

# Daniel Carrion's experiment: the use of self-infection in the advance of medicine

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**ABSTRACT** In 1885, Daniel Carrion (1857–1885), a young Peruvian medical student, was trying to establish the prodromal symptoms of 'verruca disease', an infectious disease rare outside South America but endemic in parts of Peru. As part of this investigation he was inoculated with fluid from a verruca lesion from a patient with the chronic form of the disease. He recorded the clinical features which developed, including fever, malaise, arthralgia, vomiting and anaemia, and it became apparent that he had developed the anaemic, febrile, acute phase of the illness (known as Oroya fever). This did not however progress in his case to the chronic form of the disease, and he died a few weeks later on 5 October 1885. His sacrifice served to establish, supposedly, that Oroya fever and verruca disease had a common aetiology and his death stimulated further research into the cause, now established as the bacterium *Bartonella bacilliformis*. Carrion is considered a martyr of Peruvian medicine and 5 October has been designated Peruvian Medicine Day in his honour.

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## INTRODUCTION

Human bartonellosis, widely known as Carrion's disease, is unusual in several respects. It is produced by a rare gram-negative bacteria, *Bartonella bacilliformis*, transmitted by a phlebotomine sandfly, mainly *Lutzomyia verrucarum*, with man as the only known reservoir. The disease is largely confined to valleys and ravines of the Andes and higher jungles of Peru, between 500 and 3,200 metres above sea level. In recent years it has been found in coastal regions and has also been described in certain regions of Ecuador and Colombia. The illness has a biphasic clinical course. The first stage, the acute or anaemic febrile phase, occurs after an incubation period averaging two weeks. Features of the acute phase include fever, malaise and a rapid onset of haemolytic anaemia and this phase can prove fatal. Those who survive the acute phase may go on to develop a chronic or verrucose phase of the illness, which occurs after an asymptomatic period of some weeks (the intercalary period) and is characterised by the appearance of angiomatic skin lesions known as verrugas. These lesions disappear after several weeks. The accompanying immunodeficiency may result in superinfections such as salmonellosis or opportunistic infections like toxoplasmosis. The biphasic clinical picture of human bartonellosis has been emphasised in order to explain the natural history of the disease. The anaemic, febrile, acute phase correlates with bacteraemia (with bartonella organisms inside the red blood cells). The verrucose phase is characterised by the appearance of angioma-like skin lesions (Figure 1), which



**FIGURE 1** Millitary type skin lesions of verruga peruana. (Image courtesy of Dr Ciro Maguiña)

are due to endothelial cell proliferation. These are caused by angiogenic factors,<sup>1-2</sup> similar to those seen in bacillary angiomatosis and peliosis due to *B. henselae* and *B. quintana*.<sup>3</sup> These skin lesions can be of varying sizes including miliary and nodular. The severity of the disease depends on the state of the individual's immune system. It tends to be mild in native Peruvians, exposed to repeated mosquito stings in childhood, and severe in foreigners. This disease became treatable with the advent of antibiotics and rare from the 1970s onwards as a result of the widespread use of fumigation as part of a national programme for the eradication of malaria. At present, the acute phase is treated with beta-lactam antibiotics or ciprofloxacin, together with support measures such as hydration, blood transfusions, steroids and treatment of the concomitant infections. The verrucose phase is treated with antimicrobials such as rifampin or azithromycin. The reported annual incidence of the disease in Peru has fallen in recent years from 11,127 cases in 2004 to 741 in 2009. Currently the mortality rate for acute cases is less than 5% but it remains 40% to 90% in untreated cases.<sup>4</sup>

## OROYA FEVER APPEARS

In 1870 construction began on the Central Railroad from Lima to La Oroya, a mining town 3,750 m above sea level, in the mid-Andean region of Peru. The majority of railway workers were foreigners, or from the coastal region, while others were Chilean and North-American workers who came with Henry Meiggs, an American engineer hired by the Peruvian Government to oversee the construction. In the early phases of the project the most common illnesses to affect the workers were diarrhoea and malaria, the latter readily treated with quinine. But, at altitudes higher than 500 metres, a rare fever appeared which did not respond to quinine and which carried a high mortality rate. The population of Lima became concerned that this rare disease might reach the capital. Despite widespread consultation and discussion, doctors had little idea about the origin and aetiology of the disease. At that time, the miasma theory was still prevalent in Western medicine. A Venezuelan doctor, Ricardo Espinal, who lived in Lima, reported an unusual variant of the illness. One of his patients, an American engineer named Wilson, developed the febrile, acute disease and, after recovering and returning to the United States of America, sent a letter reporting that he had developed multiple verrucose skin lesions. Espinal duly reported this to the Medical Society of Lima.<sup>5</sup> By 1872 most, but not all, doctors agreed that this new and rare disease had two phases: febrile and verrucose. The fever was called Oroya fever, an eponym from the fever of the workers on the railroad to La Oroya – this name proved paradoxical as no cases occurred in Oroya because of its altitude. When the 1870–1872 outbreak occurred Carrion was a schoolboy in his early teens and lived too far from the outbreak area to have had any knowledge of Oroya fever.

## DANIEL CARRION'S EARLY YEARS

One hundred and twenty-six years after his death, Daniel Carrion remains the most important personality in Peruvian medicine. In 1991 the Peruvian government officially declared him a national hero. Many papers and books have been written about his experience and the importance of his legacy. Yet Peruvian historians remain divided about Carrion. The majority have exalted him as a martyr, hero and pioneer of research, while a minority have been critical.<sup>6-8</sup>

Daniel Carrion was born on 15 August 1857 in the former mining city of Cerro de Pasco, in the central Andean region of Peru, 4,340 m above sea level. His father was the Ecuadorian doctor Baltazar Carrion, who had been deported from his native country on political grounds, but confined by the Peruvian government to Cerro de Pasco. His mother, Dolores Garcia was Peruvian. Carrion went to Lima to continue his high school studies at the Guadalupe School, the most respected school in the capital at that time. During 1877 and 1878 he studied at the Faculty of Sciences of San Marcos University. The following year he tried to enter the Faculty of Medicine, but failed the entrance examination and had to continue studying sciences for a further year, before he was able to begin medical studies in 1880.

On 5 April 1879, Chile declared war against Peru and Bolivia, in what became known as the Saltpetre War. As Chilean troops advanced into Peruvian territory, all social, economic and educational activities were affected. By January 1881 the Chilean army had occupied Lima, but the University authorities decided to continue medical teaching despite looting of university facilities and damage to libraries and laboratories by the occupying army. The Chilean troops left Peru at the end of 1883 after a peace treaty was signed. General Miguel Iglesias, who had signed that treaty, assumed the Presidency of Peru but was opposed by an army leader, General Andres Caceres, because the treaty meant Peru would lose three provinces. So the Saltpetre War was followed by a civil war in Peru which continued to disrupt virtually all national activities.

In 1885, Carrion began his internship in San Bartolome Hospital and he soon developed an interest in patients with verruga disease. By visiting the nearby Dos de Mayo Hospital, he was soon able to collect case records of nine patients with the condition. He thought that this might form the subject for his doctoral thesis, as patients with the acute phase of the disease were very rare in hospitals in Lima. This was because the journey from areas where the disease was endemic meant travelling long distances over many days, so that patients were usually over the illness or dead by the time they reached Lima.

Carrion's early interest in verruga disease was marked by his first publication. With two colleagues, he described collecting urine from verrucous patients and submitting these for chemical analysis by Sebastian Barranca, a professor in the Engineering School.<sup>9</sup> Thus by 1885 Carrion had personally amassed a large amount of data about verruga disease from the cases he saw in the two hospitals, from cases notified to him by his teachers and from reading information about the disease published in the medical journal *La Gaceta Médica* many years before.<sup>10</sup>

The Free Academy of Medicine was established on 29 July 1885 to provide, among other things, a forum to discuss the country's health problems. The Academy set out a series of scientific medical objectives, one of which was to establish a competition for the best work on the aetiology and pathology of verruga disease, the winner of which was to receive a diploma and gold medal.<sup>11–13</sup>

At that time, the main public health problem in Peru was yellow fever, but the movement to promote research into verruga disease had aroused the interest of some foreign researchers. These included the Chilean histologist Vicente Izquierdo, who had published a paper describing the histopathologic characteristics of verruga and claimed to have found bacteria in some alcohol-immersed verrugas that were sent to him.<sup>14</sup> Within a small medical community it is likely that everyone, including Carrion, was aware of this work. It is not clear if this was the trigger for his decision to inoculate himself with material from verruga lesions, or whether he was motivated by the competition. He was not able to carry out personal research in microbiology and pathology because these disciplines were not practised locally but only known through translated European (mainly French) papers published in the local medical journals.<sup>15–19</sup>

## CARRION'S EXPERIMENT

On 27 August 1885 Carrion went to the Dos de Mayo Hospital, having decided to inoculate himself. He was met by his colleague, fellow intern Julián Arce, and by the Chief of Service, Dr Leonardo Villar. It appears that he had previously announced his intention and that this had been accepted since no objection was raised. Carrion inoculated himself with the extracted serum from a young patient's facial verruga, with the help of Dr Evaristo Chavez, a medical assistant. The only written documentation about the inoculation was a brief report published in *El Monitor Médico* and no other comment was made by local doctors.

Carrion performed his experiment to establish the prodromal features of verruga disease and in order to achieve this it was necessary to forgo any treatment. This concept is essential to understanding his behaviour. His motive was confirmed later by the eyewitnesses to the experiment, Julián Arce and Leonardo Villar; Carrion

declared it and it was registered later by Casimiro Medina and the other five colleagues who attended him. As a result it was published in the newspaper *El Comercio* after Carrion's death.<sup>20</sup>

Little is known of Carrion's progress in the early days after inoculation. On day 20, 17 September, he developed arthralgia in his left ankle and malaise. This was followed in the ensuing days by fever, headache, anorexia, polydipsia and insomnia. He went on to develop generalised arthralgia and persistent tachycardia. His colleagues, who were recording these clinical features, noted that he was mildly jaundiced. Carrion believed that he was suffering the early features of verruga disease and was convinced that when the verrugas appeared, recovery from the acute phase of the disease would follow. He went on to develop diarrhoea, and was visited by one of his teachers, Dr Jose Maria Romero, who prescribed quinine in the unlikely event that he was suffering from malaria. The symptoms worsened with limb cramps, abdominal pain, nausea and vomiting. By 2 October, he had become wasted and dehydrated. Despite the papers from France (reproduced in local journals) describing recent discoveries on the infectious origin of many diseases, at no time was an infectious cause for Carrion's illness considered or recorded.

Carrion was now attended by a medical board composed of doctors Leonardo Villar, Jose Mariano Macedo and Evaristo Chavez who prescribed chlorate of potassium, iron and a hydrochloric acid solution and oxygen. They had his room sprayed with phenol, an antiseptic. When a bladder catheter was passed only 4–5 ml of urine was obtained. As the illness worsened he began to develop amnesia and psychomotor agitation. On 3 October, he was visited by Dr Ricardo Flores, who found him to be grossly anaemic and recommended that Carrion should move to hospital and undergo blood transfusion. On 4 October, Carrion was transferred to the French Hospital or Maison de Santé Clinic where he was again visited by the medical board. The transfusion was postponed and he died on 5 October. Carrion never thought that he would die as a result of the experiment, and the letters he wrote before his death show that he was making plans for the future.

## CONSEQUENCES OF CARRION'S DEATH

Carrion's death was widely covered in local newspapers the following day. Some of the teachers in the Faculty of Medicine criticised Carrion's doctors (who belonged to the opposing political party, the Civilian Party) for allowing the experiment, and went on to accuse them of murder. At this stage the local police investigating his death had to determine if it resulted from suicide or homicide. The ad hoc committee that attended Carrion's autopsy, carried out on 7 October reported marked pallor; decreased body fat, hepatomegaly, mesenteric lymphadenopathy and a small-volume spleen. They

concluded that Carrion died of the febrile phase of verruga disease and that Dr Evaristo Chavez was guilty of malpractice but not malice. Carrion was buried that afternoon in the General Cemetery. Dr Chavez was tried and acquitted two months later.

An anonymous editorial in the local journal *El Monitor Médico* criticised those involved in the Carrion experiment on the grounds that no prior physiological experiments had been performed and the advice of their teachers had not been sought.<sup>21</sup> However, it was acknowledged that the experiment had demonstrated transmission of the illness by inoculation and that verruga disease and Oroya fever shared a common aetiology, confirming the hypothesis which had first been suggested in 1875.<sup>22</sup> But the conflict between the two groups of medical school professors continued. The lay press brought a new dimension to the debate by describing Carrion's death as a sacrifice. Carrion soon came to be regarded as a martyr and was compared to famous medical researchers such as Jenner, Pasteur and Koch.

### THE LEGACY OF THE EXPERIMENT

It is important to appreciate the historical background against which the Carrion experiment took place. Peru had begun a slow and painful reconstruction after losing the war against Chile and suffering the ravages of the subsequent civil war. In a country desperate to compensate for what was seen as national social, economic and moral disgrace, Carrion's sacrifice served as a focus, a heroic act binding together Peruvian society. Carrion's image was quickly changed from Mestizo to Caucasian in a local medical journal. 'He was frenchified' said the historian Uriel Garcia.<sup>6</sup> Rather than a deliberate attempt to disguise Carrion's Mestizo physical appearance, this change of image probably arose from the wish to idealise Carrion as a European figure in a society culturally subservient to Europe at that time. The bronze busts of Carrion sculpted at the time do not look like the young and fragile Mestizo we know from his photographs (Figure 2).

A major question that remains about the Carrion experiment is what caused his death. He developed a fever that lasted for five days followed by the clinical features described above. Typhoid fever, malaria, viral hepatitis and other febrile illnesses have all been suggested as possible causes. Yet none of these resembles Carrion's clinical picture. Malaria is unlikely as he received quinine without any benefit. The fact that he quickly developed anaemia and jaundice suggests the possibility of an acute haemolytic anaemia. The febrile phase of verruga disease or Oroya fever remains the most plausible theory – or does it? Carrion's experiment was repeated many times in animals and by different researchers. The result was that inoculation from a verruga donor, animal or human, to a recipient, animal or

human, always produced just verrugas, but no recipient developed the acute febrile phase of the disease.

Richard Strong of the Department of Tropical Medicine at Harvard University came to Lima in 1918 leading the first scientific expedition to South America. When he inoculated fluid from verrugas into animals and humans, verruga development was the inevitable result. On this basis he concluded that verruga disease and Oroya fever were two different diseases.<sup>23</sup> This work stimulated Peruvian investigators to undertake further research in order to demonstrate beyond doubt that verruga disease and Oroya fever were distinct phases of a single disease. They concluded that only splenectomised monkeys develop an acute febrile illness following inoculation of verrugas.

So what produced Carrion's anaemia? Was it another form of haemolytic anaemia or did he develop an unrelated autoimmune haemolytic anaemia after the inoculation? Did he have a form of immunodeficiency? We know that a small spleen was present at autopsy, and it is possible that he suffered from functional hyposplenism. We shall probably never know for sure. Carrion latterly showed signs of malnutrition and dehydration and developed sepsis and almost certainly multiple organ failure. The medical management at that time offered little or nothing in the way of treatment. This was the pre-antibiotic era and the management of dehydration and electrolytes disorders was, by modern



**FIGURE 2** Daniel Alcides Carrion (1857–1885). Photograph taken in the Courret Brothers' studio.

standards, primitive. Even the much vaunted blood transfusion would have been hazardous in the era before the discovery of blood groups.

## AN ANIMAL MODEL?

Carrion could have opted for an animal experimental model. Twenty years earlier, in 1865, Claude Bernard published *An Introduction to the Study of Experimental Medicine*, where he established the principles of experimentation and medical scientific research using animals.<sup>24</sup> Moreover, the local medical journals *La Crónica Médica* and *El Monitor Médico* reproduced European, particularly French, papers and articles, many of which related to animal experimentation. A pioneer medical experiment on animals was carried out in Lima, and was published just prior to Carrion's inoculation.<sup>25,26</sup> So we must assume that Carrion knew about animal experimental method and chose not to practice it. Animals after all were not going to tell him about the prodromal features of verruga disease in man.

## SELF-EXPERIMENTATION

Was Carrion right to undertake this experiment? We believe that he was. This was, after all, the era when autoinoculation was commonly undertaken in order to discover the manifestations of an unknown disease. There are many examples in medical history, before and after Carrion, of medical researchers performing self-inoculation, injection and ingestion. Dr Villar cited a long list of famous inoculations in his letter attempting to justify Carrion's fatal experiment. These included Dr Caré who, six months earlier, had self-injected blood from a patient with osteomyelitis, survived and was hailed in the French Congress of Surgery. In the years after Carrion, Jesse Williams Lazear, a physician and member of Dr Walter Reed's Commission, allowed himself to be bitten by a mosquito in his quest to learn about the transmission of yellow fever. He died from the disease in 1900 and is considered by many to be a martyr of American medicine. Dr Jonas Salk inoculated himself with his polio vaccine and won a Nobel prize for medicine for its development. In more recent times Dr Barry Marshall ingested a culture of the organism *H.*

*pylori* in his attempt to find the cause of gastritis and peptic ulceration. He developed the condition but survived and he too was rewarded with a Nobel prize for medicine.

Carrion's self-experimentation served to confirm the unitary theory: both the anemic febrile disease (Oroya fever) and verruga disease were in fact part of one disease, which became known as Carrion's disease.<sup>27</sup>

## EPILOGUE

The legacy of Daniel Carrion remains with us today. Research continues into this interesting disease which eponymously bears his name. In recent years, there have been remarkable discoveries about the genus *Bartonella*, now totalling more than 20 species, of which at least seven produce disease in humans. They are responsible for conditions including human bartonellosis or Carrion's disease, trench fever, endocarditis, bacillary angiomatosis, peliosis hepatis and cat scratch disease. Infections caused by *B. quintana* and *B. henselae* occur particularly in association with HIV/AIDS. Current studies are at the molecular level and these have now tended to displace clinical research into the disease. The most recent advances have come from North American and European laboratories, where the diverse species of the genus *Bartonella* are being studied. The great genetic variation that *B. bacilliformis* has shown is probably related to the co-existence of more sub-species.<sup>28</sup> A new species, with the proposed name *B. rochalimae* causes a clinical picture that resembles Oroya fever.<sup>29</sup>

Like many other exponents of the heroic or romantic medicine of the late nineteenth century, Carrion chose, as he said, the quickest way to discover the prodromal symptoms of verruga disease. Carrion had the courage of his convictions. He lost his life but achieved posthumous fame and glory. It is worth bearing in mind that he was an idealistic young medical student worried about a common local disease and that he died in his quest for a better understanding of that disease. In this context his status as a martyr of Peruvian medicine, and indeed of world medicine, becomes easier to understand.

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