A Century After Chagas Disease Discovery, Hurdles to Tackling the Infection Remain

Rebecca Voelker

EARLY IN THE 20TH CENTURY, THE State of Minas Gerais in southeastern Brazil was rife with malaria. So severe was the epidemic that it sickened hundreds of railroad workers, threatening government efforts to expand Brazil's railway system from the mouth of the Amazon River south to Rio de Janeiro. The government needed a malaria mastermind, someone who could halt the spread of disease and help railway construction resume.

Government officials contacted Oswaldo Cruz, MD, Brazil's famed infectious disease fighter and director of the Manguinhos Institute (now the Oswaldo Cruz Institute), a vaccine and sera production center in Rio de Janeiro. Cruz sent a young researcher from the institute, Carlos Chagas, MD. By age 28 years, Chagas already had 2 successful antimalaria campaigns under his belt, and he prevailed once again in Minas Gerais. But it was not his fight against malaria that eventually placed his name in the history books of infectious disease, epidemiology, and tropical medicine.

One hundred years ago, in the spring of 1909, Chagas reported on one of the most remarkable feats in public health and tropical medicine of the 20th century. In Minas Gerais, he came across nocturnal blood-sucking triatomine insects, also known as kissing bugs, that bite human victims on the face near the lips and eyes. Chagas wanted to know more about the bugs' biology and whether they were capable of transmitting disease. He suspected that triatomines might be associated with unexplained cardiac abnormalities he found in many railroad workers, regardless of their malaria status.

NEW SPECIES

Chagas examined the bugs and found they harbored a new species of trypanosome that, when transmitted in the laboratory to monkeys and other small animals, could be fatal. He named the protozoan parasite *Trypanosoma cruzi* for Cruz, his boss and mentor. In the small Minas Gerais town of Lassance, where he had examined malaria patients in a boxcar, Chagas found an ill cat that was infected with *T cruzi*. In the same household was a young girl with a high (40°C) fever and additional symptoms—an enlarged spleen, liver, and lymph nodes, as well as facial swelling. A blood sample from the girl revealed the presence of *T cruzi*.

By combining his knowledge of insect-transmitted malaria with a high level of clinical suspicion and shoe-leather epidemiology, Chagas made a unique discovery. In a span of just 2 years, he linked triatomines with a new species of parasite that caused acute and chronic infectious illness. Miguel Couto, MD, one of Chagas' teachers who became president of the Brazilian Academy of Medicine, named the disease for his former student.

"[Chagas] is the only researcher to describe solely a new infectious disease, its pathogen, its vector, and its host, as well as the clinical manifestations and epidemiology," said Howard Markel, MD, PhD, the George E. Wanz distinguished professor of the history of medicine at the University of Michigan, Ann Arbor. "That's quite remarkable." Even with today's more sophisticated research tools and scientific know-how, Chagas' achievement from a century ago has never been repeated by any single researcher.

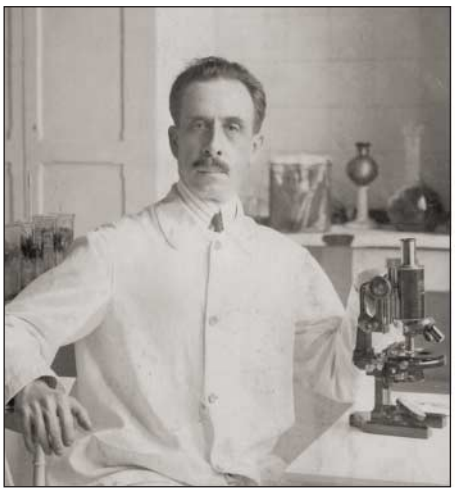

Photo credit: Casa De Oswaldo Cruz/Fiocruz

2009 marks the centennial of the discovery of Chagas disease, named for Carlos Chagas, MD (left), a Brazilian physician who linked clinical symptoms, an insect vector, and an infectious parasite to the syndrome. Triatomine bugs (right), also called kissing bugs because they bite near the lips and eyes, carry the parasite that causes Chagas disease.

"He's a hero to almost every Latin American scientist working in this [field]," said Caryn Bern, MD, MPH, a medical epidemiologist with the Centers for Disease Control and Prevention (CDC) in Atlanta, who investigates Chagas disease and leishmaniasis.

A CENTURY LATER

A parasitic disease is hardly a cause for celebration, but this year's centennial of Chagas's accomplishments is being observed with events in Brazil and elsewhere. In July, hundreds of international scientists gathered in Rio de Janiero for a symposium sponsored by the Oswaldo Cruz Foundation to discuss the historical importance of Chagas' work, continued vector control in endemic countries, and prospects for improving patient diagnosis and care.

Also, the Oswaldo Cruz Institute's journal, *Memórias do Instituto Oswaldo Cruz*, published a special issue in July on Chagas disease and *T cruzi* research. The journal *PLoS Neglected Tropical Diseases* published several papers on Chagas disease in July as well.

During the Rio symposium, leaders from the Drugs for Neglected Diseases Initiative (DNDI), a not-for-profit drug development partnership, and the international humanitarian organization Médecins Sans Frontières (MSF, or Doctors Without Borders) announced new campaigns calling for the development of safer, more effective medications and improved diagnosis and treatment for patients with Chagas disease. In October, both groups will sponsor a symposium on Chagas disease in Los Angeles in partnership with the University of California, Los Angeles (UCLA).

The CDC and World Health Organization (WHO) have reported that 8 million to 10 million individuals are infected with *T cruzi* worldwide, and about 11 000 of them die each year. Most cases are in Mexico, Central America, and South America. Despite this substantial toll, progress over the past 100 years in preventing, diagnosing, and treating Chagas disease has been slow. The reasons are complex, involving scientific, socioeconomic, political, and financial issues.

FALSE STARTS

Trypanasoma cruzi strikes primarily in poor rural areas where substandard housing enables triatomine infestations. Government vector-control programs that provide insecticides and better housing have succeeded in reducing infection, mortality, and prevalence rates since 1990, according to WHO. But diagnosis and treatment have lagged.

"There were quite a number of false starts in terms of understanding the infection and disease process," said Rick Tarleton, PhD, distinguished research professor and founding director of the Center for Tropical and Emerging Global Diseases at the University of Georgia, Athens. "It's not fully worked out yet."

Diagnosing *T cruzi* infection can be as tricky as finding a parasite in a haystack. During the acute phase of infection, microscopy easily can detect parasites in the blood. But the acute phase is brief, lasting several weeks, and patients often remain asymptomatic or have mild symptoms. Bern said only a small proportion of infections, perhaps fewer than 1%, are diagnosed during the acute phase.

As chronic infection sets in, parasites become very difficult to detect in the blood. "It's hard to demonstrate them by xenodiagnosis or by culture; the only methods we had pre-PCR [polymerase chain reaction]," said Bern. "Even with PCR, the proportion who are PCR-positive in the chronic phase can be as low as 30% to 40%."

Diagnostic difficulties led many in the scientific community to deny for decades that Chagas' conclusions were valid. They attributed acute symptoms to other infectious illnesses, including malaria. Cardiomyopathy, central nervous system abnormalities, and other symptoms of chronic infection either were not considered part of a unique syndrome or were thought to be symptoms of an autoimmune disease. Chagas still was defending his theories when he died in 1934, of heart failure.

Today, there is little or no doubt about the veracity of his work. Yet obstacles in addressing the disease remain. "The biggest problem in terms of diagnosis and treatment is that there is not a gold standard for determining whether or not someone is infected," said Tarleton.

The US Food and Drug Administration approved an enzyme-linked immunosorbent assay that has been used since 2007 to screen donated blood for *T cruzi*. It is used with the radioimmune precipitation assay for confirmatory testing. But these screening tests are not approved as diagnostics.

An estimated 20% to 30% of infected individuals will progress to clinical disease, but symptoms of chronic infection do not appear for decades, and clinicians have no way of knowing which patients will develop such symptoms. For those who do, treatment choices are limited.

"Our medications aren't that great," said cardiologist Sheba Meymandi, MD, director of the Center of Excellence for Chagas Disease at Olive View-UCLA Medical Center in Sylmar, Calif. The options are nifurtimox or benznidazole. Benznidazole currently is not available in the United States, but Meymandi said the CDC may gain access to the drug by the end of this year. Both medications can cause severe gastrointestinal tract and neurological adverse effects.

CROSSING THE BORDER

The detection and treatment of *T cruzi* infection is becoming a more prominent issue in the United States as the population diversifies and physicians find themselves treating more patients from endemic areas. "Chagas disease is prevalent in the United States, and it should be part of our differential diagnosis," said Meymandi.

In a recent analysis of Latin American immigrant populations in the United States, based on data from the Pew Hispanic Center and the US Department of Homeland Security, Bern estimated that 300 000 individuals with *T cruzi* infection and between 30 000

and 45 000 with clinical disease are now living in the United States (Bern C and Montgomery SP. *Clin Infect Dis*. doi: 10.1086/605091 [published online ahead of print July 29, 2009]). The analysis also showed that about 180 congenital infections occur in the United States annually.

Meymandi said that in her clinic, medical management of patients whose heart failure is a result of *T cruzi* infection is "incredibly aggressive." These patients receive standard heart failure medication as well as an implantable defibrillator and the antiarrhythmia drug amiodarone, which has been shown to decrease parasitemia and work synergistically with the antifungal drug posaconazole (Benaim G et al. *J Med Chem*. 2006;49[3]:892-899). Nifurtimox is given as well.

"We know treatment delays progression," she said. Meymandi also tests children of infected mothers and pregnant women who may be at risk of transmitting *T cruzi* to their infants.

Despite the remaining challenges, some experts are optimistic about the outlook on Chagas disease. "Twenty years ago, I thought we were stabbing in the dark," said Tarleton. "But now with our understanding of the infection and the parasite, the tools available to study it, the ability to answer questions, and the prospects for drug development—we have real possibilities." □

Aggressively Treating Hypertension Remains Strategy of Uncertain Benefit

Mike Mitka

CONVENTIONAL WISDOM ON treating hypertension argues that the greater the reduction in patient blood pressure, the better the outcome. Now, a contrarian view is gaining traction.

This view holds that there are limits to the benefits of reducing blood pressure in patients with hypertension and that continued efforts to lower it beyond various targets only increases cost and inconvenience for the patient.

The latest counterargument to lower-is-better comes from a Cochrane Collaboration review that assessed 7 hypertension treatment trials involving more than 22 000 participants. The authors concluded that compared with standard therapy, treating patients' blood pressure levels to targets of lower than 140 to 160 mm Hg systolic and 90 to 100 mm Hg diastolic, while reducing systolic and diastolic blood pressure levels by about 4 mm Hg and 3 mm Hg, respectively, does not reduce all-cause mortality and rates of myocardial infarction, stroke, congestive heart failure, major cardiovascular events, and end-stage renal disease (Arguedas JA et al. *Cochrane Database Syst Rev*. 2009;3: CD004349).

"We realized that blood pressure targets recommended in hypertension clinical guidelines were mainly based on indirect data or on data obtained from observational studies," said lead author Jose Arguedas, MD, of the Universidad de Costa Rica, San Pedro de Montes de Oca. "Therefore, we wanted to know whether such targets were also supported by more scientifically robust data, such as that obtained from properly designed randomized controlled trials directly comparing clinical events associated with different blood pressure targets."

A new review suggests that treating hypertension to aggressive target levels does not result in outcomes that are better than those achieved with standard treatment.

Franz H. Messerli, MD, of St Luke's-Roosevelt Hospital in New York City, said the issue is complex and that setting target blood pressure readings to establish diagnosis or treatment goals is arbitrary. "The benefits of antihypertensive therapy are most obvious in patients with the highest blood pressures," Messerli said. "The closer we get to 'normotension,' the more difficult it becomes to show benefits of blood pressure lowering."

Organizations that issue hypertension guidelines are also recognizing that evidence of benefit from aggressive hypertension treatment is limited and note that findings suggest harm of such intervention in selected populations. Some groups are considering revising their guidelines accordingly.

The European Society of Hypertension, which is revising its treatment guidelines for publication later this year, is considering recommending a threshold blood pressure level of about 120 mm Hg systolic and 70 mm Hg diastolic for patients at high risk of cardiovascular complications or stroke because of recent findings suggesting increased risk of harm for these patients if blood pressure is decreased further (Sleight P et al. *J Hypertens*. 2009; 27[7]:1360-1369). And in the United States, the Joint National Committee on Prevention, Detection, Evaluation, and