The Kinetoplastids
Leishmania spp.
Trypanosoma spp.

Carlos Chagas observed infectious stages of T. cruzi & isolated it from many species of mammals. He named it after his teacher & friend Oswaldo Cruz.

Both Chagas & Cruzi are on Brazilian money.
Terms from the documentary-Chagas

Bolivia: country in central South America; bordered by Brazil, Paraguay, Argentina, Chile & Peru.
Bolivia GDP per capita: $4,800 (2011)

Vinchuca = triatomine or “kissing bugs” = T. cruzi vector
Vector: insect/other living carrier that transmits infectious agent

Benznidazole & nifurtamox: drugs given to treat T. cruzi infection, these are not always effective or without side effects.

Protease inhibitor: proteases are enzymes that break down proteins; an inhibitor would prevent this function, which is essential.

Kill or Cure:
Chagas
Season 2 Episode 1

16 million people in South America carry the parasite that causes Chagas Disease - a parasite that will kill a quarter of them in middle age. The parasite is transmitted by the so-called kissing bug - in Bolivia they call it Vinchuca - which bites at night, sucking blood while its victims sleep. We travel from the mountain villages of Bolivia to the laboratories of San Francisco in search of a safe, effective cure.

http://www.rockhopper.tv/programmes/27/
Kinetoplastid Morphological Forms:

American trypanosome = *Trypanosoma cruzi*

Epimastigote: replicative form in insect

*metacyclic trypomastigote*: shed by bug in feces, infects mammal.
*some amastigotes in mammal become trypomastigotes → infectious for kissing bugs.*

*amastigote* (mammal, intracellular, no flagellum)

- **epimastigote**
- **insect**
- **trypomastigote**
- **metacyclic trypomastigote**
- **mammal**
- **amastigote** in macrophages
- **mammal**

---

**Trypanosoma cruzi**

- found through Central & South America
- occasionally southwestern portion of US
- intracellular parasite for majority of its life cycle
  - infects macrophages and muscle cells
- infects all mammal species native to South & Central America
- vector borne: kissing bugs are only insect vectors
- chronic infection → life-threatening diseases of **hollow organs**
- world’s leading cause of **cardiomyopathy**

**Hollow organ**: visceral organ that is a hollow tube or pouch (stomach or intestine) or that includes a cavity (heart or bladder).

**Cardiomyopathy**: structural or functional disease of heart muscle.
Marked by hypertrophy, enlargement of the heart, loss of heart wall flexibility, or narrowing of ventricles. Not due to a developmental defect, atherosclerosis, or to hypertension.
Trypanosoma cruzi

~5% acute phase disease fatality rate (highest in children) transmitted by
  kissing bug feces
  blood transfusion
  bone marrow transplant
  organ transplant
  mother can infect fetus across placenta

outbreak in Brazil linked to sugar cane extract (popular drink)
  extract contaminated with “extract of kissing bug”
  30 people infected $\rightarrow$ high mortality rate
  first reported case of oral infection route

important reservoir hosts: rats, dogs, sloths, bats & non-human primates

---

Trypanosoma cruzi - Life Cycle

reduviid bugs: triatomid or kissing bugs
  large, robust insects, feed on blood at night
  bites sleeping victim near mouth or eyes
  bite is painless (“kissing” bug)
  ingests a large quantity of blood
  to make room for new meal, it defecates last meal next to bite
  salivary secretions of the bug induce itching
  metacyclic trypomastigote stage in feces of infected bug
**Trypanosoma cruzi - Life Cycle**

transmission – metacyclic trypomastigotes rubbed into mucous membrane (eye)
bite wound

*infection can occur without direct contact with vector*

thatched roof houses harbor large numbers of bugs
feces fall on people while they are sleeping
infection by rubbing parasites into eye or mouth

![Thatched roof hut](image)

![Eye infection (Romana's sign)](image)

---

**Trypanosoma cruzi - Life Cycle**

- triatomids infected feeding on blood from infected person
- trypomastigotes migrate to the midgut of insect
- transform into *epimastigotes* →
  - 1,000s organisms are produced in 1 insect (without effect)
  - remain infected for life (1-2 years)
  - *epimastigotes* maintain place in insect gut
    - parasite surface glycoproteins
    - lectins on insect gut cells
- *epimastigotes* transform into *metacyclic trypomastigotes*
  - migrate to hindgut
  - excreted with feces

![Triatomids](image)
Trypanosoma cruzi - Pathogenesis

Trypomastigotes invade a variety of cells in parasitophorous vacuole escape mechanisms aid survival neutralize pH (escape lysosomal protein exposure)
parasite proteins aid survival in host cell inhibition of lysosomal cysteine proteases degradation of lysosomal enzymes penetrates into host cell cytosol differentiate to amastigotes \( \rightarrow \) several division cycles some parasites transform back into trypomastigotes

infected cells die & released parasites are distributed throughout body via bloodstream
infection causes partial immunosuppression
aids parasite in remaining in host for longer time
complement regulatory protein binds C3b & C4b
(inhibits alternate pathway of complement activation)
host protection can develop
infected individuals remain so for life (no sterilizing immunity)
Chagas disease appears in all hollow organisms
parasites infect many cell types (CNS, heart, myenteric plexus, urogenital tract & reticuloendothelial system)

**Myenteric plexus:** a neural network that regulates gut motility.

---

Myenteric plexus damage: (reduced innervation of GI track)
loss of muscle tone & organ enlargement
mega-esophagus & mega-colon
Heart damage (apparent early in infection)
erosion of heart tissue
aneurism & heart failure
Auto-antibodies in Chagas disease
not sole cause of cardiomyopathy (viable *T. cruzi* in heart)
disease progression
*rapid* when parasites are *abundant*
*slower* when parasites are *harder to find*

**Aneurism:** A dilation or rupture of the coats of an artery.
Chagas’ Disease - Chronic Stage:
• 10-40 years after infection
• 20-30% of infected people develop serious symptoms
• Enlarged heart
• Enlarged esophagus or bowel

Normal heart  Chagas’ heart

Normal intestine  Chagas’ intestine

Darwin & The Voyage of the Beagle

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 Banchua (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 & Chagas Disease

Darwin may have suffered from chronic Chagas disease
*In Voyage of the Beagle* he wrote of waking covered with “well-fed” bugs

Today >70% of triatomids in region are infected with *T. cruzi*
Darwin brought back some triatomids (fed them on sailors)
Darwin was active hiker & mountain climber during expedition
1836 - he returned to England
1838 - his health became poor (vomiting, flatulence & fatigue)
1845 – his diaries describe his mysterious illness: I believe that I have not had a whole day, or rather night without my stomach being greatly disordered during these last three years & most days great prostration of strength.

Darwin may have contracted Chagas disease on the voyage
~5 year latency before chronic disease
his symptoms are symptoms of Chagas Disease
death attributed to heart disease (*angina pectoris*)
Cellular & Molecular Pathogenesis

**Acute stage:**
- incubation period: 4-12 days post infection
- often asymptomatic
- generalized symptoms (*commonly mis-diagnosed*)
- **chagoma** develops at bite site in 2-4 days
  - adjacent area is **erythematous** & firm to touch
  - chagoma disappears → skin depigmentation

infection by rubbing into eye (*through mucous membranes*)
- **Romana’s sign**: unilateral chagoma swelling
  - swollen eyelid is firm to touch
  - may be associated conjunctivitis

**Erythematous**: redness of the skin produced by congestion of the capillaries, which may result from a variety of causes

---

**Cellular & Molecular Pathogenesis**

- **AIDS patients**: *if untreated, will die from overwhelming infection*
  - Patients with chronic *T. cruzi* infection who acquire HIV can experience a reactivation resembling acute phase of disease.
  - **Treatment**: nifurtimox & benznidazole
    - associated with high toxicity & incomplete cure rates

  - cardiomyopathy & heart transplantation: *cyclosporine use* (*immunosuppresses to prevent transplant rejection*) *T. cruzi reproduces in uncontrolled fashion* → *patient death in most cases*
  - **Control**: ~15 million cases in Central & South America
    - vector control by **insecticides**
    - screening blood used for transfusion
      - this route of infection is increasing
      - occurs in countries where disease is not vector-borne