Sulfamerazine, sulfadiazine and sulfisoxazole (sulfafurazole) are the sulfonamides of choice. The dose is 3 or 4 gm daily for 3 to 6 weeks; if further treatment is needed, the dose should be decreased to 2 gm daily. Sufficient fluid must be given to maintain a urinary output of 1500 ml per day to avoid precipitation of sulfonamide within the kidney. Inadequate treatment may give rise to resistant strains. Although a combination of tetracycline and sulfonamide therapy may be optimal, in some cases in which these drugs have failed a combination of penicillin and ampicillin has produced regression of the disease.

The antimonials are not recommended. It is probable that the value ascribed to these preparations in the past has been due to confusion of diagnosis with granuloma inguinale or chancroid, or to an effect on secondary bacterial infection.

Bartonellosis

ARISTIDES HERRER

Synonyms. Verruga peruana, Oroya fever, Carrión's disease.

Definition. Bartonellosis is a specific infection caused by *Bartonella bacilliformis*, presenting two clinical types of disease. The severe form, Oroya fever, is characterized by fever, a rapidly developing macrocytic anemia, and frequently intercurrent infection with high mortality. The benign form, verruga peruana, is characterized by a verrucous eruption of hemangioma-like nodules and by a negligible mortality (Fig. 30–4).[11]

Distribution. The disease is restricted to the western portion of South America between latitudes 2° North and 13° South, occurring especially in Peru, Ecuador and Colombia. Its distribution is further restricted to narrow river valleys and canyons at altitudes between 800 and 3000 meters above sea level. It has been reported from both sides of the Andes.

Etiology. *Bartonella bacilliformis* Strong, Tyzzer and Sellards, 1915 is a minute gram-negative, rod-shaped or rounded organism found in varying numbers within both the red blood cells and cells of the reticuloendothelial system, especially those of the lymph nodes, spleen, liver, and kidney. *Bartonella bacilliformis* may be classified among bacteria.

In stained preparations of blood, both rod-shaped and rounded forms are seen. The rods are often slightly curved, occurring singly or end-to-end in pairs or in chains. Frequently, they lie parallel or are arranged in V's or Y's. The rod forms when stained by Giemsa's method commonly show a deep red or purplish granule at one end suggestive of chromatin, the remainder taking a bluish stain (Fig. 30–5).

They may be cultivated best in semisolid nutrient agar containing 10 per cent rabbit serum and 0.5 per cent rabbit hemoglobin. Proteose peptone produces high-intensity growth.[12]

Epidemiology. The disease is endemic in certain arid river valleys of the Andes region and is coextensive with the distribution of the sandflies *Lutzomyia verrucarum* and *Lutzomyia noguchii* in Peru. However, the latter does not bite humans and only rarely enters houses. At the present time only *L. verrucarum* has been incriminated as a vector. Other species are reported from the endemic areas in Colombia. The disease is especially prevalent at the close of the rainy season when these flies are most numerous.

Proboscis infections with *Bartonella* have been found in wild-caught female *Lutzomyia*. The source of these infections is unknown since there is no known reservoir host.

The disease is often mild among people of endemic areas, and latent infections without significant symptoms are observed in adults. Immunity is believed to follow both Oroya fever and verruga peruana.

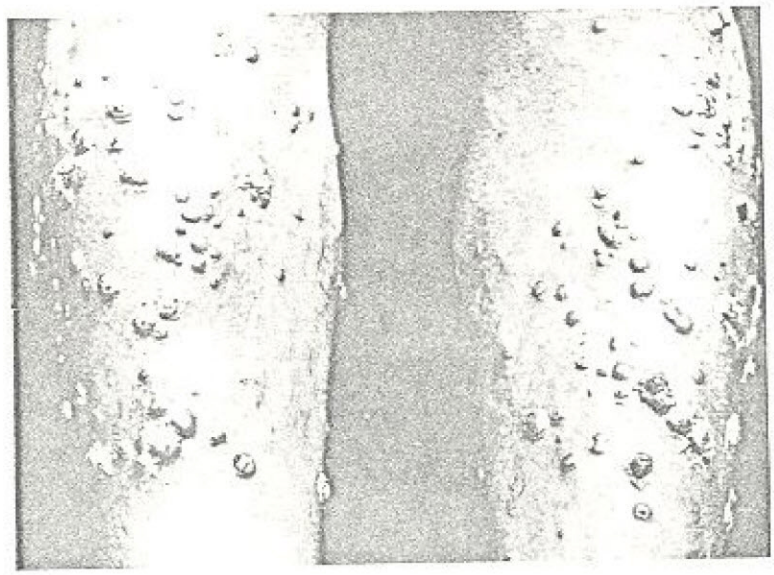

Figure 30–4. Miliary hemangiomatous lesions of verruga peruana. (Courtesy of Dr. Olga Palacios.)

Pathology. In the severe form of the disease the lymph nodes and the spleen are enlarged, the latter containing melanin-like pigment and sometimes showing areas of infarction. The liver is likewise increased in size, contains pigment, and may present areas of degeneration. On microscopic examination the reticuloendothelial cells of the lymphatic system and of the viscera are seen to be packed with organisms. The bone marrow is megaloblastic and hyperplastic. Patients who survive show hemangioma-like nodules.

The benign form, verruga peruana, is characterized by hemangiomatous nodules in the skin and subcutaneous tissue. The early lesion consists of newly formed blood vessels within edematous connective tissue. There are marked proliferation of the endothelial lining and pronounced capillary dilatation. Late lesions may resemble fibrosarcomas. The causative organisms are often

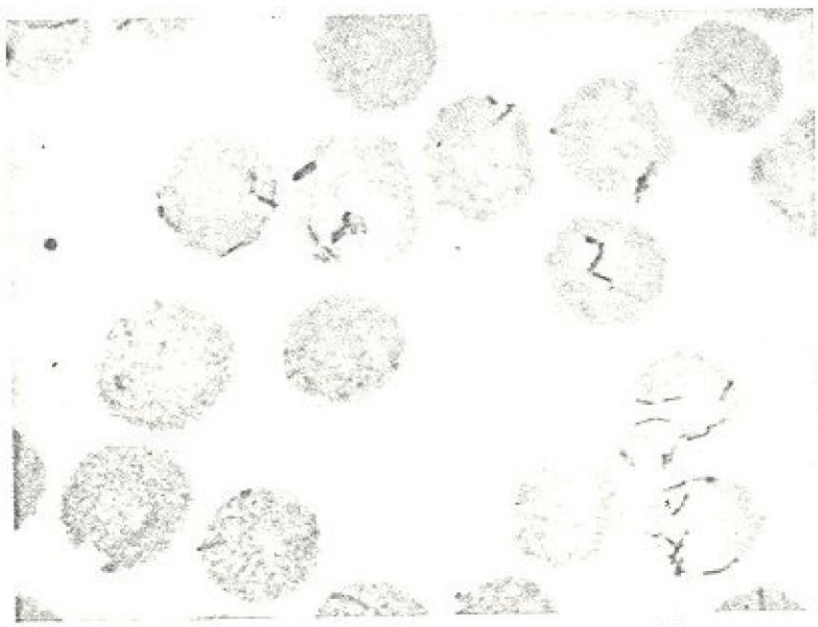

Figure 30–5. *Bartonella bacilliformis* in stained blood film.

demonstrable in the endothelial cells, although they are usually much less numerous than in acute Oroya fever.[13]

Clinical Characteristics. Bartonellosis presents four stages: incubation, invasion, the pre-eruptive and the eruptive. An incubation period of from 19 to 30 days, rarely up to 100 days, precedes the gradual onset of Oroya fever.

Oroya Fever. The early symptoms are frequently vague and indefinite. In the invasive period, fever is usually moderate and is accompanied by the characteristic progressive anemia and slight jaundice. Although the organisms are commonly not demonstrable microscopically early in the course, they can be recovered by blood culture. Subsequently, great numbers of the bacillary forms appear in the erythrocytes.

The anemia progresses with great rapidity. Within 2 weeks the hemoglobin may fall to 20 or 30 per cent and the erythrocyte count to 1 or 2 million. There is marked evidence of new blood formation with reticulocytosis, at times up to 50 per cent. The erythrocytes are macrocytic, frequently hypochromic, and normoblasts and megaloblasts may be numerous. The mechanical fragility of the red corpuscles is increased in the majority of cases. No agglutinins or hemolysins have been demonstrated.[14] Leukocytosis is variable, apparently depending upon the presence or absence of intercurrent infection.

The "critical stage" is characterized by the apparent beginning of convalescence. The *Bartonella* change from bacillary to coccoid forms, the parasitized red cells become less numerous, and there are fewer organisms within the cells. Macrocytosis diminishes, the erythrocyte and reticulocyte counts rise; lymphocytosis and reappearance of monocytes and eosinophils occur, and there is a shift of the polymorphonuclear series to the right.

Intercurrent infections accompanied by high fever, diarrhea, splenomegaly and marked leukocytosis are prone to occur at this time. They are associated with mortality rates well above 50 per cent. It is thought that *Bartonella* anemia predisposes to fatal septic invasion by organisms from the gastrointestinal tract. In the presence of *Salmonella* and *Entamoeba histolytica* infections and of pulmonary tuberculosis, the prognosis is very grave. Deaths likewise occur from complicating thrombocytopenic purpura.

Verruga Peruana. This is the benign form of bartonellosis. It usually runs a course of 2 to 3 months and is characterized by miliary and nodular hemangiomatous lesions which have a definite tendency to hemorrhage and occasionally to ulcerate; in the absence of intercurrent infection it is almost never fatal.

The incubation period is thought to be 30 to 60 days. The onset is usually accompanied by joint pains and fever seldom exceeding 37.8° C (100° F). The fever commonly subsides shortly after the onset of the eruptive stage.

The miliary type of eruption is more common and is most abundant on the face and the extensor surfaces of the extremities, appearing first as pink macules, later becoming bright red, nodular and bleeding easily (Fig. 30–4). The mucous membranes of the eye, nose and throat may be involved. The eruption disappears without scar formation.

The nodular subcutaneous lesions develop slowly and may reach 1 to 2 cm in diameter. Not infrequently they break down, producing an ulcerating and fungating process which may be a source of danger from hemorrhage. They do not occur in the mucous membranes and are commonly confined to the regions of the appendicular joints. They tend to appear in successive crops. Scarring varies with the extent of tissue destruction.

Diagnosis. The strictly limited geographic distribution and the distinctive clinical features of the infection almost eliminate any diagnostic difficulties. Definitive diagnosis depends upon the demonstration of *Bartonella* in Giemsa-stained blood films or on culture (Fig. 30–5).

Treatment. Patients with acute bartonellosis show dramatic clinical response when treated with penicillin, streptomycin, chloramphenicol or the tetracyclines. Fever disappears in 4 to 8 hours or less, and the orga-

nisms diminish markedly. Even though satisfactory clinical response is obtained, the patient may continue to have positive blood cultures and develop verrugas, but death will not result from the disease. Presumably the antibiotics control the acute infection and allow low-grade infection and the development of a protective immunity. The choice of an antimicrobial drug should depend on the presence of secondary bacterial infection. The high incidence of salmonella septicemia in patients with bartonellosis has led to the use of chloramphenicol as an adjunct to treatment of this disease (p. 179). Transfusions of whole blood are recommended for symptomatic relief of the acute anemia.

After the development of cutaneous lesions the response to antibiotic therapy is minimal. Excision of the large, necrotic, secondarily infected nodules may be indicated.

Prophylaxis. The prophylaxis of bartonellosis consists of control of or protection against *Lutzomyia*.[15] Residual spraying of buildings and adjacent potential breeding areas with 5 per cent DDT in kerosene gives excellent results that persist for several months. Temporary individual protection may be obtained by the use of insect repellents (p. 800).

REFERENCES

1. Page, L. A. 1968. Proposal for the recognition of two species in the genus *Chlamydia* Jones, Rake, and Stearns, 1945. Int. J. Systemat. Bacteriol. *18*:51–66.
2. Storz, J. 1971. Chlamydia and Chlamydia-Induced Diseases. Charles C Thomas, Springfield, Illinois. 358 pp.
3. Kuo, C. C., Wang, S. P., and Grayston, J. T. 1972. Differentiation of TRIC and LGV organisms based on enhancement of infectivity by DEAE-dextran in cell culture. J. Infect. Dis. *125*:313–317.
4. Darougar, S., Kinnison, J. R., and Jones, B. R. 1971. Simplified irradiated McCoy cell culture for isolation of *Chlamydiae*. *In* Nichols, R. L. (ed.): Trachoma and Related Disorders Caused by Chlamydial Agents. Excerpta Medica, Amsterdam. pp. 63–70.
5. Schachter, J., Mordhorst, C. H., Moore, B. W., and Tarizzo, M. L. 1973. Laboratory diagnosis of trachoma: a collaborative study. Bull. W.H.O. *48*:509–515.
6. Bietti, G. B., and Werner, G. H. 1967. Trachoma: Prevention and Treatment. Charles C Thomas, Springfield, Illinois. 227 pp.
7. Schachter, J., Rose, L., and Meyer, K. F. 1967. The venereal nature of inclusion conjunctivitis. Am. J. Epidemiol. *85*:445–452.
8. Wang, S. P., Kuo, C. C., and Grayston, J. T. 1973. A simplified method for immunological typing of trachoma-inclusion conjunctivitis-lymphogranuloma venereum organisms. Infect. Immun. *7*:356–360.
9. Meyer, K. F. 1965. Lymphogranuloma venereum agents. *In* Horsfall, F. L., and Tamm, I.: Viral and Rickettsial Infections of Man. 4th ed. J. B. Lippincott Co., Philadelphia. pp. 1024–1041.
10. Schachter, J., and Meyer, K. F. 1969. Lymphogranuloma venereum. II. Characterization of some recently isolated strains. J. Bacteriol. *99*:636–638.
11. Hennemann, H. H. 1963. Oroya-fieber (carrionsche Krankheit): eine akute erworbene hämolytische Anämie. Deut. Med. Wschr. *88*:1759–1767.
12. Méndez Mondragón, M. 1974. Verruga peruana. Evaluación de nutrientes de la *Bartonella bacilliformis* en gel. Rev. Lat. Am. Microbiol. *16*:1–7.
13. Urteaga-Ballon, O. 1967. Verruga peruana o enfermedad de Carrión. Arch. peruanos Patol. Clin. *21*:107–136.
14. Reynafarje, C., and Ramos, J. 1961. The hemolytic anemia of human bartonellosis. Blood *17*:562–578.
15. Reynafarje, C. 1972. Enfermedad de Carrión. Acta Méd. peruana *1*:139–144.