CHAPTER III

# Bartonellosis

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Bartonellosis is a specific infectious disease, at times fatal, caused by *Bartonella bacilliformis* and transmitted by the bite of *Phlebotomus*. The disease is limited to certain parts of Peru, Ecuador, and Colombia. The disease was not a military problem in World War II. American troops stationed in Peru (Talara) and Ecuador (Salinas) were outside the endemic areas. However, since some of the experimental work on protective measures and control of sandflies and sandflyborne diseases was done in the Peruvian verruga zone, an account of the disease and its setting may be appropriately included in this history.

## HISTORICAL NOTE

Bartonellosis sprang into prominence in the 1870's when the railroad from Lima to Oroya was being built.[1] After the construction reached elevations above 1,000 meters and 45 or 50 kilometers inland from Lima, there were a great many fatal cases of what was apparently a new disease. Of some 7,000 deaths among the workmen, from all causes, the majority were thought to be from the new disease, which received its name, Oroya fever, from the railroad's projected terminus. There began a controversy in medical circles as to whether or not Oroya fever had any relation to the well-known verruga, a relatively mild eruptive disease endemic in the same region. The name Carrión's disease, applied to both types, was derived from the classic experiment of Carrión, a medical student, who in 1885 inoculated himself from an eruptive case and died apparently with the anemic form of the disease. The controversy was finally settled only with the cultivation of the etiologic agent by Noguchi and Battistini,[2] in 1926, which provided the clinching evidence that the two chief clinical syndromes, which differ so remarkably, are actually manifestations of one and the same disease.

## ANEMIC AND ERUPTIVE FORMS OF BARTONELLOSIS

### Symptomatology

The anemic form of the disease (Oroya fever) has an incubation period of about 3 weeks. The onset, with irregular fever and general malaise, is followed

[1] For a historical summary see Hertig, M.: Phlebotomus and Carrión's Disease. Am. J. Trop. Med. 22 (Suppl.): 1–80, July 1942.

[2] Noguchi, H., and Battistini, T. S.: Etiology of Oroya Fever. I. Cultivation of *Bartonella bacilliformis*. J. Exper. Med. 43: 853–864, June 1926.

by a rapidly developing profound anemia, accompanied at times by pains in bones and joints.[3] The mortality of this form of the disease varies from 20 to 70 percent. During the anemic phase, the minute rodlike, coccoid, and filamentous forms of *B. bacilliformis* may be found, often in great numbers, in or on the red cells. If the patient survives, there usually follows, after a variable interval, the typical eruption.

The eruptive form (verruga peruana) usually has no marked anemic phase. This benign type of the disease includes by far the largest proportion of the total number of infections. The incubation period is variable and may be as much as a month or two. The onset is characterized by bone and joint pains, irregular fever, and malaise. Sooner or later, at times after months, during which there may have been remission of the symptoms, the eruption appears, with or without the initial symptoms. The eruption takes the form of hemangioma-like nodules, commonly from 2 to 3 mm. in diameter but varying from minute points to raised nodules of 10 or 20 mm. in diameter, which give the disease its name, verruga (Spanish for wart). The nodules are distributed chiefly on the extremities and face and vary in number from few to thousands. They are not painful. The eruption usually lasts a month or two and finally heals without leaving scars.

## Proportion of Severe Anemic to Eruptive Cases

The evidence is rather unsatisfactory as to the proportion of total infections which develop the severe anemia. It appears that it may vary in different places and at different times. In any case, the anemic form has been rare among natives of the verruga zone in Peru in recent years. Most of the anemic cases have been in adults, who, without previous exposure to the disease, were engaged in construction work, exploration, or guard duty. During the early history of the disease in Peru, the proportion of severe anemia and the mortality must have been very high, to judge from the great number of fatal cases that occurred during the railroad construction and from the separate accounts of 10 to 75 percent of the specific groups dying from the disease.[4] (The mortality in the Colombian epidemic (see p. 27) was also very high.) However, during the author's stay in Peru, 1937–42, the proportion of anemic cases was distinctly low. The author was able to follow more or less closely the fate of guards stationed at railroad bridges in the Rimac Valley verruga zone during the war.[5] About three-fourths of the nonimmune persons contracted the disease during a 1-month tour of duty. When the tour was extended, about nine-tenths acquired the infection within 4 months. About 150 men, immune and nonimmune, were involved, with about 100 cases among them, only 4 of which were fatal. During this same period before any control method was known, there were

[3] For a clinical account, see Strong, Richard P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. 7th edition. Philadelphia: The Blakiston Co., 1944, vol. II, pp. 997–1014.

[4] See footnote 3.

[5] Howe, C., and Hertig, M.: Prophylactic Immunization Against Carrión's Disease. J. Immunol. 47: 471–482, December 1943.

several large construction projects with many workmen, but there were only scattered cases of the severe anemic form.

### Vaccination

A detachment of 22 nonimmune bridge guards, not included in the aforementioned totals, was inoculated with formalized suspension of *B. bacilliformis*.[6] While slightly over one-half the guards became infected during the 7 months they were under observation, the clinical course was remarkably mild. It was concluded that vaccination might be of value in ameliorating the course of this potentially serious disease.

### Therapy

There is no specific therapy. In a recent visit to Peru, the author was informed that results with the newer antibiotics were conflicting. In the treatment of the severe anemic cases, massive blood transfusions have at times been valuable.[7]

### Immunity

The immunity from a single attack is considerable but not solid. Repeated attacks are known but usually run a mild clinical course. Natives of the verruga zone usually acquire the disease as mild childhood infections and in general do not regard the disease seriously. In certain surveys, about 10 percent of the local population have been shown to harbor *B. bacilliformis*, with or without a previous history of the disease.[8]

### Etiology

*B. bacilliformis*, of uncertain systematic position, is probably related to the bacteria. It is a minute, gram-negative micro-organism comparable in size and general appearance to the rickettsiae, with rodlike, coccoid, and filamentous forms. It is cultivable in Noguchi's semisolid medium and its later modifications. Subcultures, but not primary isolations, are successful on ordinary blood agar. The organism is at times motile by means of a terminal tuft of flagella. *Bartonella* may usually be recovered in culture from the blood at any stage of any clinical form of the disease and also from the nodules.

## EXPERIMENTAL INFECTIONS

Monkeys are the only animals known which can be readily infected. Intradermal injections of cultures or tissue from nodules give rise to typical nodules at the sites of inoculation, which, however, is ordinarily not the case with *Bartonella* from other sources, for reasons not understood. The inocula-

[6] See footnote 5, p. 24.

[7] Hodgson, C. H.: The Treatment of Carrión's Disease With Large Transfusions. Am. J. Trop. Med. 27: 69–72, January 1947.

[8] Weinman, D., and Pinkerton, H.: Carrión's Disease. IV. Natural Sources of *Bartonella* in the Endemic Zone. Proc. Soc. Exper. Biol. & Med. 37: 596–598, December 1937.

tion of blood or tissues from an anemic patient, or suspensions of sandflies, or infective bites of sandflies, produce infection in Rhesus monkeys, which is demonstrable by blood culture but without any external sign. The anemic form of the disease is extremely rare in experimental infections. A single specimen of field mouse has been found naturally infected, but attempts to infect this specimen and other rodents in the laboratory failed.[9]

## TRANSMISSION

For many years, it was thought that the disease came from drinking water of the endemic area, but with the realization about 1909 that the disease was contracted only at night, attention was immediately directed to insects as vectors. Townsend, in 1913, first discovered the presence of *Phlebotomus* in Peru and showed that the distribution of *Phlebotomus verrucarum* was correlated with that of the disease.[10] Noguchi [11] and his associates showed that sandflies of the verruga zone harbored the etiologic agent. The author [12] was able to transmit the infection to Rhesus monkeys by the bites of wild-caught *P. verrucarum*.

*P. verrucarum* is the principal and perhaps the sole vector. Only one other species, *Phlebotomus noguchi*, is found throughout the verruga zone, and it does not feed on man. *Phlebotomus peruensis* is limited to the upper half of the verruga zone, and *Warileya phlebotomanica*, a close relative of *Phlebotomus*, is rare.

There are still a number of unsolved phases of the transmission problem. The source of the sandfly infection is unknown. From the readiness with which the infection may be acquired in certain areas which are all but uninhabited the reservoir is probably other than man. There has been mentioned the instance of a naturally infected field mouse, but the failure to infect this and other animals leaves the question open. No cycle of development of *Bartonella* in the sandfly has been demonstrated. Certain massive infections of the tip of the proboscis with various micro-organisms of unknown origin may eventually be shown to have some bearing on the source of the *Bartonella* infection. The great majority of the proboscis infections are caused by a cultivable, unidentified micro-organism, but *B. bacilliformis* has been isolated twice in cultures from such infected proboscides.[13]

It may be remarked that in the Peruvian verruga zone cutaneous leishmaniasis also occurs, but its distribution by no means coincides with that of bartonellosis. It is limited to the upper part of the verruga zone, though it also occurs in other parts of Peru where there is neither verruga nor *P. verrucarum*, but where there are other species of *Phlebotomus*.

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[9] See footnote 1, p. 23.

[10] See footnote 1, p. 23.

[11] Noguchi, H., Shannon, R. C., Tilden, E. B., and Tyler, J. R.: Etiology of Oroya Fever, XIV. The Insect Vectors of Carrión's Disease. J. Exper. Med. 49:993-1108, June 1929.

[12] See footnote 1, p. 23.

[13] See footnote 1, p. 23.

The life history of *P. verrucarum* is essentially similar to that of *Phlebotomus papatasii*, described in chapter IX, p. 113. Breeding is continuous throughout the year and there is no diapause. (Bartonellosis is likewise contracted at any time of the year.) Breeding places are chiefly in rock crevices and under boulders or stone walls. The vegetation of the verruga zone is scanty, and there are few large trees. Diurnal shelters include the breeding places, together with caves and houses, which the sandflies enter freely. They are active from dusk to early morning, and only rarely do they bite by day.

The nocturnal habit of the sandfly has been taken advantage of in one very effective method of preventing the disease which has been practiced for 40 years by the Central Railroad of Peru. Construction crews are removed in special work-trains every afternoon to a town below the verruga zone and taken back in the morning.

## DISTRIBUTION

In Peru, the disease is limited chiefly to the Pacific slope of the Andes between 6° north and 13° south and at altitudes between 800 and 3,000 meters above sea level. The most intense foci and those which have been best studied are in the valley of the Rimac River and its tributary, the Santa Eulalia, and in the Callejon de Huaylas, a portion of the valley of the Santa River in the Department of Ancash. *P. verrucarum* is found throughout the Peruvian verruga zones, as far as studies have gone, and has not been found elsewhere in Peru or in other countries.

In Ecuador, bartonellosis has been reported from the Provinces of Loja and Oro. This author[14] cultivated *B. bacilliformis* from a blood specimen sent to Lima from the latter Province. There is very little recorded information about the incidence of the disease in Ecuador and none whatever about *Phlebotomus* in the endemic region.

Early in 1936, in Colombia in the Department of Nariño near the Ecuadorian border, an epidemic broke out which caused an estimated 4,000 deaths in a district with a population of 100,000. The disease was finally diagnosed as bartonellosis.[15] The severe anemic form apparently predominated. It was thought to be a newly introduced disease. The author visited this region in 1945.[16] By that time, the epidemic had apparently died out completely in those places where it had first appeared. The only known focus, which unfortunately could not be visited, was represented by a very few cases at the northern edge of the area which the disease had reached. Three years previously, sandflies, mostly *Phlebotomus colombianus* (a species very closely related to *P. verrucarum*), had been very abundant in several towns, as witnessed by collections, examined by this author, which had been made by Colombian investigators. In 1945, the author, in company with Colombians who had

[14] Hertig, M.: Cultivo de la *Bartonella bacilliformis* de un caso de verruga en El Ecuador. Bol. Ofic. San. Panamer. 19: 756–758, August 1940.

[15] Patiño, C. L.: Un nuevo foco de bartonellosis en América. Bol. Ofic. San. Panamer. 18: 305–313, 1939.

[16] Annual Report of The Gorgas Memorial Laboratory, 1945.

taken part in the previous studies, made collections in a number of the same places, during the same month of the year, and by the same methods (mostly with horses as bait)—sandflies were extremely scarce. Whereas in 1942, catches often consisted of a hundred or more sandflies, in 1945 only scattered specimens, often none at all, were obtained. Clearly something had happened to the sandflies. It is to be regretted that this epidemic, which bore every appearance of a new introduction, came and went without adequate entomologic studies throughout its course.

## PROTECTIVE AND CONTROL MEASURES

Studies on repellants and control with DDT were undertaken during the war by Dr. G. B. Fairchild and this author[17] in the Rimac Valley near Lima (fig. 1) and are summarized in chapter IX (p. 125). This area was chosen because sandflies attacking man were abundant in a region easily accessible and intimately known to the author. Many species of *Phlebotomus* are so similar in the essentials of their life history and in their flight and feeding habits, especially those species which enter houses and bite man, that it seemed likely that results obtained in control studies with one species might readily be applied to the control of other species. This has proved to be the case. Residual DDT has been shown to be extremely effective in the control of *Phlebotomus* wherever it has been tried.

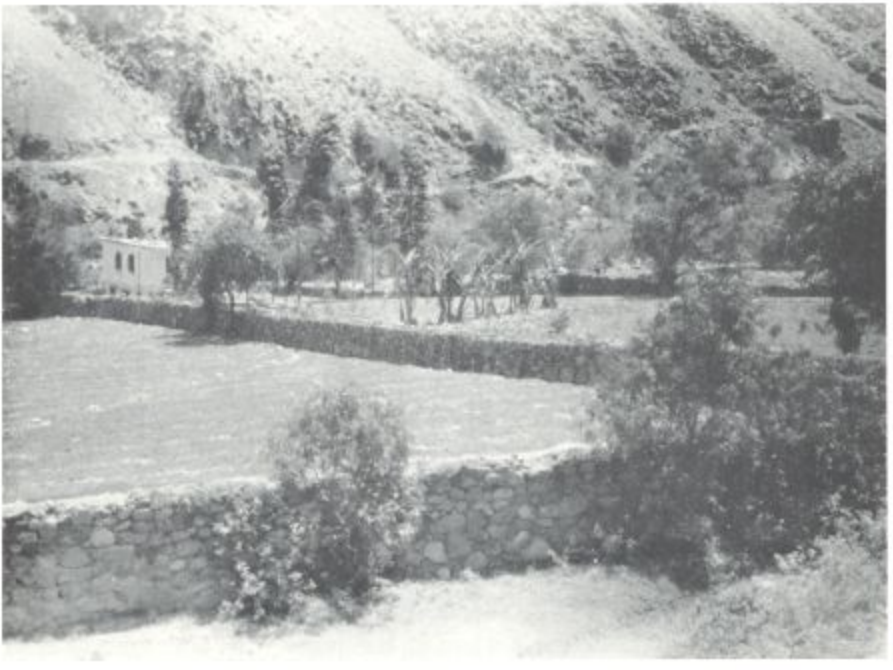

FIGURE 1.—Loose laid stone boundary walls, a frequent source of the *Phlebotomus*, in the vicinity of a dwelling.

[17] Hertig, M., and Fairchild, G. B.: The Control of *Phlebotomus* in Peru With DDT. Am. J. Trop. Med. 28: 207–230, March 1948.