, see</td>
<td>Colp7</td>
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<td>Peptic ulcer</td>
<td>See Colp p130</td>
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<td>Duodenal ulcer</td>
<td>See Colp p130</td>
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<td>Appendicitis</td>
<td>see Colp p130</td>
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<td>Smouldering hepatitis</td>
<td>See Colp p130</td>
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<td>Cholecystitis</td>
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<td>Amoeba infection</td>
<td>See Colp7</td>
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<tr>
<td>Allergy</td>
<td>Smith, 1990, 1992</td>
<td>Campbell and Matthews, 17-18</td>
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<td>Systemic lactose</td>
<td>Campbell and Matthews, 17-18</td>
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<td>intolerance</td>
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<td>1st psychoanalytical theory</td>
<td>Kernf, 1918\textsuperscript{19}</td>
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<td>Hypochondria</td>
<td>Hubble, 1943\textsuperscript{20}</td>
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<td>Hubble, 1943\textsuperscript{20}</td>
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<td>Chronic depression</td>
<td>Alvarez, 1959\textsuperscript{21}</td>
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<td>Woodruff, 1965\textsuperscript{22}</td>
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<td>Bereavement syndrome</td>
<td>Bolby, 1965, 1990\textsuperscript{23, 24}</td>
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<td>Neurosis</td>
<td>Colp, 1977\textsuperscript{7}</td>
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<td>Mixed psychosomatic</td>
<td>Colp, 1977\textsuperscript{7}</td>
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<td>Anxiety state</td>
<td>Bernstein, 1982\textsuperscript{25}</td>
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<tr>
<td>Panic syndrome</td>
<td>Barloon and Noyes, 1997\textsuperscript{26}</td>
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</table>
A recent suggestion is lactose intolerance (Campbell and Matthews, 2005).

Darwin wrote that: “The sickness starts usually about two hours after a meal.” His wife, Emma, had a cookbook that confirmed his love of sugar and rich foods.

Table 2: Systemic lactose intolerance compared with Darwin’s disease

<table>
<thead>
<tr>
<th>Symptoms of systemic lactose intolerance</th>
<th>% People with lactose intolerance who have this symptom*</th>
<th>Darwin’s description of his symptoms</th>
<th>Occurrence of Darwin’s symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut symptoms (pain, bloating, diarrhoea)</td>
<td>100</td>
<td>Stomach ache</td>
<td>Common</td>
</tr>
<tr>
<td>Flatulence</td>
<td>100</td>
<td>Flatulence (belching)</td>
<td>Very common</td>
</tr>
<tr>
<td>Headache</td>
<td>86</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>Light headedness and loss of concentration</td>
<td>82</td>
<td>Swimming head and difficulty to concentrate</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>78</td>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Muscle and joint pain</td>
<td>71</td>
<td>Rheumatic pain</td>
<td>Often</td>
</tr>
<tr>
<td>Tiredness and chronic fatigue</td>
<td>63</td>
<td>Chronic fatigue and exhaustion</td>
<td>Very common</td>
</tr>
<tr>
<td>Allergy (eczema, hay fever, rhinitis, sinusitis)</td>
<td>40</td>
<td>Skin rash and boils</td>
<td>Often</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>30</td>
<td>Mouth sores</td>
<td>Common</td>
</tr>
<tr>
<td>Heart palpitations</td>
<td>24</td>
<td>Palpitations in the chest</td>
<td>Common</td>
</tr>
<tr>
<td>Depression</td>
<td>Common, but not quantified</td>
<td>Depression</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

*Represents proportion of people diagnosed as lactose intolerant who have this particular symptom within 48 hours of taking lactose. Darwin’s occurrence is based on his notes and letters during periods of the episodes. The systemic symptoms of lactose intolerance are described previously.
Or - Did Darwin have Chagas Disease stemming from his stay in Mendoza during the Beagle voyage?

He died in 1882 from an apparent heart attack.
Darwin is buried in Westminster Abbey - just next to Isaac Newton

PCR could perhaps distinguish between Chagas Disease and a C to T mutation in the lactase gene