

REFLECTION PAPER

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One hundred years after the expedition by Harvard University to Peru to investigate Carrion's disease. Lessons for science

Cien años de la expedición de Harvard a Perú para investigar la enfermedad de Carrión. Lecciones para la ciencia

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| Abstract |

In 1913, around 100 years ago, the Harvard University sent an expedition to Peru, led by Richard Strong, to investigate Carrion's disease. This paper provides a critical review of the scientific research carried out in this expedition.

Richard Strong was a physician who performed unethical human experimentation in the Philippines and China. In Peru, Strong conducted experiments on humans to inoculate wart secretions to a psychiatric patient, which led him to replicate the Peruvian wart in this individual, although he could not replicate Oroya fever. Based on this experiment, and without taking into account epidemiological and clinical evidence, the Harvard expedition erroneously concluded that Oroya fever and Peruvian wart were two different diseases.

A retrospective review of the scientific work conducted by the expedition in Peru allows drawing the following lessons for science: a) disapproving unethical human experimentation conducted by the expedition; b) to determine the cause of infectious diseases, it is necessary to obtain the best scientific, experimental and observational evidence, and c) to acknowledge that, despite the poor infrastructure, researchers in developing countries are able to produce high-quality scientific knowledge that may surpass the knowledge generated by researchers in developed countries

Keywords: Carrion's Disease; Bartonella Infections; Oroya Fever; Bioethics (MeSH).

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| Resumen |

Hace poco se cumplieron 100 años de la expedición de la Universidad de Harvard a Perú, liderada por Richard Strong, para investigar la enfermedad de Carrion. El presente estudio realizó una revisión crítica de la investigación científica de dicha expedición.

Richard Strong era un médico con antecedentes relacionados con la realización de experimentaciones humanas antiéticas en Filipinas y China. En Perú, Strong realizó experimentación humana al inocular secreciones de verruga en un paciente psiquiátrico, logrando reproducir en este la verruga peruana, pero no la fiebre de la Oroya; con base en este experimento, y sin considerar la evidencia epidemiológica y clínica, la expedición de Harvard concluyó erróneamente que la fiebre de la Oroya y la verruga peruana eran dos enfermedades diferentes.

Una visión retrospectiva de la labor científica de la expedición de Harvard en Perú lleva a extraer las siguientes lecciones para la ciencia: a) se debe condenar la antiética experimentación humana realizada por la expedición de Harvard; b) es necesario obtener la mejor evidencia científica, experimental y observacional en la causalidad de las enfermedades infecciosas, y c) es necesario reconocer que en países subdesarrollados se puede generar conocimiento científico de alta calidad y que, pese a la escasa infraestructura, puede ser mejor al de los países desarrollados.

Palabras clave: Enfermedad de Carrion; Infecciones por Bartonella; Fiebre de Oroya; Verruga Peruana; Bioética (DeCS).

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Introduction

Carrion's disease or Bartonellosis by *Bartonella bacilliformis*, also called Peruvian wart or Oroya fever, is a South American infection, scientifically reported only in Ecuador, Colombia and Perú, the latter being the most affected country, where it has been documented even in mummies from pre-Inca times (1).

This disease has two clinical stages: the stage known as Oroya fever, which is characterized by fever and severe hemolytic anemia type, and a later one, in which the patient develops the Peruvian wart. Common sense suggests that since these two phases are so dissimilar, they constitute two different diseases; however, it has

been proven that both conditions are part of the same pathology. This assumption was established by the unicist theory of bartonellosis by *B. bacilliformis* (2) (Figure 1). After quinine, this concept is considered the second most important contribution of the Peruvian medicine to the science community. In general terms, there is little information on the scientific achievements of Latin American science, so its actual history is unknown.

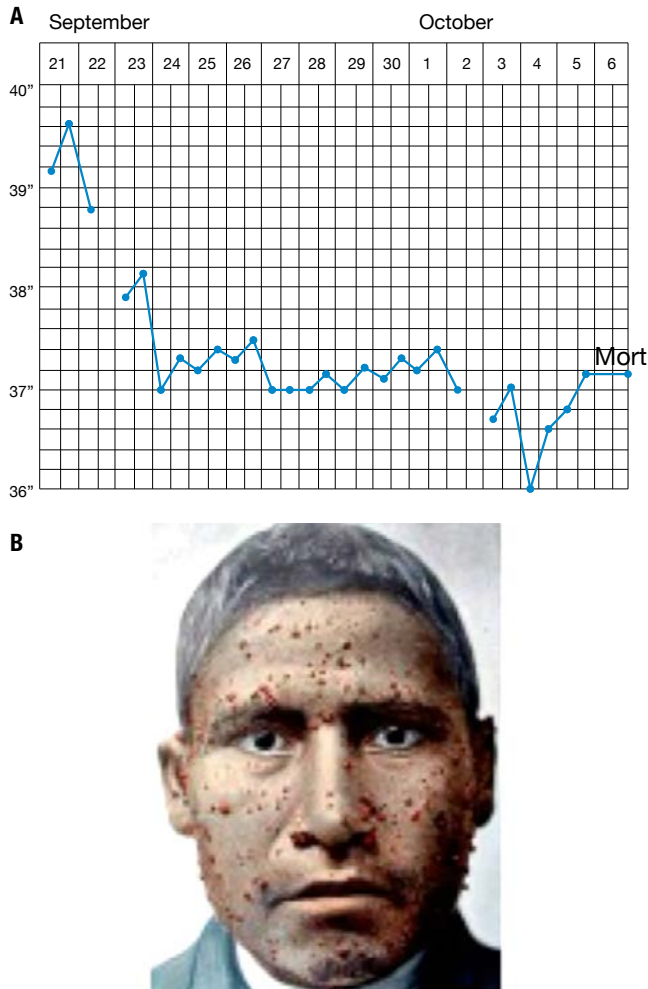


Figure 1. Unicist theory of Carrion's disease. A) Febrile curve by Daniel Alcides Carrion, who suffered from Oroya fever; B) Patient with Peruvian wart. Source: (3).

Recently, the expedition to Perú by the School of Tropical Medicine of the Harvard University, headed by Richard Strong who was highly interested in Carrion's disease, celebrated its hundredth anniversary. This study provides a critical review of the scientific research conducted in this expedition.

Richard Strong

Richard Strong, American M.D., was born in Virginia in 1872, graduated from Yale University and John Hopkins University, and participated in the war between Spain and the US, which resulted in the transfer of several Spanish colonies, including the Philippines, to American dominance. After the war, Strong remained in the Philippines as the head of the biological laboratory of the Scientific Office (4,5); there, in 1906, he performed experimental

inoculations with a vaccine for cholera in 24 men secluded in the Bilibid Prison, Manila, of which 13 died of the plague according to the autopsy. These vaccines may have been contaminated with *Yersinia pestis*.

Strong received harsh comments for his involvement in this event. The General Committee of the Philippines, in charge of the investigation, accused him of negligence; nonetheless, the prosecution exonerated him because his acts were informed to the US Congress and to the president, Theodore Roosevelt, who ordered not to conduct a research or a formal trial (6,7) against him. In 1911, with the support of the Red Cross and the U.S. War Department, Strong was sent by his government to China to investigate the bubonic plague in Manchuria (8); there, he relapsed into his unethical research practices when performing experiments with intravenous therapies. Chinese doctors suspected this behavior since patients who received his treatment died within the same day. This situation prompted the scientist to abandon his experimental therapeutic research, and work on etiological and anatomopathological research instead (8).

In 1912, Strong returned to the Philippines and performed illegal human experimentation on prisoners sentenced to death to determine whether a diet based on rice produced beriberi in them; as a reward, the 29 "volunteers" received all the cigarettes and cigars they wanted (7). It seems that this researcher was the first to use prisoners as subjects for large-scale unethical human experimentation (9). Decades later, during the Nuremberg trial, the defense of Nazi doctors —like Gerhard Rose, director of the Department of Tropical Medicine of the Robert Koch Institute in Germany and author of torture and experiments on Jews— cited that the experiments conducted by Strong were never sanctioned (10). Despite his unethical background in human experimentation, the Harvard University appointed him in 1913 as the first director of the newly established School of Tropical Medicine and appointed him to lead an expedition to Peru.

Harvard research expedition in Perú

In 1913, the School of Tropical Medicine Committee of the Harvard University traveled to Peru to obtain samples for the study of the Peruvian wart; this commission was headed by Richard Strong, with the collaboration of David Matto —Head of the Department of Bacteriology and Microscopic Techniques of the Faculty of Medicine from Universidad de San Marcos and director of Manicomio del Cercado (11-13)— and of Julio C. Tello, director of the Museum of Anthropology. In the final report of the expedition, the scientific community declared that the help of Julio C. Tello was indispensable, and he was appointed as delegate of the United States to the Fifth Latin American Medical Congress held in Lima. In this congress, held from November 9 to 16 in 1913, a preliminary report of the expedition was presented by the Peruvian microbiologist Gastiaburu, a member of the commission.

The national press covered the Fifth Latin American Medical Congress for a week, so the preliminary report of the Harvard expedition was exposed not only to the medical community, but to the general public; all activities performed by foreign delegations were published daily by the press, thus, the findings of the expedition were published in the social and scientific spheres (14-20).

After arriving in Peru, the expedition worked in the laboratory of the Municipal Institute of Hygiene, where experiments were performed on animal, as well as in a patient with a psychiatric disorder.

Bacteriology in Peru was just consolidating by the time when the Harvard expedition arrived. Ricardo Flores donated a bacteriology laboratory to the Faculty of Medicine and gave a free course on microscopic and bacteriology techniques for a year; then the course was assigned to David Matto, who was the main scientific collaborator of Richard Strong upon his arrival in Peru.

The textual conclusions by Harvard were:

“From our research, we concluded that the eruptive Peruvian wart and the severe Oroya fever represent two different diseases; the first is caused by a virus, [...] while the latter is caused by a parasite organism located in the red blood cells [...]” (11, p5).

From a scientific point of view, there are four important facts in the report by the Harvard expedition:

1. It recognized the *B. baciliformis* as the etiologic agent of Oroya fever and its name was proposed in honor to Barton.
2. It wrongly raised the dualist theory, stating that the Oroya fever and the Peruvian wart were different diseases caused by different etiologic agents and ignoring the scientific conclusions of Carrion.
3. It acknowledged that bartonellosis by *B. baciliformis* begins in the endothelium; endothelial cells were named Strong cells for years after the expedition.
4. It carried out unethical human experimentation on a psychiatric patient.

Microbiological research on Peruvian wart was initiated by Vicente Izquierdo, Chilean, in 1885 (21); at the same time, a Peruvian medical student named Daniel Alcides Carrion, considering that a Chilean scientist was leading an investigation on this disease, decided to make a historic experiment with autoinoculation of secretions of Peruvian wart to further studies. The scientific interest that Carrion had was stimulated by a scientific nationalism since Peru had lost the war against Chile (22).

Harvard proposes the name of *Bartonella baciliformis*

Alberto Barton Thompson became a medical student at Universidad de San Marcos in 1894 and devoted his research to the microscopic observation of several samples of patients diagnosed with Peruvian wart since 1898. In 1899, he worked as a temporary intern at Hospital Italiano, where his main goal was to look for patients with suspected diagnosis of this disease in order to obtain blood samples and further research on his thesis project, which aimed to find the germ that killed Carrion (23,24).

Barton investigated and graduated as a doctor with the thesis “The pathogen of the Carrion disease” (25), study where a recurrent germ located in the spleens of five patients with severe Carrion fever was described; Barton was granted a scholarship and continued his studies in London due to his bacteriological findings. Meanwhile, in Lima, doctors Ugo Biffi, Manuel Tamayo and Julio César Gastiaburu reported that the germs found in his thesis were contaminating bacteria. Barton himself, after returning from Europe, acknowledged his mistake (26). Also by that time, Biffi observed the *B. bacilliformis*, but did not recognize it in the same the way as done with photomicrographs (26).

In 1905, after conducting graduate studies at the School of Tropical Medicine in London, Barton specialized in the study of

the Peruvian wart in the laboratory of Hospital Guadalupe del Callao. When evaluating the peripheral blood smears of two of his patients, structures that resembled bacilli in red blood cells drew his attention. In the meeting that commemorated Carrion’s sacrifice, held in October 5, 1905, the researcher released these findings on a preliminary basis; then, on January 15, 1909, he published his full work entitled “Description of endoglobular elements found in patients with wart disease” in *The Medical Chronicle* (27), although, few Peruvian scientists believed in his discovery after its publication. During the Fifth Latin American Medical Congress held in Lima days before the Harvard report, Ernesto Odriozola and Julian Arce did not mention the discovery of Barton in their lectures, the most anticipated of the event (16,27). Furthermore, Julian Arce, the main witness of the Carrion’s experiment, stated in this conference, in relation to the etiology of the Carrion’s disease, that “this is not a bacterium [...] we can say that is a protozoan” (17)

The Harvard expedition recognized the *B. baciliformis* and proposed the genus name in honor to Barton. In the Fifth Latin American Medical Congress, Barton was invited to present the details of his discovery (19).

Harvard’s dualist theory

Oroya fever and Peruvian wart are two different diseases

The Harvard commission conducted an experiment inoculating a wart exudate from the shoulder of a psychiatric patient; scientific findings included:

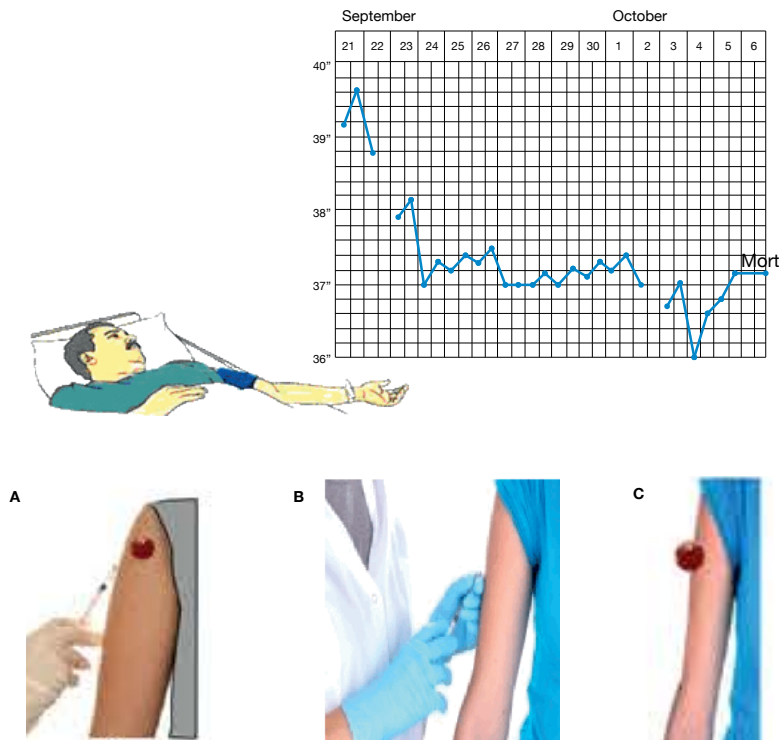
1. The patient did not reproduce Oroya fever, only the Peruvian wart.
2. No bacteria were found in histological sections of warts, and since warts resemble smallpox eruptions, a virus similar to this disease was proposed.

These two findings, along with the recognition of the *B. baciliformis* in the samples from patients with Oroya fever, caused the erroneous conclusion that the Peruvian wart and the Oroya fever were two different diseases caused by different germs: Peruvian wart was caused by a virus and Oroya fever by *B. baciliformis*; in this way, Harvard raised a dualist theory. The verbatim report of the findings of the commission stated:

“After studying these conditions in Perú, we conclude that the Peruvian wart and the Oroya fever are two different diseases. We have been able to show that the first is caused by a virus, and the second by an organism that parasitizes erythrocytes and endothelial cells” (12, p14).

Given the prestige of Harvard University, the erroneous conclusions of the committee were disclosed and reached medical texts worldwide; for example, the *Treaty of Tropical Diseases* by Manson, at the time, exposed the Oroya fever and the Peruvian wart in different chapters, while various journals indicated that the wart was caused by a virus. (28,29) (Figure 2).

The expedition erroneously concluded that the Oroya fever and the Peruvian wart were different diseases based only on experimental evidence without considering observational, clinical and epidemiological facts. This conclusion was wrong because science must seek as much evidence as possible on the causality of an infectious disease.



First finding:
 - *Bartonella bacilliformis* was isolated in patients with Oroya fever.
First conclusion:
 - Oroya fever is caused by *Bartonella bacilliformis*.

Second finding:
 - The Peruvian wart was experimentally reproduced.
 - Oroya fever, previous to the Peruvian wart, is not reproduced.
 - No *Bartonella bacilliformis* culture is achieved in the experimental wart.
Second conclusion:
 - Oroya fever and Peruvian wart are different diseases; the Peruvian wart is caused by a virus.

Figure 2. Harvard report. a) A wart tissue is removed from a patient. b) wart secretions are inoculated from a experimental wart in a psychiatric patient. c) the patient develops a wart experimentally. Source: Own elaboration based on the data obtained in the study.

The rejection of the Harvard dualist theory in Peru

The publication of the report by the Harvard commission was criticized in various publications and conferences by various Peruvian researchers like Alberto Barton, Julián Arce, Ernesto Odriozola, Raúl Rebagliati, Oswaldo Herculles, Carlos Monge, among others. (29-33). Oswaldo Herculles, regarding the Harvard report, stated:

“The American Commission of the Harvard School, headed by Dr. Strong, designated the disease with the name of *Bartonella bacilliforme*, but this same commission made a mistake, [...] by concluding that the Peruvian doctors were making a mistake and that these were two different diseases [...] consequently, the clinical interpretation of all Peruvian doctors had been wrong for many years, which brought serious moral damage, as it was the equivalent to declaring to the world that the sacrifice of Daniel Alcides Carrión had been completely useless” (30, p240).

Odriozola proclaimed the unity of Oroya fever and Peruvian wart based on clinical and epidemiology data and describes that there are countless cases of Oroya fever during which wart rash appears; among these, several cases of patients who traveled to Europe and developed the wart stage on the continent were found (32). Carlos Monge Medrano, recognized for his studies in heights, also conducted a productive scientific work on this disease; at the School of Tropical Medicine in London, he studied and noted that the mistakes of the Harvard expedition were the consequence of its short stay in Peru (three months) and, therefore, its conclusions were premature (33) (Figure 3).

In 1926, Noguchi *et al.* (34) cultured and conducted serological cross-germs tests isolated from Oroya fever and Peruvian wart; these tests resulted in both diseases being caused by a single etiologic agent: *B. bacilliformis* (34). The Harvard University conducted a

second expedition confirming the findings of Noguchi (35-36) and concluding the following:

“The *Bartonella* culture in both forms of the disease confirms the idea that the Peruvian wart and the severe Carrion fever are produced by the same microorganism.

[...] Hopefully our studies will serve to correlate and complete the important work done by Peruvians and other researchers on this disease” (35, p41).

Even after the bacteriological demonstration of the unicist theory by Noguchi, French scientists at the Pasteur Institute (37) interpreted wrongly Noguchi's findings when two seeds were observed in photomicrographs and tried to revive the dualist theory, postulating again that different germs caused Oroya Fever and Peruvian wart; the main exponent of this position was the scientist André Lwoff, head of the laboratory at the Pasteur Institute and member of the French Society of Exotic Pathology.

Lwoff, Nobel Prize of Medicine in 1965 for his scientific contributions in microbiology (38), ignored the findings of the medical student Daniel Alcides Carrión and the Peruvian Medical School and persisted in the theory that the Oroya fever and the Peruvian wart were two different diseases. The main advocate of the unicist theory, before French scientists, was the Peruvian doctor Ramon Ribeyro. The Peruvian National Academy of Medicine, in response, issued a joint statement defending and consolidating the unicist theory to date (39).

The contrast between the two theories caused a broad scientific discussion between the Harvard University and the Peruvian Medical School and several hypotheses were proposed: on the one hand, the mistaken dualistic theory of Harvard (Figure 3), which stated that the Peruvian wart and the Oroya fever were two different

infections; on the other, the theory that stated that Oroya fever was caused by *B. bacilliformis* and the Peruvian wart by a virus, and finally, the defense of the unicist theory (Figure 5), whose validity was demonstrated through subsequent bacteriological research.

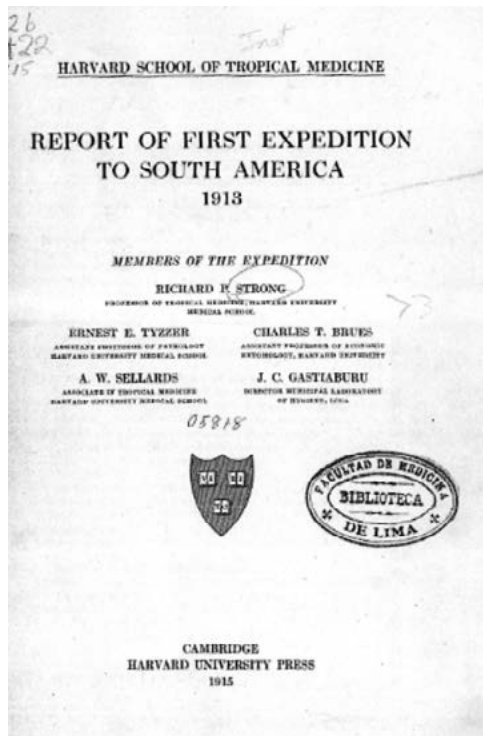


Figure 3. Scientific debate between the Harvard University and the Peruvian Medical School. Dualist theory. Source: (12).

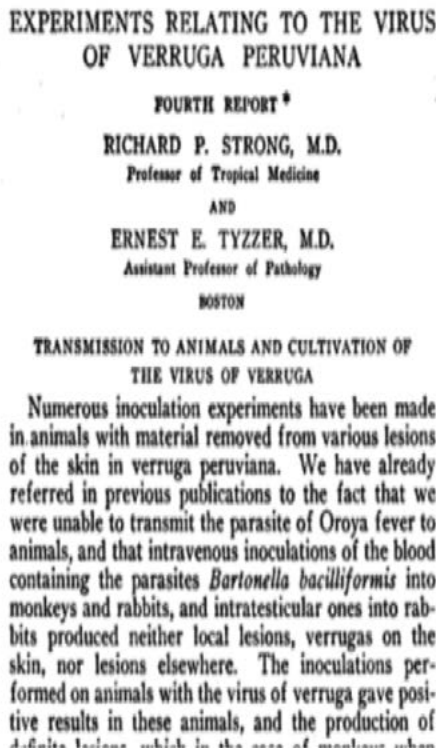


Figure 4. Scientific debate between the Harvard University and the Peruvian Medical School. Different causes of Oroya fever and Peruvian wart. Source: (28).

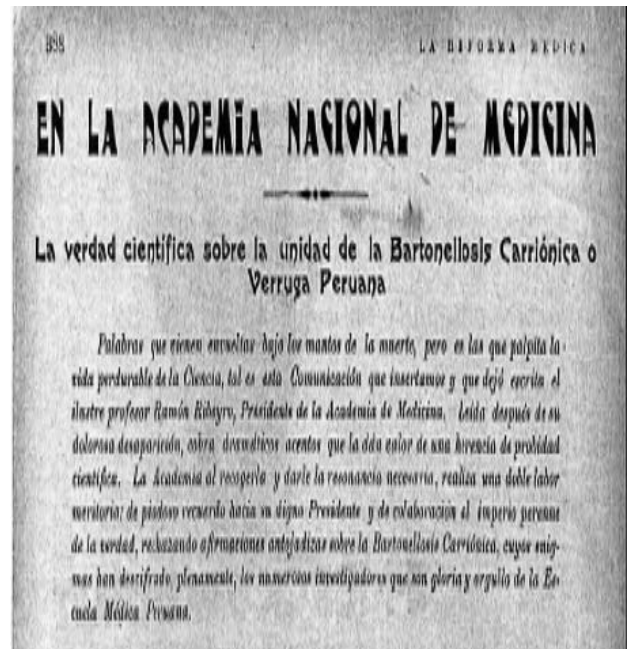


Figure 5. Scientific debate between Harvard University and the Peruvian Medical School. Unicist theory. Source: (39).

Strong cells

The Harvard committee identified only one case of an endothelial cell with abundant *B. bacilliformis*; despite this being an isolated case, that the parasitized cells were the histobacteriological feature of Carrion’s disease was declared. 14 years later, Aldana (40), based on findings from autopsies of patients with Carrion’s disease, acknowledged the findings of Harvard and proposed the name Strong cells.

The probable vector of Carrion’s disease, the *Lutzomyia verrucarrum* mosquito, inoculates the Bartonella with its sting in the endothelial cells of capillaries (Strong cells), which then release bartonellae in the blood “parasitizing” red blood cells; this stimulates macrophages and produces erythrophagocytosis and severe anemia.

The unethical human experimentation conducted by Harvard in Peru

Regarding human experimentation by the Harvard expedition in Peru, the report by Strong *et al.* argues that:

“Inoculation was performed in a man with a warty product of two types of wart [...] 16 days later, on the site of scarification, two small groups of cherry-colored papules appeared. These small tumors gradually grew and were cut at 35 days, two of them to be studied [...]”

¹ This inoculation was practiced on an insane and Dr. David Matto, director of Manicomio del Cercado and vice-president of the Fifth Latin American Medical Congress, was aware of it” (11, p10).

In the English version of the publication (12), the Harvard Commission changed the report and stated that the patient who was inoculated was a Chilean volunteer (4). Ironically, in the same Fifth Latin American Medical Congress, where Harvard confirmed the dualist theory based on human experimentation in a psychiatric

patient, the first motion of the members of Congress was to improve the health of psychiatric patients (20).

Lessons for science

A retrospective view of what happened with the Harvard expedition in Peru leads to reflect and draw three lessons related to U.S. ethics on human experimentation, with the causality of an infectious agent and scientific ethnocentrism:

U.S. ethics on human experimentation in Latin America

For years the Peruvian Medical School criticized Strong for ignoring Carrion's finding, the unicist theory, however, there is no documentation of disapproval against his unethical experiment on a psychiatric patient.

It is important to note that this procedure involved Dr. David Matto, a health authority who, taking advantage of his position as director of the mental hospital, allowed the experiment when he should have been the first to prevent or condemn it.

Strong was recognized for his work and was elected president of the American Society of Tropical Medicine, which publishes one of the most important journals worldwide to date: *The American Journal of Tropical Medicine and Hygiene*. It is noteworthy that this society was granted a palladium medal and a prize of thousands of dollars for the research conducted in honor to Strong (41,42).

Although American biographies describe him as a good Samaritan (41) and a friendly person (43), according to his team, Strong should have been given the nicknames "tourniquet" and "autopsy" (8); the American Society of Tropical Medicine created a medal of honor with his name and today, it is the symbol of American tropical medicine (Figure 6).



Figure 6. Richard Strong: scientific awards at the expense of unethical human experiments. Source: (44).

The scientific evidence on the causality of infectious diseases

The scientific evidence regarding the cause of infections is experimental and observational. Observational evidence does not determine causality, that is, an association between a particular infection and a particular infectious agent does not mean that the agent causes the disease.

In research on the Peruvian wart, the Harvard expedition, which traveled to Peru, and the scientists from the Pasteur Institute, determined the causation of this disease based on experimental evidence, ignoring the correlative clinical and epidemiological evidence previously obtained in Peru, which described several patients with Peruvian wart developing Oroya fever after its onset; this was a historical mistake. Critics by the Peruvian Medical School to the biased conclusions of Harvard and the Pasteur Institute, based only on experimental evidence, were not unfounded; Robert Koch himself recommended that, regarding the causality of infection, postulates should not be adopted rigidly, and that other aspects should also be considered.

Several scientific researchers say that there was a delay the studies of infectious diseases because of the adherence to Koch's postulates, which did not allow the identification of many infections. Science needs to base its findings on the best evidence and reasoning available (45,46).

Quality science can be generated in developing countries

Scientific ethnocentrism states that the ethnic group is superior and the most relevant. Although this ideology is based on the prejudices of

developed countries (47,48), it is reinforced by the very underestimation of developing countries; this is known as inverted ethnocentrism and makes reference to local scientists who consider that they cannot achieve relevant scientific research because of the little advanced technology found in their countries (49).

Ethnocentrism can be fought by acknowledging that science can be developed in any country, culture or civilization; thus, it is necessary that medical students from developing countries know, objectively, scientific advances made in their countries, such as the one achieved by the Peruvian medical school with the unicist theory of Carrion's disease (50).

Conclusions

More than 100 years ago a Harvard expedition went to Peru to investigate Carrion's disease; although the expedition made a historical recognition of Barton's bacteriological findings by naming the bacteria *B. bacilliformis* in his honor and by recognizing the role of endothelium in the onset of Carrion's disease, it also conducted unethical human experimentation practices on a psychiatric patient. In parallel, the findings of the expedition revealed the limitations of science to explain the causality of an infectious agent and the need to consider all the scientific evidence when building a scientific theory.

Conflict of interests

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