American Trypanosomiasis History

- *Trypanosoma cruzi* - Chagas disease
- Species name was given in honor of Oswaldo Cruz - mentor of C. Chagas
- By 29, Chagas described the agent, vector, clinical symptoms - new disease

- 16-18 million infected
- 120 million at risk
- ~50,000 deaths annually
- leading cause of cardiac disease in South and Central America
**Trypanosoma cruzi**

- Intracellular parasite
- Trypomastigotes have ability to invade tissues - non-dividing form
- Once inside tissues convert to amastigotes - dividing forms
- Ability to infect and replicate in most nucleated cell types

**Cell Invasion**

- Trypomastigotes induce a Ca\(^{2+}\) signaling event
- Ca\(^{2+}\) dependent recruitment and fusion of lysosomes
- Differentiation is initiated in the low pH environment, but completed in the cytoplasm

Transient residence in the acidic lysosomal compartment is essential: triggers differentiation into amastigote forms
**Trypanosoma cruzi life cycle**

**Triatomine Bug Stages**
- Trypanosome takes a blood meal
- Metacyclic trypomastigotes infect various cells of the host
- Tissue stages
- Bloodstream stages

**Human Stages**
- Metacyclic trypomastigotes penetrate various cells at bite wound sites
- Inside cells, they transform into amastigotes
- Amastigotes multiply by binary fission in cells of infected tissues
- Trypanosomes can infect other cells and transform into extracellular amastigotes in new infection sites
- Clinical manifestations can result from the infectious cycle
- Transsudate amastigotes transform into trypanosomes, then burst out of the cell and enter the bloodstream.

**Triatomid Vectors**
- >100 species can transmit Chagas disease
- 3 primary vectors
  - *Triatoma dimidiata* (central Am.)
  - *Rhodnius prolixis* (Colombia and Venezuela)
  - *Triatoma infestans* (*‘southern cone’ countries*)

**Common Names**
- triatomine bugs
- reduviid bugs
- assassin bugs
- kissing bugs
- conenose bugs

*One happy triatomid!*
Vector Distribution

- 4 principal vectors
- 10-35% of vectors are infected
- Parasites have been detected in *T. sanguisuga*
- Enzootic - in animal populations at all times
- Many animal reservoirs
  - Domestic animals
  - Opossums
  - Raccoons
  - Armadillos
  - Wood rats

Factors in Human Transmission

- Early defication - during the triatome bloodmeal
- Colonization of human habitats
  - Adobe walls
  - Thatched roofs
- Proximity to animal reservoirs
Modes of Transmission

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td>Vector</td>
<td>Natural transmission by triatome bugs through contamination with infected feces.</td>
</tr>
<tr>
<td>Transfusion</td>
<td>A prevalent mode of transmission in urban areas. Gentian violet treatment (24 hr) eliminates parasites in blood.</td>
</tr>
<tr>
<td>Congenital</td>
<td>Occurs during any stage of T. cruzi infection. Can result in premature labor, abortion neonatal death.</td>
</tr>
<tr>
<td>Accidental</td>
<td>Ingestion of food contaminated with metacyclic trypomastigotes. Laboratory accidents.</td>
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Trypanosoma cruzi in the US

- triatome bugs found in U.S.
- parasite common in wild animals
- 5 confirmed cases - natural transmission
- why limited transmission?
  - late defecators
  - zoophillic vectors
  - better houses

[Map of the United States showing distribution of T. cruzi]
RIPA test for antibody to *T. cruzi*

Chagas' Biovigilance Network

Chagas' Biovigilance: RIPA Positive Map  2007-today
Clinical course of Chagas

• **Acute Phase**
  active infection
  1-4 months duration
  most are asymptomatic (children more symptomatic)

• **Indeterminate Phase**
  10-30 years of latency!
  relatively asymptomatic with no detectable parasitemia
  Seropositive - low number of circulating parasites

• **Chronic Phase**
  10-30% of infected exhibit cardiomyopathy or megasymphomases

**Acute phase**

• 1-2 week incubation period
• local inflammation
  • Romaña’s sign
  • chagoma
• symptoms can include: fever, malaise, lymphadenopathy, hepatosplenomegaly, nausea, diarrhea

• acute, often fatal, myocarditis develops in a few individuals
• high parasitemias in myofibrils
Chronic Inflammation

- long latency characterized by seropositivity and no parasitemia
- higher prevalence of ECG abnormalities in asymptomatic seropositive persons
- progressive development of abnormalities
  - right bundle branch block
  - left anterior hemiblock
- clinical presentations include:
  - arrhythmias and conduction defects
  - congestive heart failure
  - Apical aneurysm (left ventricle)

Cumulative effects of small but chronic amounts of parasites in body for decades

Chronic conditions

- Megaviscera
  - prevalence varies by geographical zones
  - Chili, central Brazil
  - colon and esophagus most frequently affected
  - megaesophagus
    - painful swallowing
    - regurgitation
  - megacolon
    - severe constipation
Megacolon

Basis of Pathogenesis

- Still unknown, hotly debated - several hypotheses
  - **Autoimmunity** (indirect effects)
    - Low parasite numbers
    - Delayed onset with tissue specificity
    - Auto-self antibodies detected
    - Immunosuppression exacerbates infection!
  - **Alteration of immune response**
    - Switching of Th1 to Th2 correlates with disease
  - **Chagasic factor or toxin** (none identified yet)
    - Irreversible damage to parasympathetic neurons
  - **Parasite mediated destruction**
    - Correlation between parasites and inflammation, but low levels of detectable parasites
Diagnosis

- Standard methods
  - Parasite detection (Acute)
    - Stained blood smears
    - *In vitro* culture
    - Inoculation in mice
    - PCR
  - Serological
    - Immunofluorescence
    - Hemagglutination
    - ELISA

- Xenodiagnosis
  - Laboratory reared insects
  - Feed on patient
  - 10-30 days - examine insect gut contents

Treatment for kinetoplastid diseases

- Chagas
  - Acute
    - Nifurtimox
      - 60-90 days
      - Mode of action (?) ROS - then DNA damage
    - Benznidazole
      - 30-120 days
      - Mode of action - thought to inhibit nucleic acid synthesis (ROS?)
  - Chronic
    - Virtually untreatable - just treat symptoms
# Treatments for Chagas

<table>
<thead>
<tr>
<th>Stage</th>
<th>1985</th>
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<td>Pre-clinical stage</td>
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<td>Antifungal triazoles</td>
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<td>Cruzipain inhibitor</td>
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</table>

**What is happening in invasion?**

- The invasion mechanism is distinct from phagocytosis
- Large particle phagocytosis
**T. cruzi invasion- non phagocytic**

Phagocytosis  
Active invasion  

Yeast  
*Trypanosoma cruzi*  

Actin filaments - phalloidin staining  

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Lamp-1  
major marker  
for lysosomes  

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Extracellular parasite  
Lysosomes  

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Insensitive to actin disrupting drugs, but **Sensitive to microtubule disrupting drugs**, 

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**T. cruzi invasion summary**

Parasite agonist  

IP3 - mediator for release of Ca2+ from intracellular stores  

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Signaling Process involved in this unique invasion  

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Sensitive to microtubule disrupting drugs, and insensitive to actin disrupting drugs.