Ancient, Exotic, Endemic, Deadly
My Experience with Chagas Disease

Simon Bolivar Visiting Professor, National University, Caracas, Venezuela 1970
Additional Experience

Progress in Cardiovascular Diseases
1970

Uncommon Causes of Heart Failure
(With a Section on Chagas Disease)

Joseph K. Perloff, Keith M. Lindgren
and Bertron M. Groves
Osler called syphilis the great imitator because the signs and symptoms were similar to so many other diseases.

Another Great Imitator:

South American Trypanasomiasis, *(Trypanosoma Cruzi).*
How Ancient is Ancient?

Chagas disease began millions of years ago as an enzootic (non-human) disease of wild animals.
DNA evidence of *Trypanosoma Cruzi* has been found in 4000 year old South American mummies.
Caused by a *hemoflagelate* that enters the bloodstream after a bite of the *reduvid sandfly*.
Chagas disease is endemic in Mexico, Central and South America. Annual death toll is 50,000. 18 million are already infected, and 100 million--25% of the population--are at risk of acquiring the infection.
Types of Trypanosomiasis:

African Trypanosomiasis
Sleeping Sickness

American Trypanosomiasis
Chagas Disease
African Trypanosomiasis

Caused by the parasite *Trypanosoma brucei* that enters the bloodstream after a bite by the Tsetse fly.
American Trypanasomiasis
Chagas Disease
Animal-to-human and human-to-human transmission by a blood sucking reduvid bug---the phlebotomine sandfly.
Upper left--circulating flagellates.
Upper right--pseudocysts light blue
Lower left--myocardial fibrosis.
Lower right--dilated cardiomyopathy.
Who Was Chagas?
Was 29 years old when he described the parasite in the bloodstream, the cycle of the vector in the digestive tract, cultivation in agar-blood, and transmission to vertebrates by the bite of the infected reduvid sandfly.

In 1911, Oswaldo Cruz announced Chagas’ discovery at the National Academy of Medicine in Rio de Janeiro. In 1922, Chagas was awarded the Pasteur Prize.
Chagas was born on a Brazilian coffee farm in July 1879. His father died when the boy was four years old. An uncle urged young Carlos to study medicine. In 1908, while investigating malaria in the Amazon, Carlos learned of the existence of “kissing bugs,” so-called because of their habit of biting (kissing) sleeping human beings on the face. In 1909, Chagas described the case of a nine month old infant with the kissing bug disease.
Who Was Cruz?

The mentor of Carlos Chagas

Oswaldo Goncalves Cruz’s great work was the eradication of malaria and yellow fever in Rio de Janeiro.
At age 15, Cruz began his studies at the Rio de Janeiro Faculty of Medicine, and in 1892 he graduated. Inspired by Louis Pasteur, Cruz wrote a thesis on water as a vehicle for the propagation of microbes.
A Paradigm of Scientific Deduction

Chagas proposed that the kissing bug---a sandfly---transmitted a parasite to human beings and to other vertebrates. He recovered flagellates in the hindgut of the bug and in the bloodstream of domestic animals, and soon announced “a new species different from any other species of the same genus.”

The parasite was first named *Schyzotrypanum Cruzi* in honor of Oswaldo Cruz, and was later renamed *Trypanasoma Cruzi*. 
The Parasite

The Vector

1. *Rhodnius Prolixus*
2. *Panstrongylus megistus*
Transmission of Chagas Disease

The insect is found in palm fronds of roofs and in cracks of the mud or adobe walls of thatched houses of the poor.
Congenital Chagas Disease
An infected mother passes the disease onto her baby either by placental transmission (chronic placentitis) or at delivery or from breast milk.
Chagasic Fetal Hydrops
Intrauterine Heart Failure Detected by Ultrasound.
Additional Forms of Transmission

Blood transfusion

Organ transplantation
Chagas Disease is an opportunistic infection among patients with HIV and other types of immunosuppression.
The Kissing Bug Kissing
Bed Net
Simple, effective, cheap, but not cheap enough for the poor.
During the nocturnal bite, the infected bug deposits feces laden with parasites. Transmission is enhanced when the skin is scratched at the bite site.
Charles Darwin is believed to have contracted Chagas disease during his 1833 South American expedition.
Genetics

Within the clinical spectrum of Chagas Disease, the role of parasitic genetic variability is emerging. *T. Cruzi* is now divided into two divergent subgroups isolated from human beings, from insect vectors, and from sylvatic (wild) mammals. The two lineages diverged 37 to 88 million years ago. It has been hypothesized that lineage two is indigenous to South America, while lineage one was introduced more recently with North American placental mammals.
Symptomatic Chagas in Newborns and Young Children

Chagoma—reddish area at bite site.

Rash

Romana’s sign---Unilateral periorbital edema.

High fever

Inappropriate (disproportionate) tachycardia.

Myocarditis/pericarditis

Meningoencephalitis

Hepatomegaly

Lymphadenopathy
CHAGAS DISEASE
Chagoma

Bite Site

(Courtesy of Dr. R. Pinckney, U. of Wisconsin)
Chagasic Rash
Romana’s Sign

Painless unilateral periorbital edema
Laboratory Tests

*Complement fixation* —1913

*Xenodiagnosis* (1914) exposure of an infected individual or tissue to a clean vector (laboratory -bred mosquito or tick).

*Sero-diagnosis* ---1970. Detection of antibodies against the parasite. Of limited value in diagnosing the acute phase.
Life Cycle

Triatomine Bug Stages

1. Triatomine 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.

5. Triatomine bug takes a blood meal (trypanomastigotes ingested)

6. Epimastigotes in midgut

7. Multiply in midgut

8. Metacyclic trypomastigotes in hindgut

Human Stages

1. Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.

2. Amastigotes multiply by binary fission in cells of infected tissues.

3. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell.

4. Triatomine bug takes a blood meal (trypanomastigotes ingested)

5. Epimastigotes in midgut

6. Multiply in midgut

7. Metacyclic trypomastigotes in hindgut

8. Triatomine bug takes a blood meal (passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)
When host cells rupture, flagellated parasites are released into the lymphatics and bloodstream through which they spread to distant sites and invade new host cells. The process continues for the life of the host.
Acute to Chronic Disease

**Acute Phase** -- Most acute cases escape medical attention because symptoms are non-specific (fever, malaise, vague signs of infection). Flagelates vanish from the blood stream as symptoms disappear.

**Latent Period** --- As long as 20 years.

**Cardiac Involvement** --- Conduction defects (RBBB/left anterior hemiblock, sudden death (complete heart block, ventricular tachyarrhythmias), cardiomyopathy, heart failure, unique LV apical aneurysm, mural thrombus.

**Involvement of Hollow Viscera** --- Esophagus, stomach, colon.
Despite a century of research, the pathogenesis of chronic Chagas cardiomyopathy remains incompletely understood.
Pathogenetic Mechanisms of Chagas Heart Disease

1) Cardiac dysautonomia
2) Microvascular involvement
3) Parasite-dependent myocardial damage
4) Immune mediated myocardial injury
Dysautonomia
Disease or malfunction of the autonomic nervous system

In 1922, Carlos Chagas and Eurico Vilella reported a blunted chronotropic response to atropine. Cardiac neuronal damage was described in 1949.

Oria and Ramos. Arq Bras Cardiol.
The Autonomic Nervous System.

Parasympathetic Denervation

Major neuronal damage of the heart with parasympathetic denervation confirmed morphologically. Abnormal cardiac reflexes (Valsalva maneuver). Denervation of the sinus node with lack of parasympathetic inhibitory action, and lack of vagally mediated response to changes in blood pressure and venous return.
Neuronal Depopulation With Degenerative Changes

Atrial Ganglia
Parasympathetic Denervation

**Heart**—Abnormal cardiac reflexes. Sinus node denervation. Neuronal damage at necropsy.

**Urethra/Bladder**—Abnormal function

**Iris**—Exaggerated pupillary responses
Parasympathetic Denervation of the Iris
Is There Parasite-dependent Myocardial Damage?

Myocardial lesions are usually devoid of parasites.
Poor correlation between the level of parasitemia and disease severity.
Seropositivity for T cruzi antigens is far more frequent than the incidence of cardiac involvement.
Immune Mediated Myocardial Injury

Chronic Chagas heart disease has the hallmarks of delayed hypersensitivity reaction, namely, mononuclear inflammatory infiltrates with immunoglobulin and complement deposition in myocardial tissue.

Eosinophilia
Acute Chagasic Myocarditis

Tissue parasitism elicits a strong cellular and humeral immune response against *T. cruzi* but does not eliminate the parasite.
Chronic Chagasic Cardiomyopathy
Left ventricular Apical Aneurysm.
Left Ventricular Apical Aneurysm
Twenty year old Argentine male with asymptomatic bifascicular block.
Color Doppler M-mode velocity propagation of LV inflow tract (vertical arrow). Diminished slope of color edge in early diastole (white line) represents lower blood flow velocity toward the aneurysmal apex.
Thromboembolism

Thrombus
Electrocardiographic Abnormalities

- Sinus bradycardia
- Atrioventricular block
- Right bundle branch block
- Left anterior fascicular block
- Bifascicular block
- Complete heart block
- Multiform PVC’s
- Abnormal ST-T segments
- Abnormal T waves
- Abnormal Q waves
Sudden Cardiac Death

Third degree heart block

Ventricular tachycardia/fibrillation
SAECG With Late Potentials
AV Conduction Defects
Right Bundle Branch Block
Bifascicular Block

Apical Aneurysm
Hollow Organ Involvement

Gastrointestinal symptoms with chronic *T. cruzi* infection result from denervation of hollow viscera, especially esophagus and colon, rarely stomach, bladder and ureter.
Megacolon
Mega Esophagus
Acute Chagasic pancreatitis results from local parasitism. Necrosis is caused by release of pancreatic enzymes from ruptured parasitized cells and pseudocysts.
Treatment of American Trypanosomiasis

There is no preventive vaccine. Anti-trypanosomal medications achieve only a 50% rate of parasitologic cure even in the early acute stage, and are accompanied by significant toxicity. Chronic stage---No effective treatment.
Heart Transplantation

Transplantation is problematic for chronic Chagas heart disease.
Heart transplantation in patients with Chagas' cardiomyopathy is accompanied by high rates of acute reactivation. A new acute phase is experienced, with fever, skin lesions, and myocarditis. Trypanosoma cruzi can be recovered in myocardial biopsies and in skin lesions.
Marta Del Carmen Sandoval (391-28-13)

The pathology report (read by Dr. Fishbein) from 2/7/2009 (labeled "MEDIASTINAL HEM") is the explanted heart which shows intracellular parasites and amastigotes. There is also diffuse myocarditis with eosinophils.
In December 2005, a 64 year old man with idiopathic cardiomyopathy underwent heart transplantation. In January 2006, he was treated with enhanced immunosuppression for organ rejection. In February, he was admitted to hospital with anorexia and fever. A peripheral blood smear revealed T Cruzi. Blood cultures were positive, and endomyocardial biopsy contained the parasite.
National Reference Centers for the Chagas Disease

The Chagas Disease Laboratory of Argentina serves as a National Reference Center.

Health Ministry initiatives have been established in Brazil, Bolivia, Chile, Paraguay and Uruguay.
Summary

Ancient, Exotic, Endemic, Deadly

Chagas disease began millions of years ago as an disease of wild animals. DNA evidence of Trypanosoma cruzi has been found in 4000 year old South American mummies. In 1909, Carlos Chagas of Brazil described the clinical picture of a new disease and identified the causative agent as a blood-sucking triatomine reduvid parasite.
Chagas disease is the commonest cause of heart failure and sudden cardiac death in Mexico, Central and South America.
What Next? Where Next?

Never make predictions, especially about the future,

BUT

Latin American immigration to the United States is likely to spread this ancient, exotic and deadly disease.
Emergence of Chagas disease in the United States and Canada

Transfusion-Associated Chagas' Disease in the United States.

Increasing Chagas seroprevalence among blood donors in Los Angeles County.