

## **A Medical Student Named Daniel A. Carrión and His Fatal Quest for the Cause of Oroya Fever and Verruga Peruana**

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Bartonellosis or Carrión's Disease is an infection caused by the bacteria *Bartonella bacilliformis*. It is endemic to the Andes Mountains of South America, especially in Peru, at 500 to 3000 meters above the sea level (1). The organism is transmitted by the bite of the sand fly, especially *Lutzomia verrucarum*. In the acute phase (known as Oroya fever), bartonellosis presents with fever, myalgias, arthralgias, headache, and delirium. The organism attacks the erythrocytes, causing severe anemia and microvascular thrombosis. Complications include seizures, meningoencephalitis, hepatic and gastrointestinal dysfunction, angina, and ultimately, death in up to 40% of untreated cases (2). Infection also leads to immunosuppression and the victims become susceptible to opportunistic infections, such as salmonellosis and toxoplasmosis (2,3). Patients that survive the acute phase develop crops of nodular lesions (verruca peruana), usually on face and trunk, about 4-6 weeks after the initial infection. These evolve into vascular (mulaire) lesions (2).

Bartonellosis has been described since ancient times and there are pre-Columbian ceramic figures (*huacas*) of individuals with abundant lesions. Furthermore, there are words in Quechua (a language spoken since the time of the Incas) that suggest that bartonellosis was present before the Spaniards arrived in the Americas. The words *tikrizapa* (wart) and *tictiyan* (a state of been full of warts) are examples of words in Quechua that suggest the presence of this disease in pre-Columbian times. The major limitation on the documentation of bartonellosis before the arrival of the Spaniards lies in the absence of written language of the Peruvian Amerindian cultures; thus, some experts

have stated that the *huacas* represent other diseases (2). However, lesions similar to verruca peruana have also been found in a hydrated pre-Columbian mummy (3).

It has been proposed that the Spanish expedition led by Pizarro suffered from an outbreak of bartonellosis and that it produced a high mortality rate, as described by Miguel de Estete, the official chronicler of the conquest of the Incas. The conquistadors initially suffered from a debilitating febrile illness, followed by a phase in which the inflicted had cutaneous blood-filled vesicles (3). However, whether or not this was verruga peruana has been a matter of contention, given that the site where the outbreak occurred was below the altitude where the habitat of the *Lutzomia* sandfly is typically located (2).

Although there were also sporadic reports of verruga peruana over the years in its endemic areas, the disease did not gain recognition as a public health problem until an ambitious engineering project in Peru in the 1870s brought a large number of susceptible persons into contact with the sandfly vector. The trans-Andean Railway, initiated in 1870, was built to connect the silver-rich mining towns of the high Andes with the Peruvian seaport of Callao and was the highest altitude railroad of its time (up to 16,000 feet above the sea level)(4,5). In 1871, bartonellosis struck the railroad workers near the mining town of La Oroya (2). The mortality rate was high, with estimates of 4000-7000 deaths, and many of the workers refused to return to their jobs (2,11).

In 1885, a young 6th year medical student from the Peruvian San Fernando medicine faculty, Daniel A. Carrión, was determined to find the cause of Oroya fever and ascertain its relationship to verruga peruana. Thus, he decided to inoculate himself with samples obtained from a patient with verrucous skin lesions. Carrión was unable to perform the inoculation himself, so he enlisted the help of a physician, Dr. Evaristo Chaves, who agreed to participate despite the risks to the young student (6).

Daniel A. Carrión was a modest, mestizo student, born in Cerro de Pasco, Peru. He studied natural sciences and then applied to medical school at the Universidad Mayor de San Marcos. Carrión had been studying the verruga peruana over the previous three years and he was well aware that he was taking a significant risk. Carrión kept a diary in which he recorded the natural evolution of his disease; he suffered myalgias, arthralgias fever, severe anemia, and jaundice. When he was too weak to write his observations, his classmates assumed the job until he perished from the disease, 21 days after onset (2, 6,7). After his death, Carrión was considered a martyr of Peruvian medicine and he contributed to the professional prestige of Peruvian physicians.

There were multiple factors that may have contributed to his decision to undertake the self-inoculation. Among them was the fact that the “Academia Libre de Medicina” (Free Academy of Medicine) was offering a prize to the person able to find the cause of the verruga peruana, which included public recognition as well as support for the scientific publication of the findings. Carrión may have felt the urge to achieve fame, to facilitate attaining his dream of going to Europe (3,6). At the time, it was difficult to go to the areas where the disease was endemic due to disturbances in the public order, so there were few other competitors for the prize.

In 1909, another Peruvian physician, Alberto Barton, the son of British immigrants, described the organism causing the Oroya fever, when he observed foreign

bodies within the erythrocytes of patients with this disease (11). However, his observation was not accepted by the scientific establishment of the time, and the foreign bodies were considered to be mere red cell alterations. However, in 1913, the Peruvian Harvard expedition, directed by Richard P. Strong confirmed Barton's findings (2,11). They named the organism *Bartonella bacilliformis* in his honor. Nevertheless, they questioned Carrión's original hypothesis on the common etiology of verruga peruana and Oroya fever, due to the inability to produce Oroya fever in an inmate inoculated with samples from a patient with verruga peruana (11). In 1920, Hideyo Noguchi from the Rockefeller Institute was able to culture the etiological agent of Oroya fever and confirmed the common etiological agents of both Oroya fever and verruga peruana, when he inoculated monkeys and was able to cause both syndromes (2,11).

The sandfly vector of bartonellosis was discovered by Charles Townsend, an American entomologist hired by the Peruvian government to find the agent responsible for the transmission of this disease. He hypothesized that there had to be an insect with the same geographic distribution as the disease and he identified the offending nocturnal sandfly, initially named *Phlebotomus verrucatum* and later *Lutzomia verrucatum* (11).

The discovery of the etiology of Oroya fever and verruga peruana, although not well known, illustrates two recurring themes in the history of medicine, one being the self-sacrifice of physicians and scientists to further medical knowledge and the second is that progress in infectology often occurs when economic forces puts a new population of humans into contact with a disease. Self-inoculation of an infectious pathogen has been used by several scientists and physicians to prove the cause and effect of exposures and disease. Motivations to pursue self-experimentation may vary, and may include the romanticism of self-sacrifice to achieve the noble goal of attaining a rapid advance in medical knowledge when other methods are difficult or time-consuming (6). There are several examples of self-inoculation in the history of medicine. To determine the cause of gonorrhea, in 1767, the English physician John Hunter inoculated himself with pus from a patient with gonorrhea. Although there is some controversy over the matter, the pus was apparently was co-infected with *Treponema pallidum* (the causative organism of syphilis) and this may have ultimately resulted in Hunter's death from syphilitic aortitis. In 1892, Max von Pettenkofer, a Bavarian hygienist, in an effort to disprove Robert Koch's theory that cholera was caused by *Vibrio cholerae* alone, ingested a culture broth of the bacterium and suffered only mild diarrhea, perhaps due to prior immunity. In the early 1900s, American physicians James Carroll, Aristides Agramonte, and Jesse Lazear (members of the Yellow Fever Commission, along with Walter Reed) allowed themselves to be bitten by infected mosquitoes in order to prove the link between mosquitoes and yellow fever. Both Carroll and Lazear died in the course of their work; Agramonte survived, presumably because of immunity from prior exposure. More recently, in 1984, Barry Marshall, an Australian physician, sought to establish the relationship between gastritis and infection with *Helicobacter pylori*. When his attempts to prove his hypothesis by infecting piglets failed, he ingested the organism himself and then underwent endoscopy and gastric biopsy (8,9,10). Marshall survived his self-experiment and went on to win the Nobel Prize in Physiology or Medicine in 2005.

The quest to determine of origin of Oroya fever and verruga peruana was stimulated by Peru's drive to exploit the mineral wealth of the Andes. Likewise, the settlement of Montana's Bitterroot Valley prompted efforts to deduce the organism and vector responsible for Rocky Mountain Spotted Fever (12). Many discoveries in tropical

infectious diseases, including those of the vectors of yellow fever, malaria, and lymphatic filariasis, were also stimulated by the acquisition of colonies by the United States and Great Britain.

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