PRESENT STATUS OF HUMAN BARTONELLOSIS

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INTRODUCTION

From 1936 to 1939 the government of Colombia had to face a disastrous and mysterious epidemic which appeared at the southern part of the Colombian Andes and killed over 5,000 people in a population of 150,000. Successively the disease was considered as acute pernicious malaria, typhoid, typhus, and brucellosis, without success in the corresponding methods of control, until in the middle of 1939 Patiño-Camargo, Professor of Tropical Medicine, found and revealed that the historical Carrion's disease, or Bartonellosis, was the real cause of the disaster. With this discovery and subsequent reports of the disease from the Ecuadorian Andes, it is no longer restricted to the Peruvian mountains, and it seems possible that it may be found in other territories where the tropics and the Andes present suitable conditions for its development. This fact justifies at least a short discussion of this entity on this occasion.

Human Bartonellosis is an infectious disease, exclusively American and exclusively tropical, of the most peculiar and constant epidemiology, and which manifests itself by fever and anemia or by a typical skin eruption, or by both manifestations combining or alternating. The etiologic agent is the *Bartonella bacilliformis*, a gram-negative, multiform micro-organism, which can be cultured in serum agar and is demonstrated to be pathogenic for man and *Macacus rhesus*. The Colombian strain is also pathogenic for the dog.

GEOGRAPHIC DISTRIBUTION: EPIDEMIOLOGY: TRANSMISSION

Three countries are at present affected by the disease: Peru, Ecuador and Colombia. The distribution follows the direction of the Andes Mountains between 2 degrees north latitude and 13 degrees south latitude, and at altitudes between 500 and 3,000 meters (1,666 and 10,000 feet). In Colombia it is found only between 1,300 and 1,850 meters (4,330 to 6,160 feet).

The distribution strictly corresponds to a unique geologic system determined by the "Andes cordillera." In Peru three ranges of mountains run from south to north. Two of these pass through Ecuador and all converge at the south of Colombia in a tangling and solid knot from which three Colombian and diverging branches emerge again. Enormous and abrupt mountains descend laterally from the main ranges, making deep and narrow ravines and defiles, in the depths of which streams and small rivers run their course toward the ocean or the large interandean rivers. Such a topography produces special conditions of temperature. While high at the top, there is a permanent cold; in the depths the heat from the sun is violently felt during the day since there are no winds, no ventilation, and the air is not changed. At night, however, the cold replaces completely the heat of the day for the same reasons of narrowness and enclosure, and humidity from

the running streams and abundant rains is added to the atmosphere. In the clefts water deposits are formed and many mosquitoes have their breeding places there. The environment has in this way a tropical condition. The natives live humbly and poorly, and their homes, made of adobe or canne and straw, give appropriate breeding places to the blood-sucking *Phlebotomus*, found to be the main vector of the disease.

In this way a topographic systematization closely related to the oro-hydrography explains the epidemiology of the disease. Here Bartonellosis is sustained due to special reasons: the *Phlebotomus*, not fond of the extreme heat, shelters itself during the day in the crevices and cracks of the badly constructed houses and of the heavy rocks, and stimulated at night by the humidity, darkness and cold, comes out and repeatedly bites the sleeping persons. Thus the infection in the houses of the natives is acquired while sleeping.

In Peru, the *Phlebotomus verrucarum* is the principal agent in the transmission of Bartonellosis, and second comes the *Phlebotomus noguchi*.

In the Colombian focus, several Phlebotomi have been found: *Phlebotomus panamensis*, *Ph. squamiventris*, *Ph. longipalpis*, *Ph. evansi*, *Ph. colombianus*, *Ph. monticulus*, variety *incarum*, and *Ph. osornoi*.

No one knows which of these is the main vector. The fact that the population of the affected zone are heavily infected by ticks and human lice, and the fact that the infection is acquired at night in the huts of the natives, have made Dr. Patiño-Camargo suspect strongly those other two arthropods as vectors of the disease, but proof is still lacking. However, the original theory corresponds more closely to the habits of the blood-sicking Phlebotomi as explained before, and furthermore, the distribution of the Phlebotomi and the area of the disease coincide to a great extent.

In Peru no other hematophagous arthropod has been found carrying the Bartonella and only experimentally is the *Dermacentor andersoni* able to transmit the infection to the Macacus monkey. On the other hand, *Bartonella bacilliformis* has been recovered and cultivated from the sandflies, monkeys have been infected by exposure to the wild sandflies, and the closest correlation exists between the distribution and habits of the Phlebotomus and the epidemiology of the Verruga (the other name of the same disease).

There are some facts in the epidemiology which are still unexplained. Marshall Hertig found the occurrence of infection in the proboscis, not only of fed female Phlebotomi, but also in males which do not suck blood, and in females which still have not had a blood meal. He feels it is doubtful whether all those microorganisms are Bartonella since his cultures from the proboscis were not unmistakably of Bartonella except in three instances. The data are thus far insufficient to make clear the extent to which the Bartonella enter into such infections of the proboscis and whether or not they represent the mechanism of transmission of Carrion's disease. In case they do, there should be a source of infection outside of human beings and animals, perhaps in certain of the plants which make up part of the regional flora. This has been proved by the finding of Bartonella-like

elements in the latex of the regional *Euforbiaceae* which can be cultured and made to produce warts in chickens by inoculation.

RESERVOIRS

(a) If the foregoing suspicion is verified, one of the principal reservoirs of the infection would be in the vegetable kingdom and this would correspond to the most striking manifestation of parasitic development and of marked adaptability to such different hosts.

(b) Another important, and in this case proved reservoir, is the infected man, either with apparent or unapparent infection. From one unselected sample of the healthy population of the Peruvian zone of Verruga 5 to 10 percent are found latently infected with the *Bartonella bacilliformis.*

(c) Some of the domestic animals, such as horses, donkeys, dogs, chickens and doves, have also been suspected as reservoirs of the disease since the sandflies feed on them with secondary preference (after man). In Colombia, Patiño-Camargo found the guinea pig strongly susceptible to the infection, in which character the Colombian strain differs completely from the Peruvian strain to which the guinea pig is refractory. This finding made him suspect the guinea pig as a possible domestic reservoir of the disease since the inhabitants of the affected zone are very fond of breeding this class of animals.

(d) Hertig found the *Phlebotomus noguchi* especially fond of field mice, and this led him to suspect this animal as a possible reservoir in the rare cases in which the *Phlebotomus noguchi* enters the houses to bite human beings. All these reservoirs still need further investigation, however.

In the epidemiology of the disease, still other factors should be considered, such as the influence of the predisposition of the people to infection, due to fatigue, weakness, concomitant diseases, lack of acclimatization, the poor economic and nutritional conditions, and all known causes of impairment of the organic ability to resist invasive organisms. This same factor, in case the disease develops, will determine the appearance of benign or malignant symptoms, as we shall see.

SEMIOLOGY AND CLINICAL FORMS

(*According to Rebagliati*)

The experimental human inoculation of Carrión fixed the inoculation period in 21 days. In the majority of the cases it is difficult to establish it since the infection may come after many days of remaining in the Bartonellosis zone, and there are cases in which the Bartonella appears in the blood without giving rise to symptoms—unapparent infection.

If we take a case of median intensity, two periods can be considered: the one of the systemic manifestations and the one of the skin eruption.

(a) Systemic or hematic period: The development of the disease can be sudden and speedy with chills and high temperature, but more frequently it is slow with general malaise, short chills, anorexia, low degree fever and headache. These symptoms increase in intensity at the same time and are aggravated by asthenia, joint and muscular pains, and gastrointestinal disturbances. The outstanding symptom is anemia in

variable degree, and it is manifested usually by sensorial disturbances, insomnia, ringing sounds, and cardiac murmurs. After a certain time, two or three weeks, the more serious symptoms recede; the anemia does not progress any more, the fever falls, and the patient is much better. This is the period of the crisis and is of definitive importance; the disease can retrograde or come back to the first phase and probably kill the patient, or can advance toward the second phase of better prognosis.

(b) Histioid or skin period: This is manifested by tissue proliferation. This appears especially on the skin and in the subcutaneous tissue, but it can also involve the mucous membranes, serous membranes, periosteum, fascia, muscles, and also the interior of many organs, that is, all the structures which correspond to the mesenchymal tissue. When it appears on the skin, it starts as small petechiae which grow in extent and in volume in variable degree. At last they look like sessile or pedunculated pimples which are red colored and bleed easily due to the thinness and fragility of the epidermis. This is the eruption corresponding to the "Verruga", by which name the disease is also known.

If the process of proliferation is subepidermic, subcutaneous nodules are seen or felt deeply under the skin. Such nodules can grow and break out on the skin, causing great pain before they open. The eruption period lasts from two or three weeks to four months. The eruption usually comes by "poussées" preceded by a febrile state. Finally the skin elements dry off or are reabsorbed without leaving any scar unless secondarily infected. As the evolution of the nodules can occur in any part of the organism, it is understood how the symptoms now can vary in relation with the affected organs and the corresponding sensorial or functional disturbances; so there can be gastrointestinal trouble, respiratory manifestations such as bronchitis and hemoptysis, pleural friction and exudation, peritoneal pain with ascitis, renal or vesical pains or hematurias, meningeal symptoms, etc.

However, these two periods do not always follow each other so closely. There are cases in which the hematic first period appears alone in all its intensity without giving any chance to the development of the second and kills the patient quickly in the most extreme anemia. This is what occurred in the epidemics in Colombia. Other cases, on the contrary, are characterized directly by eruption, and there are others in which the process is inverted so that the retrocession from eruption to anemia, fever and death are frequently seen. On the other hand, the two phases can coexist in all the stages of the process. Therefore, instead of two phases, they are in reality two aspects of the infection which do not exclude one another and do not depend upon each other.

PATHOLOGY: PATHOGENESIS

(a) Blood changes: These are predominant during the hematic period, and when this is severe the blood changes are of the highest magnitude ever known. In such a case the anemia is progressive, there may be a loss of from 200,000 to 300,000 red cells per mm. per day so that after twelve or fifteen days the red count can be below half a million per cubic millimeter.

Hurtado has shown three factors in the determination of the anemia: (1) the direct parasitic action of the Bartonella, which grows and reproduces in the same erythrocyte; (2) the hemorrhages which may occur in all tissues, plus the hema-

tophagous action of the reticulo-endothelial system; and (3) a probable hemolytic toxin of the Bartonella.

The anemia is macrocytic and hypochromic, which is another peculiarity not known in any other anemic process. These findings are coincidental with the ones obtained in the canine and murine bartonellosis. Moreover, in both human and animal bartonellosis, macrocytosis and hypochromia are more accentuated during the retrocession of the anemic process.

(b) The liver is another organ which is markedly affected during the severe Bartonella infections. At autopsy it is found enlarged with infarctions present and dispersed areas of toxic degeneration. These changes correspond to the general disturbances found in most of the liver functions during the disease.

(c) The spleen and lymph glands are found enlarged and showing numerous infarctions. The bone marrow is soft and dark red, that is, hyperplastic. The *Bartonella bacilliformis* is found in clusters in the endothelial cells of the lymphatics and in the vascular endothelial cells of the lymph glands, spleen, liver, and kidneys. This means that the cells of the reticulo-endothelial system are especially invaded.

(d) Finally, during the histioid phase, the skin and subcutaneous elements show special development and proliferation of angioblasts and vascular tissue; hence the tendency to hemorrhage of such elements.

CONTROL AND PROPHYLAXIS

Three links determine the endemo-epidemiology of the disease:

RESERVOIRS ⟶ VECTOR ⟶ MAN

Destruction of the reservoirs is, up to the present time, impossible for obvious reasons. All the human carriers should be first checked and treated and both things are today impossible. No specific treatment is available against the Bartonella, and even if it were possible, there would still exist the other reservoirs.

The vector is known to be the *Phlebotomus spp.* predominantly, but nothing is known of the cycle of the Phlebotomus in nature. The breeding places are apparently localized very deeply in the cracks and crevices of walls and rocks, and it is extremely difficult to find a simple larva of the *Phlebotomus*. The basis of the fight and control of the diptera resides in the destruction at the appropriate moment of the larval stages. In this case, it is today impossible.

The control should reside in the last step, vector-man, which can be broken up into the following rules:

(a) All individuals who work in the suspected zone should leave it before 6 P.M.

(b) All individuals who are compelled to spend the night in such a zone should carefully screen all the house, destroy the insects, and use repellents.

(c) The houses should be built in such a way that they get the most light possible, without dark corners and without any cracks or crevices. All the walls should be painted once monthly with creosote, the odor of which is repellent for the *Phlebotomus*.

(d) Instruction of the public and improvement of the nutrition and living conditions are, of course, of prime importance in order to build up physiologic resistance to the infection.

SUMMARY

(a) Three foci of Bartonellosis exist at present in America: in Peru, Ecuador, and Colombia. The distribution is closely tied up with the Andean topography and many other Andean zones with a similar environment may also harbor the disease.

(b) The *Phlebotomus verrucarum* is the main vector of the disease in Peru. In Colombia several *Phlebotomi* have been found, but the most responsible one is still unknown. Ticks and human lice are suspected.

(c) The only proved reservoir of the infection is the infected man with apparent or unapparent infection. There are some data which point to *Euforbiaceae* plants and the domestic animals as possible reservoirs of the disease.

(d) Predisposing causes in the individual are evident, as conditioning the infection or at least its severity.

(e) Two aspects are considered in the semeiology of the disease: a hematic and a histioid, or proliferative. They can succeed one another, coexist, or exist independently.

(f) The blood and the reticulo-endothelial system are the structures most affected.

(g) To date, the only effective means of control reside in the breaking up of the epidemiological cycle. The only way today is personal protection.

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Inmunidad pasiva al tétano.—J. V. Cooke y F. G. Jones (*Jour. A. M. A.*, pp. 1201, ab. 15, 1943) en un estudio de la inmunidad activa del tétano, hicieron las siguientes observaciones: aunque la dosis profiláctica de 1,500 unidades o menos produce inmunidad que suele durar unas dos semanas o más, las dosis mayores obtienen una inmunización mucho más prolongada y administrando 100,000 unidades o más pudo encontrarse un centésimo por cc al cabo de tres a cuatro semanas, 0.1 de unidad al cabo de seis a 10 semanas y 0.01 de unidad de ocho a 11 semanas después. Con una dosis de 10,000 unidades la inmunidad pasiva fué menos prolongada, aunque en casi todos los casos 0.1 de unidad duró de cuatro a seis semanas y 0.01 de seis a 10 semanas. En cuato niños con tétano clínico la curación no fué seguida de inmunidad antitóxica. Las inyecciones subcutáneas e intracutáneas repetidas de toxoide no produjeron inmunidad antitóxica por unas semanas, y sólo tienen valor en la profilaxia del tétano cuando el sujeto ya ha recibido una o más inoculaciones sensibilizantes. La inmunidad pasiva puede convertirse en activa por medio de inyecciones de toxoide. Esta observación también indica que es mejor demorar la inmunización activa hasta dos a cuatro semanas después de inyectar la antitoxina.