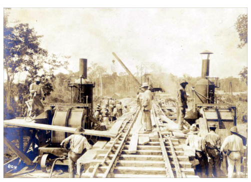
[1] **The Railroad Worker's Disease**

by Nathália Helena Azevedo and Thiago Marinho Del Corso

[2] Prologue: Brazil, Railroads and Malaria

[3] It is 1907. We are in Rio de Janeiro, the capital of Brazil. The president of the Brazilian Central Railroad, Aarão Reis, sits in a coffee shop, enjoying his daily cup of world-famous Brazilian coffee. He admires the decorative flourishes in the woodwork overhead and the stately architecture along the street outside the window, all an inspiring reminder of the recent upturn in the nation's prosperity.



[4] He is proud that his railroad is contributing to the economic growth by expanding transport and commerce with the country's interior in the state of Minas Gerais to the north. That will support the booming latex trade, for example.

[5] He enjoys another sip of coffee and opens the daily newspaper. And then, on page 7, his attention is arrested... There he finds a letter addressed to himself. He reads:

> *"Defender as you are of the worthy employees of the Brazilian Central Railroad, ... I beg to report to you the awful sufferings that the worthy employees who are assigned to work between Curvelo and Contria must undergo. You cannot imagine?! It is a horror, a true calamity! ... Life for the road worker is martyrdom, horrible suffering, where everything is lacking, even the basic necessities!"*

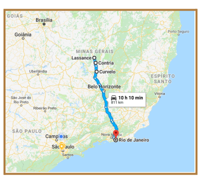
The President sighs in dismay and pulls on his shirt cuffs. He quickly glances through the remainder of the text:

> *"A few kilometers from Contria, a bridge is currently being built over the Bicudo River, but the road building is already struggling with serious difficulties in finding people who want to work in the Hinterland because everyone knows that fevers have devastated [so] many people! ... I ask ... that his lordship, studying the issue, promote the measures that the case requires, giving his subordinates the means to act with true selflessness the duties incumbent on them in the difficult jobs they exercise in those backwoods regions, true graveyards of life."*

[6] The letter is unwelcome news. “Fevers,” the president knows, refers to malaria -- a familiar scourge of workers in the interior.

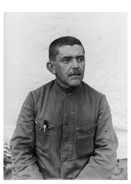
[7] He recalls the recent troubles with malaria at the hydroelectric project in the neighboring state of São Paulo. He also thinks about Brazil’s Sanitary Movement of 1902 and all the new health institutes which have helped protect him and others in the capital and other cities from such diseases. Perhaps he should contact his chief construction engineer, Cornélio Homem Cantarino Motta, to inquire about the status of the workers and this apparent interruption in the progress of clearing the forest and constructing the new railroad line north to Belém.

[8] [**Think Question 1**] As president of the railroad, what would be your response regarding the workers? What are your concerns, and what actions are available to you?

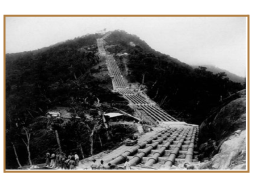


[9] Meanwhile, Chief Engineer Motta is working in Lassance, a small town near the current construction, 700 kilometers north of Rio. He, too, reads the same newspaper article. But it is hardly news to him.

[10] Hoping for a solution, Motta contacts Oswaldo Cruz, the director of the Manguinhos Institute in Rio de Janeiro, which has been given responsibility for public health problems, and he asks for assistance.



[11] Cruz sends two doctors: Carlos Ribeiro Justiniano and Belisário Penna. While a young researcher, Carlos is a malaria expert. He received his medical degree in 1903 with a final thesis on malaria and conducted studies on malaria and how to avoid it in 1905. He discovered new ways that the disease spread. Hence, he is well versed in the life cycle of the mosquito, which transmits the disease. His research has resulted in multiple scholarly publications.



[12] Cruz had already enlisted Carlos’s help in the earlier malaria campaign in nearby São Paulo. Now, he would put that experience to work in the Lassance region.

[13] Chapter 1: The Lassance Disease

[14] The physicians arrive in Lassance in June 1907, pausing long enough for a photo.

[15] They set up shop in a railway car that can travel along the tracks and serve as a mobile consulting room, laboratory, and residence.

[16] Carlos and Belisário soon discover that most of the workers are sick, with many suffering from severe symptoms. They provide them with quinine, a known treatment used to prevent and cure malaria.

[17] In addition, workers are protected from malaria-carrying mosquitos by using screens on doors and windows and mosquito nets over their beds. Carlos believes that the mosquito should be addressed not only by eliminating the larvae in stagnant water (the conventional approach), but also by targeting the adults flying within the buildings using insecticides.

[18] Carlos records the symptoms of all his patients. He recognizes the fevers, and the bug bites, along with pain, appetite loss and vomiting. But he also finds a number of conditions that are not typical of malaria cases he has encountered in the past: excess fluid (edema) and red spots instead of yellowish skin. He wonders whether the patients are indeed suffering from malaria.

[19] Symptoms found in the sick population of Lassance vs. malaria

Known symptoms of malaria	**Symptoms observed in Lassance**
1. single bite, symptoms appear after 8 to 25 days 2. high fever, intense chills alternating with heat waves and profuse sweating (appears and disappears every 2 or 3 days) 3. head and body pain 4. appetite loss 5. anemia with yellowish skin (jaundice) and fatigue 6. liver and spleen enlargement 7. vomiting 8. encephalitis with retinal lesions (retinal bleaching) 9. can lead to death	1. swelling near bite (chagoma) 2. acute phase: symptoms usually go away within 3 to 8 weeks 3. low fever (goes away after a few days) 4. head and body pains (moderate) 5. appetite loss (moderate) 6. red spots on skin (exanthema) 7. liver and spleen enlargement 8. vomiting 9. meningitis and encephalitis (uncommon complications) 10. enlarged nerve ganglia 11. swelling (edema) 12. hardly leads to death

[20] **[Think Question 2]** Given the list of symptoms, how would you determine if the railroad workers' disease in Lassance is a variant form of malaria or a different disease entirely? What additional information would you like to collect? What criteria would you apply before seeking an alternative treatment or remedy?

[21] Carlos decides that the symptoms observed in the sick railroad workers and others in the local population are sufficiently distinct from those of malaria and that the people in Lassance must be suffering from another disease. He later writes in recollection:

> *...What first impressed our attention was the existence of a set of frequent and uniform symptoms, more prominent in the beliefs, symptoms that, from the very beginning, imposed themselves on our clinical reasoning as expressive of an autonomous morbid entity.* (1909)

People affected by Lassance disease have symptoms that include neurological, cardiological, and endocrinological features, with specific issues in the thyroid. When bites are near the eyes, as they often are, there are distinctive swellings. These seem to indicate a pathogen with different effects. Carlos begins to document the conditions of the Lassance disease as further indicators of a difference. If a different disease-causing microorganism is involved, it might also be transmitted by different carrier organisms - which might account for the apparent difference in bite marks that Carlos has noticed. Carlos is now alerted to look for possible other clues.

[22] Chapter 2. Of insects and men

[23] The railroad engineer, Cornélio, has lived in the area since 1902 and is familiar with the local people. At a gathering with Belisário, Carlos and others, he asks the visiting doctors, "*Since you, gentlemen, are here, any chance you could investigate an insect that locals say sucks blood from everyone's faces and that may be the source of numerous maladies among the local populace?*" The conversation quickly returns to other topics, but Carlos remains silent, thinking.

[24] On another occasion, Cornélio tells Carlos about a wild blood-sucking insect that he and other engineers experienced camping while researching the route for the railroad line. The bug bit people's faces! Cornélio wonders if there might be a

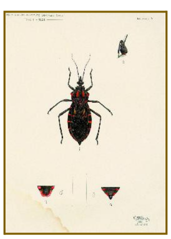
link between the sick people and the presence of the “kissing bugs” in the local homes. Carlos had never heard of the bug before, nor ever seen a specimen of it.

[25] **[Think Questions 3]** Should Carlos take Cornélio’s suggestion seriously? Give at least one reason for heeding his advice and at least one reason for doubting it. What could you do to investigate Cornélio's information further?

[26] Although Carlos has never heard of the bug, he knows from his work on malaria that insects can certainly transmit diseases. So he decides to search for the bug. He goes with Belisário on an expedition to the region where the engineers had camped. He also starts collecting insect specimens locally around Lassance. Penna finds and captures Cornélio’s so-called “kissing bug”, and shows them to Carlos. He observes its behavior. It is a member of the blood-sucking insect family Reduviidae, subfamily Triatominae.

[27] Carlos notes in his records that "*the insect bites at night, hides in cracks, is common in unplastered and grass-covered houses where it reproduces freely, dislikes light, and disappears in the absence of people in the dwellings*.”

[28] Chapter 3. Protozoa and Disease

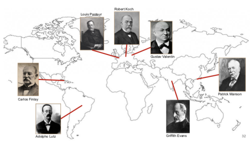


[29] Carlos suspects now that the kissing bug is connected to the spread of Lassance's mysterious new disease. In search of evidence to support his suspicions, he decides to examine the insect's intestines. There he discovers flagellated protozoa belonging to the genus *Trypanosoma*. However, he cannot yet distinguish which species it belongs to.

[30] Despite having been trained in medicine, Carlos believes that it is important to look beyond the patient and the illness themselves to their context. He studies the environments in which the diseased people live. His experience in insects and microorganisms related to malaria now leads him to look for whether Cornelio's bug is biting other animals in the Lassance area. Carlos discovers trypanosomes in the blood of local marmosets, a small primate (*Callitrix penicillata*). At the same time, he is puzzled that the marmosets seem unaffected by the protozoan. In addition, Carlos cannot be sure whether the *Trypanosoma* forms discovered in kissing bugs’ intestines belong to the same species as those found in the marmosets’

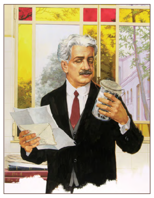
blood. He proposes that both trypanosome variants might occur naturally as a nonpathogenic form, including the stage he discovered in marmosets.

[31] **[Think Questions 4]** How might you determine if the trypanosome forms observed in the kissing bug and the marmoset are different species or variants of the same species? What expertise and resources do you need for this investigation? How will you secure them?

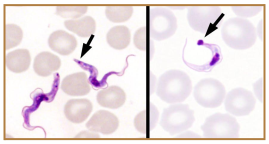


[32] In the past few decades, many protozoan, vector-borne illnesses have been described. European nations have been concerned with fighting diseases in their colonies, and some of their medical schools now focus on tropical medicine. As a result, many ailments caused by "hot climates" are now better understood. The views of Louis Pasteur and Robert Koch about the role of "germs" (or microorganisms) in causing disease are now widespread. Between 1881 and 1900, Carlos Finlay identified a mosquito that transmitted yellow fever in Cuba, and Patrick Manson identified a mosquito that spread elephantiasis. In Poland in 1841, Gustav Valentin located *Trypanosoma* parasitising trout; in 1880, Griffith Evans identified *Trypanosoma evansi*, the agent of the chronic wasting syndrome, which affects horses and camels. Here in Brazil, Adolpho Lutz has observed *Trypanosoma*. Carlos is aware of all these findings, so having found a new species of *Trypanosoma* in the kissing bugs, he begins searching for an associated illness without assuming that this was necessarily the disease already known.

[33] Carlos has been in Lassance for about a year now. He is finally able to describe the species found in the marmosets as a *Trypanosoma minasense*. Carlos is still unsure whether the forms discovered in the insect identified by Cornélio Mota is a variant of the same *Trypanosoma*. The facilities of the laboratory in Lassance are improvised, so he seeks assistance from Oswaldo Cruz at the Manguinhos Institute back in Rio de Janeiro for further investigation. The Manguinhos Institute has been a key player in Brazil's sanitary reform. For example, they helped eradicate the region's bubonic plague and yellow fever. The institute was originally formed to produce sera and develop vaccines, but it has also greatly improved public health in Brazil. The institute is one of the few in Brazil with the financing, facilities and equipment to aid Carlos's research.

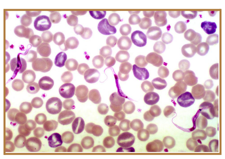


[34] Carlos sends some insects to Manguinhos. Oswaldo Cruz exposes the monkeys, raised in isolation in the laboratory, to the insects. About a month later he tells Carlos that he has found trypanosome forms in the blood of one of the animals, which had fallen ill.



[35] Based on these findings, Carlos decides to travel back to Rio de Janeiro himself. Once there, he begins the exacting work of breeding the insects in the laboratory and extracting the protozoa from their guts. By analyzing their morphology and variety, he finds that the microbe now detected in the marmosets' blood is not *T. minasense,* but rather a new species. Carlos names it *Trypsanoma cruzi* in honor of his senior colleague, Oswaldo Cruz. He announces the new discovery of two new species in a German journal.

[36] **[Think Question 5]** How can you confirm that the disease in the marmoset is the same as that in the Lassance group after ruling out one of the trypanosomes as pathogenic?



[37] Still at the Manguinhos Institute, Carlos starts closely observing the *T. cruzi* life cycle. He reasons that other vertebrate hosts, such as humans, might also contain the protozoan.

[38] Carlos returns to Lassance to find the situation there essentially unchanged. There are still many sick workers and residents, and the likelihood of a cure or effective treatment seems slim. With the information he has gathered on the progression of the illness in marmosets as a basis for comparison, he can now confirm the presence of the protozoa in the blood of a domestic cat. This is consistent with his hunch that the kissing bug of Cornelio Motta may be spreading the sickness in the rural area. Carlos then goes on to test blood from some of the Lassance patients who exhibit symptoms of the disease, expecting to find the telltale flagellated protozoan. However, even with several samples, he fails to detect *T. cruzi.*

[39] **[Think Question 6]** Should the blood investigations be abandoned or continued? If so, for how long? What factors guide your decision?

[40] Carlos and his team continue to collect blood samples. One sample comes from a sick 2-year-old child, Berenice. It, too, is negative. Four days later, Berenice's condition worsens, and the family contacts the clinic again. The doctors examine her and decide to take another blood sample. This time they find flagellated protozoa in her blood! Moreover, the evaluation of the flagellates' morphology proves them to be *T. cruzi*.

[41] **[Think Question 7]** In what ways does this finding change the course of the investigation? How might such unexpected events affect how you plan and conduct scientific investigations?

[42] **[Think Question 8]** Is the presence of *T. cruzi* in the patient's blood in this one case sufficient to show that it causes the disease? If not, why not? How else might you link together the relevant evidence about the protozoa in kissing bugs, patients' blood, and other animals?

[43] Carlos continues to look for new cases of the disease in the local population and evidence of *T. cruzi* in patients' blood. He takes a series of several samples from the same patients to understand how the pathology changes over time. However, because of his limited laboratory in the railroad wagon, Carlos once more turns to the Manguinhos Institute to collaborate with Oswaldo Cruz on the research. First, they decide to infuse marmosets with the blood of patients–but only from patients with severe disease symptoms. To avoid misinterpretation of the findings, they implement several precautions. For example, they ensure that the animals used in the experiments have been completely isolated, with no prior chance of being bitten by a blood-sucking insect. In one of the experiments, the guinea pigs died after a few days, with the lungs containing a high concentration of *T. cruzi* cells. After about eight days, the marmosets that received blood from the same human blood sample also had high levels of flagellates in their blood.

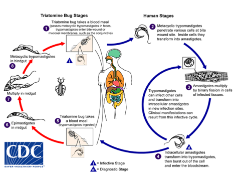
[44] While the experiments continue, Carlos cares for a child who has many symptoms of the disease. But despite the infant's definitive diagnosis, the blood shows no trypanosomes. Given the child's critical condition, Carlos decides to take blood from the child and inject it into two test guinea pigs. One dies soon thereafter, and the other develops disease symptoms in a short while. Carlos tries the experiment again with new guinea pigs and the blood of another sick child.

They become sick, and their blood shows signs of infection, which sometimes remains for more than two months. He repeats the test with a third child, yielding a set of findings:

[45] Summary of Carlos' experiments (conducted around 1909)

Exp	**Origin of infected blood**	**Animals inoculated**	**Observations after inoculation**	**Carlos' interpretation of the findings**
A	Child A	2 guinea pigs and 1 marmoset	The guinea pigs die 6 days after inoculation. The marmoset shows *Trypanosoma* in the lungs and blood after 8 days.	(+)Guinea pigs died from the disease caused by the protozoa in the child's blood. The marmoset was also contaminated with the disease.
B	Child B - severe condition with many symptoms, but with blood without *T. cruzi*	2 guinea pigs	One guinea pig dies, and another has *Trypanosoma* in the lungs 9 days after inoculation but does not show cells in the blood.	(+)One of the guinea pigs died accidentally, and the other was in the early stages of the disease triggered by the child's blood.
C	Child C- severe condition, with many symptoms, but with blood without *T. cruzi*	Guinea pigs	After 20 days, the guinea pigs have *Trypanosoma* in the blood. After 2 months of intense infection, some guinea pigs were alive and with severe infection.	(+)The guinea pigs were contaminated by the child's blood but presented different degrees of infection and resistance.

[46] **[Think Question 9]** What do you conclude from these experiments, in the context of all the other evidence gathered through Carlos's work?

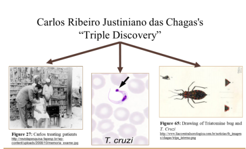


[47] Carlos is now able to understand how the railroad workers' disease is linked with the life cycle of *T. cruzi.* The inoculations of human patient blood into lab animals provide concrete evidence (finally) that the disease is based on *T. cruzi* which is transmitted from the kissing bugs to organisms when they are bitten. Carlos's initial observations documented the presence of the trypanosome in the bug's blood, but did not provide evidence that it was transmitted, or caused disease in humans. It took the laboratory work with marmosets to confirm that such transfer could occur (and differed from the trypanosome species found in their blood in the wild). Bite marks on humans indicated that they were bitten, but detection of the infection was made more difficult because symptoms could appear without large amounts of the parasite being found in the blood. The transfer of blood from patients to other animals, however, indicated that they were there, and that they were infectious. *T. cruzi* seems to follow a complex life cycle, moving from human to bug to animal to bug to another human again, using each host to grow and reproduce.

[48] [**THINK Question 10**] What types of scientific work were needed to generate this evidence, and how was each important?

[49] Many factors were significant. Clinical examination of patients was essential to yielding knowledge about the unique disease. Natural history observations in the field and microscopic examinations in the laboratory, were needed to identify the microorganism, previously unidentified, and where it is found in nature. Laboratory tests with experimental animals, coupled with more microscopic observations were integral to concluding how the microorganism is transmitted from one mammal to another via an insect. All studies were needed to assemble a full understanding of the life cycle of *T. cruzi* and its transmission. Carlos was central to all this work, but others also provided key information. Belisário Penna helped with the clinical work and with finding the bug. Cornélio Motta had provided the critical initial clue to the possible role of the kissing bug. Oswaldo Cruz provided assistance and laboratory resources at important stages. But Carlos, with his experience on malaria, was able to link the railroad workers' disease to the insect, its connection with other animals in the environment, find the microorganism and identify it and the whole transmission cycle – bridging clinical, natural history and laboratory contexts.

[50] Chapter 4. Celebrating a triple discovery



[51] This is the first time that an individual scientist has identified a novel illness *and* its causal agent (*T. cruzi*) *and* its vector (the kissing bug). With Carlos's extended efforts on all three aspects of this disease, physician Miguel Couto suggests that the new condition be named after Carlos, who we may now identify as Carlos Chagas. The railroad workers' disease becomes known as *Chagas disease*.

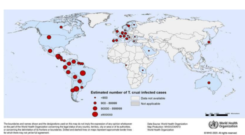
[52] **[Think Question 11]** Imagine the impact of Chagas's investigations and conclusions on the science of studying diseases. How might understanding the history of this one case shape public policy on funding science and using its results?

[53] Chagas disease, elucidated over a short period, is described in international scientific journals and has a significant impact, even outside Brazil. It opens a better understanding of other tropical protozoa and spurs the development of more effective treatments for them. By late 1909, the efforts of Chagas and others have

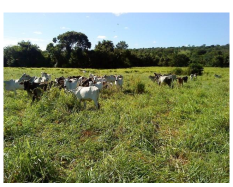
dramatically exposed the need to improve the sanitary conditions and health infrastructure in Brazil's interior region. Carlos attempts to rally even more politicians and physicians to tackle illnesses like malaria using the knowledge he gained throughout his research. Ties grow between science, health, and Brazilian politics. Between 1916 and 1920, the Brazilian government launches a series of measures to improve rural populations' health, including establishing a National Department of Public Health.

[54] [**Think Question 12**] Why and how are awards important (and from whom)? What level of recognition does a discovery like this deserve?

[55] Chagas received numerous honors and awards from around the world. He succeeded Oswaldo Cruz as director of the Manguinhos Institute, and was appointed the first director of Brazil’s National Department of Public Health in 1919. Chagas was also nominated several times for the prestigious Nobel Prize, but never received the honor.



[56] Over a century later, Chagas disease remains a challenge to public health in many areas of the world. It affects 6-7 million people globally, while many more are at risk. It is endemic in 21 Latin American countries and the southern United States. 10,000 patients die each year. To date, there is no known cure.



[57] Lassance remains a modest community, its economy centered on agriculture, cattle, and mining industries. Malaria, ironically, is still a problem, as it is throughout the interior of Brazil. Chagas disease remains a threat also, although cases have decreased largely to control of the insects, based on the knowledge developed by Carlos Chagas.

[58] **[Think Question 13]** Discuss how the case of Carlos Chagas & the Railroad Workers’ Disease illustrates various features about science and how it works:

A. The role of political and economic factors in supporting scientific research [the work of scientists.] (THINK 1, 10, 11)
B. The role of personal background, motivations and skills (THINK 3, 10)
C. The role of analogy (e.g., comparisons between a new disease and those already described) (THINK 2, 4, 8, 9, 10)

D. The role of local or anecdotal knowledge versus systematic investigation (THINK 3)

E. The role of chance or contingency (THINK 3, 7, 8, 10)

J. The role of patience and persistence (THINK 6, 7, 10)

F. The role of collaboration (THINK 8, 10, 12)

G. The relationship between laboratory studies and field studies (THINK 2, 4, 5, 6, 8, 9, 10)

H. The application of research knowledge to public health (THINK 11)

I. Incentives and rewards (THINK 12)

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