Brucellosis[1]

A Review of Its Clinical Manifestations, with Presentation of Twelve Cases Occurring in Puerto Rico

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ALTHOUGH BRUCELLOSIS of man has been but infrequently reported in Puerto Rico, it is common knowledge that this disease is quite prevalent on the Island; Morales Otero[2] and other investigators have established beyond any doubt its existence among island cattle. The purpose of this paper, therefore, is to report a series of cases of acute and chronic brucellosis, studied by the writer during the past few years, with a brief summary of the clinical picture so as to bring out the salient features of this condition. For further information, the reader is referred to the excellent studies already published.[3]

Brucellosis of man may be defined as an acute or chronic, febrile or afebrile, systemic or focal infection brought on by *Brucella melitensis*, *Brucella abortus*, or *Brucella suis*, producing more or less characteristic lesions in the presence or absence of systemic manifestations. It is frequently accompanied by a fever that usually occurs in the afternoons and/or evenings, a progressive weakness, muscular, bony or joint pains, profuse nocturnal sweats, chilliness or chills, hypochronic anemia, nervous disturbances, diminished appetite, and lassitude. The duration of the infection, with remissions and relapses, is indefinite. In Puerto Rico, the etiology of brucellosis is believed to be the strain *Brucella abortus*,[4] which produces contagious abortion in cattle.

The *Brucella* organisms are Gram-negative, non-acid fast, non-sporing, and non-capsule forming. In our experience, the isolation

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1. Received for publication November 17, 1945.

2. P. Morales Otero, *Brucella abortus* in Puerto Rico. Puerto Rico J.Pub.Health & Trop. Med., 6:3–88, 1930; Further attempts at experimental infection of man with a bovine strain of *Brucella abortus*. J.Inf.Dis., 52: 54–59, 1933; Brucella infection in Puerto Rico. Bol.Asoc. Méd.Puerto Rico, 32:35–39, 1940; Recent advances in the study of brucellosis. *Idem*, 32:113–121, 1940.

P. Morales Otero and L. M. González, Purified protein antigen from *Brucella*. Proc. Soc. Exp. Biol. & Med., 38:703–705, 1938; Allergy in *Brucella* infections, *Idem*, 40:100–102, 1939: Studies on a purified antigen from *Brucella*, Am. J. Med. Sc., 199: 810, 1940.

3. H. J. Harris, *Brucellosis (Undulant Fever). Clinical and Subclinical, 1st ed.* (New York: Paul B. Hoeber, Inc., 1941). I. F. Huddleson, *Brucellosis In Man And Animals. Revised ed.* (New York: The Commonwealth Fund, 1943).

4. P. Morales Otero, *op. cit.*

of these organisms from the blood of patients has been unsuccessful. Special culture media must be utilized and, even then, growth is very slow. Some strains grow best in CO_2 atmosphere. In addition, differentiation of the strains is at times extremely difficult notwithstanding the use of all methods for differentiation available.[5]

The disease is acquired through the ingestion of infected fresh dairy products, of meat from recently killed infected animals, by contact with infected animals or their products of conception or, accidentally, in the laboratory. In spite of the fact that the organisms are known to be eliminated in the urine (in about 10 percent of cases) and in the feces,[6] it is believed that the disease is not transmitted from one person to another. Harris[7] states that he has never seen two members of the same family ill with acute brucellosis at the same time, yet he mentions the probable occurrence of the disease in two successive babies born to an infected mother. That infected water may transmit the condition has been mentioned on several occasions.[8] Normal persons have been fed cultures of *Brucella* organisms without developing brucellosis, though the organism ingested was recovered in the feces.[9]

Observations show that the souring of milk may render these organisms innocuous.[10] Gould and Huddleson[11] estimate that 10 percent of the population in the United States has become infected, but no such figures are available for Puerto Rico. Morales Otero and González[12] reported that of 212 adults, working as milkers or general dairymen, 3.3 percent showed a positive complement-fixation; 2.3 percent a positive agglutination; 21.7 percent a positive opsonocytophagic reaction, and 29.6 percent showed hypersensitiveness only. A history of undulant fever was obtained in 3.3 percent of those examined.

Lesions have been described in practically all organs, but the scarcity of necropsy material has made it very difficult to study the pathologic features of the disease carefully. Parsons and Postin[13] reported the possible etiologic relationship between brucellosis and

5. I. F. Huddleson, *op. cit.*
6. C. M. Carpenter and R. Boak, *Brucella abortus* in milk and dairy products. Am.J.Pub. Health, 18:745–751, 1928.
7. H. J. Harris, *op. cit.*
8. *Ibid.*
9. P. Morales Otero, *op. cit.*
10. C. M. Carpenter and R. Boak, *op. cit.*
11. S. E. Gould and I. F. Huddleson, Diagnostic methods in undulant fever (Brucellosis) with results of a survey in 8,124 persons. J.A.M.A., **109**: 1971–1974, 1937.
12. P. Morales Otero and L. M. González, *op. cit.*
13. P. B. Parsons and M. A. Postin, The pathology of human brucellosis; report of four cases with one autopsy. South.M.J., 32:7–13, 1939.

Hodgkin's disease, but again no conclusions could be reached. According to Harris,[14] its microscopic picture may be so similar to that of tuberculosis that errors in diagnosis can be easily made.

The incubation period of brucellosis varies anywhere from a few days to several weeks and, at times, months. Bruce[15] reported the onset of the disease as taking place as early as six days after infection. Hardy, Frant, and Kroll[16] found the incubation period to vary between one week and four months. Harris[17] states that, in chronic cases, exposure may have occurred years before the development of a recognizable illness. According to Morales Otero,[18] the incubation period in volunteers experimentally infected varied from ten to seventeen days.

The symptomatology varies considerably. Hughes[19] classified the symptoms, according to their severity, as follows: (a) malignant type, (b) undulatory type, and (c) intermittent type. Simpson[20] described them as (a) intermittent, (b) ambulatory, (c) undulatory, (d) malignant, and (e) subclinical type. Harris[21] prefers to group his cases into acute and chronic forms.

Acute brucellosis may start with symptoms suggestive of malaria, typhoid, influenza, grippe, or any other acute illness. Chills, fever, and profuse perspiration are present quite often, hence in Puerto Rico quinine is frequently recommended as malaria is usually suspected. One generally finds the patient with a high fever and perspiring profusely but without toxic symptoms, sitting up in bed or talking to relatives or friends. In our experience, this is the most important observation. The patient may have anorexia, a coated tongue, constipation or diarrhea, vomiting, intestinal bleeding, localized or diffuse abdominal pain, distention, pharyngitis, cough, pleuritic pain, painful joints with or without effusion, neuritic and muscle pains, restlessness, confusion, depression, insomnia, skin eruptions, enlargement of the liver and spleen, adenitis, edema with or without nephritis, dyspnea, pericardial effusion, myocardial weakness, endocarditis, epididymitis, pyelitis, encephalitis, meningitis, loss of weight, pallor, leukocytosis, or leukopenia. The acute phase may last a few days or may be of long duration, though gen-

14. H. J. Harris, *op. cit.*
15. D. Bruce, cited by H. J. Harris, *op. cit.*
16. A. V. Hardy, S. Frant, and M. M. Kroll, The incubation period of undulant fever. Pub.Health Rep., 53:796–803, 1938.
17. H. J. Harris, *op. cit.*
18. P. Morales Otero, *op. cit.*
19. M. L. Hughes, *Mediterranean, Malta or Undulant Fever.* (London: Macmillan, 1897).
20. W. M. Simpson, cited by H. J. Harris, *op. cit.*
21. H. J. Harris, *op. cit.*

erally, less than one hundred days. Relapses may occur at any time.

Chronic brucellosis may be divided into the continuous and chronic recurrent types. Weakness, diminished appetite, loss of weight, emotional instability, insomnia, irritability, aches and pains are frequently the symptoms which bring the patient to the physician. Fever may or may not be present. Beatty[22] states that many cases of chronic brucellosis do not give a history of an acute stage.

The blood changes in either acute or chronic brucellosis are considerable. In the acute phase, the total white cell count may be low, normal, or elevated. Usually, lymphocytes increase either relatively or absolutely at the expense of the neutrophils; eosinophilia has been observed at times, but the red cell count shows very little variation, unless the illness is prolonged for several weeks. Anemia, when present, is generally normochromic or hypochromic.

In chronic brucellosis, the total white cell count is frequently normal, with a normal differential count or with a slight increase in the lymphocytes. Some degree of anemia, normochromic or hypochromic, is present. At times this anemia may be profound, even resembling the blood picture in pernicious anemia.[23] Diminished coagulability of the blood has also been noted; clot retraction is said to be imperfect.[24] In some, the fasting blood sugar has been found elevated. The sedimentation rate is usually normal unless complications arise.[25]

Several tests are used in the diagnosis of brucellosis, but one should emphasize here that the utmost care must be exercised in the interpretation of their results. If positive, a blood culture is obviously the most reliable laboratory procedure, but this test, unfortunately, frequently comes out negative. The *Brucella* group of organisms may be present in the blood, feces, urine, tissue, secretions, transudates, and exudates; hence special culture media and a meticulous technique must be utilized in order to achieve good results. Cultures from patients infected with the *melitensis* strain are more apt to prove positive than the *abortus* or *suis* strains, especially if the cultures are made during the acute pyrexial stage.[26]

The three other tests generally used are the agglutination, the

22. O. A. Beatty, Undulant fever; diagnosis and treatment. Kentucky M.J., 35:260–265, 1937.

23. R. M. Calder, C. Steen, and L. Baker, Blood studies in brucellosis. J.A.M.A., 112:1893–1898, 1939.

24. *Ibid.*

25. *Ibid.*
W. R. and E. L. Roberts, Undulant fever, a major public health problem. Illinois M.J., 57 247–252, 1939.

26. I. F. Huddleson and H. W. Johnson, Brucellosis, J.A.M.A., 94:1905–1907, 1930.

opsonocytophagic, and the skin tests. The first is perhaps the best known of all, but certain rules must be followed in its correct interpretation. Like all other similar tests, it denotes only the presence in the blood of specific agglutinins that have developed in response to the infection. Therefore, a positive test should by no means be interpreted as an indication of the presence of brucellosis, just as a positive Widal does not testify to the existence of typhoid fever. By the same token, failure to find agglutinins does not mean that the disease is not present; it merely denotes that resistance to the infecting organism has not yet developed on the part of the host. The test is negative in over 50 percent of cases with chronic brucellosis. In the acute stage, the agglutination test is frequently negative. Therefore, one cannot emphasize sufficiently the fact that a negative agglutination test does not rule out the presence of brucellosis. Harris[27] has made the following observations concerning the interpretation of this test:

1. Agglutination in titers of 1:80, or higher, in patients ill with symptoms suggestive of undulant fever may be accepted as evidence of the existence of infection.
2. Agglutination in titers below 1:80 (trace, 1:10, 1:20, or 1:40) in patients with symptoms suggestive of brucellosis is presumptive evidence of infection, but requires confirmation. These patients should have the benefit of the skin and opsonocytophagic tests and, whenever possible, a blood culture also.
3. Patients with negative blood agglutination tests, in whom the skin test is positive, and whose symptoms suggest brucellosis, may be diagnosed as actively infected if the opsonocytophagic index is low.
4. If the skin test is positive and the opsonocytophagic test shows a high degree of resistance, the patient has presumably recovered from an old infection, regardless of the result of the agglutination test.
5. A negative blood agglutination test and a positive skin test may not be accepted as conclusive evidence of present infection in the absence of the information furnished by a low opsonocytophagic test, or by a positive blood culture.

Cross-agglutination reaction may occur in the presence of infections with tularemia, typhoid fever, Flexner shigellosis, and *B. proteus* X19 organisms.

The skin test should never be performed until the agglutination test and opsonocytophagic index have been carried out, as the formation of agglutinins and opsonins may occur. The skin test can be

27. H. J. Harris, *op. cit.*

performed with heat-killed *Brucella* organisms, with brucellergin,[28] (a nucleoprotein solution of all the strains of *Brucella*), or with the purified *Brucella* protein.[29] A positive skin reaction produces a papule over 7 mm. in diameter, surrounded by a zone of erythema or edema that usually lasts several days and even weeks, at times. In certain cases, violent reactions with high fever, general malaise, and marked local changes may be produced; sometimes necrosis of the skin takes place. As with other skin tests, a positive reaction means only the presence of an allergic state to the proteins of the organism injected; a negative reaction does not rule out the suspected condition. This test may be negative in cases with positive blood cultures. Evans and co-workers[30] found a negative reaction in 39 percent of their cases. Because of a lower degree of sensitivity in children, the skin test is of less diagnostic importance.

In 1933 Huddleson, Johnson, and Hamann[31] described the opsonocytophagic test, based on the phagocytosis of live *Brucella* organisms by polymorphonuclear leukocytes. This test has been used mainly as a prognostic index, since the degree of phagocytic activity can be taken as a measure of the amount of resistance developed by the patient. According to the amount of bacteria phagocytosed and the number of leukocytes involved, patients are classified as infected, questionably infected, and immune but not necessarily cured, since the test does not determine whether the diseased person has been freed from the infecting organism. It has also been utilized to determine the effectiveness of the treatment and of the duration of immunity.

The differential diagnosis forces the physician to consider all febrile diseases without localizing symptoms. In Puerto Rico especially, one has to take into account such conditions as typhoid fever, malaria, typhus fever, liver abscess, renal abscess, pulmonary tuberculosis, bacterial endocarditis, and acute schistosomiasis. Our experience has shown that the most important diagnostic findings in brucellosis are the afternoon rise in temperature, profuse night sweats, and low toxicity.

As relapses may occur, prognosis in brucellosis is uncertain, but the outlook for recovery from the acute form is good. In general,

28. I. F. Huddleson, H. W. Johnson, and E. E. Hamann, Brucella infection, a study of the opsonocytophagic power of the blood and allergic skin reaction. Am.J.Pub.Health, 23:917–929, 1933.

29. P. Morales Otero and L. M. González, *op. cit.*

30. A. E. Evans, F. H. Robinson, and L. Baumgartner, Studies on chronic brucellosis. (IV) Evaluation of the diagnostic laboratory tests. Pub.Health Rep., 53:1507–1525, 1938.

31. I. F. Huddleson, H. W. Johnson, and E. E. Hamann, *op. cit.*

mortality is low, being highest only when the causative factor is the *melitensis* strain. In our limited series, no deaths occurred.

The results obtained from the use of new chemotherapeutic agents are very hard to evaluate, since many cases recover spontaneously. Serums, vaccines, brucellergin, artificial fever, and the sulphonamide compounds have been used with variable results. In some cases,[32] the sulpha drugs appear to have had a certain beneficial effect during the acute form of brucellosis; symptomatic management during this stage is important. Careful attention must be paid to diet, regulation of bowels, hydration, and rest in bed. Mild sedation and psychotherapy are at times indicated; blood transfusions are sometimes needed.

During the past four years, we have observed twelve cases of brucellosis. Eight were in the acute phase and the rest in the chronic stage. In most of the cases the disease could be traced either to the drinking of raw milk or to the handling of infected material. One patient contracted the illness while working with a *melitensis* strain in the laboratory.

The absence of brucellosis in other members of the patients' families, in spite of the fact that they, too, drank raw milk, suggested the possibility of a defective acid secretion by the gastric mucosa, which might have had something to do with the development of this condition. It is an accepted fact that gastric juices[33] kill bacteria rapidly, when a normal amount of free hydrochloric acid is present in the gastric contents. Gastric analysis was therefore performed on seven patients who volunteered for the examination. The results revealed that three of them had no free acid in the gastric residue, and that four had an anachlorhydria resistant to histamine. This incidence of histamine-resistant anachlorhydria is about three times that observed in Puerto Rico[34] and is therefore, in our opinion, of great significance. It would have been interesting to have performed gastric analyses on the relatives of our patients, but this was not possible to do.

According to Morales Otero,[35] the *abortus* strain has very little disease-producing power, if given by mouth. Cultures of this or-

32. W. W. Spink and H. W. Hall, The diagnosis and treatment of brucellosis. Med. Clin. of N. America. March, 1945, pp. 343–362.

33. F. Hernández Morales and R. S. Díaz Rivera, Anachlorhydria in Puerto Rico. Puerto Rico J.Pub.Health & Trop.Med., 17:41–50, 1941.

34. W. W. C. Topley and G. S. Wilson, *The Principles of Bacteriology and Immunity, 2d ed.* (Baltimore: W. Woods and Company, 1936).
G. F. Dick, The bacteriologic examination of the stomach contents in pernicious anemia. Am.J.Dig.Dis., 8:255–260, 1941.

35. P. Morales Otero, *op. cit*

ganism were fed to thirteen persons and in only one was the disease produced. In twelve, the organism was cultured from the feces, thus indicating that it had passed the gastrointestinal tract without destruction, but in none of the cases was brucellosis produced. A study of the gastric acidity was not made. There is the possibility that the presence of the free acid in the gastric contents may have so attenuated the organism as to prevent its developing such a condition.

It is hoped that physicians working in areas where brucellosis is more prevalent will carry out investigations along these last mentioned lines.

ACUTE BRUCELLOSIS

1. N. C., age 24. A white Puerto Rican female seen by us on August 21, 1944, at her home. She stated that during the first week of that month she had been taken sick with fever, body aches, night sweats, and anorexia. Another physician had diagnosed influenza. The fever lasted only seven days, so she had been able to return to work. One week afterwards, she commenced to feel sick once more; there had been a slight rise in temperature in the afternoons, night sweats, weakness, and anorexia, with the fever gradually becoming more severe and rising as high as 39.9° C. On questioning, the patient informed us that she had taken raw milk all her life and that her mother and sister had, as well. This milk came from their own dairy.

Physical examination revealed no evidence of disease, except for the presence of fever.

Laboratory Findings

Hemoglobin		77% (Sahli)
R.B.C.		3,950,000 per cmm.
W.B.C.		6,050 per cmm.
Differential count:	Lymphocytes	48%
	Neutrophils	44%
	Monocytes	4%
	Eosinophils	4%
Urinalysis		Negative
Gastric analysis		No free acid in residue.
Agglutination test for brucellosis		Positive (dilution of over 1:640)

Sulfadiazine was prescribed, one g. every four hours day and night. In 48 hours, the temperature had gone down to almost normal, though there was a tendency to a slight rise in the afternoons. By the seventh day, however, the patient was completely afebrile; the drug was discontinued. She returned to work and has continued in good health since then.

2. M.C.P., age 64. (Case A-6282 U. H.) An elderly white Puerto Rican widow was admitted to the University Hospital on January 27, 1945, complaining, since the beginning of the month, of a fever of unknown etiology. Until December 30, 1944, when an attack of acute lymphangitis of the left leg developed, she had felt well; she had had several similar attacks during the past 20 years. For the first 5 days of January, the patient had been in bed with a high fever, nausea and vomiting, chills and chilliness, and enlargement of the left inguinal lymph nodes; an erythematous erruption, involving the left leg, appeared. The chills had subsided during the first 24 hours, but the fever continued thereafter for a few days more, at which time the patient had been able to be up and around. Two days later, however, she was taken sick again with severe chills, high fever, headache, and profuse perspiration. The chill subsided after the first day, but the high fever continued. A physician diagnosed malaria and prescribed quinine and atabrin, but to no avail. All laboratory examinations, including X-ray of the lungs, and agglutination tests were negative. The patient was given sulfadiazine and, later on, penicillin in a total dosage of 520,000 units, but without improvement. Her past history revealed pleurisy on two occasions, attacks of recurrent tropical lymphangitis for 20 years, hypertension for 6, and colitis for 4 years. In 1923 the uterus had been removed. Family and marital histories were essentially irrelevant.

Physical examination revealed a well-developed and well-nourished woman, lying comfortably in bed, well-oriented, cooperative, and intelligent.

Temperature	99° F.
Pulse	80 per m.
Respiration	18 per m.
Blood pressure (expressed in mm. of mercury)	130/80

This examination was essentially negative.

Laboratory Findings

Hemoglobin		90% (13 g. Hellige-Wintrobe)
R.B.C.		4,530,000 per cmm.
W.B.C.		6,200 per cmm.
Differential count:	Neutrophils	52%
	Eosinophils	11%
	Lymphocytes	37%
Urinalysis		Negative
Stools		Negative
Agglutination test for brucellosis		Negative
Opsonocytophagic index		Negative
Skin test with purified *Brucella* protein		Positive
Blood culture		Sterile

Course in hospital. The patient was placed on a soft diet; no medicines were prescribed. The highest temperature recorded was 100° F. on the second day of admission. After 7 days of hospitalization, she left on February 2, 1945. Further agglutination tests for brucellosis were negative, though the skin test remained positive for one month.

3. I.B.P., age 13 (CASE A–3459 U. H.). A white Puerto Rican girl was admitted to the University Hospital (Service of Dr. Ramón J. Sifre) on October 30, 1942. Suffering from anorexia, underweight, and night sweats (she perspired so freely that it was necessary to change her gown during the night), the patient had been to see her physician in August 1942. Albumin was found in the urine, so bed rest and a salt-free diet were prescribed. Three weeks of this treatment placed her back in school but, on October 5, she developed a bad cold with much coughing, expectoration, and hoarseness. On the fourth day after the onset of this last condition, a slight fever of some four to five days' duration appeared; the respiratory infection disappeared in about 2 weeks. However, a few days afterwards, the patient was taken sick again with a high fever of 40° C. Medicines were prescribed, but the fever continued. Her temperature was around 37.2° C. in the mornings, going up in the afternoon to 38.5° C. About one week previous to admission, she underwent a thorough physical examination by her physician, but nothing abnormal was found except for the fever. Agglutination tests for typhoid, typhus fever, and brucellosis proved negative. An enlarged spleen was found on abdominal palpation; the quinine prescribed was to no avail.

Physical examination revealed an undernourished, fairly well-developed white girl in no particular distress. There was slight enlargement of the cervical and inguinal lymph glands. Her tonsils were cryptic and slightly enlarged; the liver and spleen were also both enlarged, and their edges felt about one finger's breadth below the right and left costal margins, respectively.

Laboratory Findings

Hemoglobin	11.7 g. (Hellige-Wintrobe)
R.B.C.	3,640,000 per cmm.
W.B.C.	4,650 per cmm.
Differential count: Neutrophils	26%
Basophils	1%
Lymphocytes	70%
Monocytes	3%
Urinalysis	Negative
Stools	Negative
Agglutination tests for typhoid and typhus fever	Negative
Agglutination test for *B. abortus* (November 2, 1942)	Positive (dilution of 1:6400)
Determination of heterophile antibodies	Positive (dilution, 1:32)
Blood culture	Negative
X-ray of lungs	Negative

Course in hospital. On admission, the patient's temperature was 102° F., dropping to 98.6° F. on the following day but rising again to 102.8° F. at 4 A.M. of the second hospital day. At 12 P.M. of that same day, it had gone down to 99.8° C. but was back at 101° C. at 4 P.M. From then on, the temperature declined rapidly, and she was discharged, afebrile, on November 8, 1940. There was no follow-up.

4. C.P.M., age 33 (CASE A–3297 U.H.). A white Puerto Rican male was admitted to the University Hospital on September 17, 1942, with fever, accompanied by insomnia and night sweats of two months' duration. The patient stated that he had sickened about two months previous and had detected a slight afternoon temperature and insomnia; he was hospitalized in a local hospital where several examinations were performed, but no diagnosis was made. A local physician diagnosed the case as hepatic disease and prescribed glucose intravenously; there had been no improvement as the fever rose higher and higher with the passing of days. Still another physician prescribed salol without any relief. During the last few days previous to his hospitalization in the University Hospital, his temperature had gone up to 40° C. His appetite, however, had remained normal, and there had been no gastrointestinal complaints. In spite of the fever, he had been able to continue his work except during the last several days. The patient stated that he had been having night sweats and that his perspiration gave off an offensive odor.

Physical examination revealed a fairly well-nourished and well-developed white Puerto Rican male, lying quietly in bed in no particular distress, perspiring freely, mentally alert, and cooperative. Perspiration was pronounced in the upper extremities, chest, and face. A reddish papular rash was observed over the anterior and lateral aspects of both thighs and lower flanks of the abdomen. His tonsils were enlarged and subacutely inflamed; the liver and spleen were more or less normal.

Laboratory Findings

Hemoglobin	13.3 g. (Hellige-Wintrobe)
R.B.C.	4,800,000 per cmm.
W.B.C.	4,750 per cmm.
Differential count: Neutrophils	59%
Lymphocytes	41%

Urinalysis	Occasional granular casts and abundant red blood cells in the sediment
Kahn	Negative
Agglutination test for *B. abortus*	Positive (dilution, 1: 12,800)
Skin test with purified *Brucella* protein	Negative

Further urinalysis revealed the presence of hyaline casts in the sediment, but the red blood cells had disappeared. On September 28, 1942, another W.B.C. count gave 4,500 per cmm., with 66% of lymphocytes and 34% of neutrophils. Gastric analysis revealed a histamine-resistant anachlorhydria.

Course in hospital. On admission, the patient had recorded a temperature of 100.4° E., but it had followed a remittent course, going down in the mornings and up in the afternoons to about 105.4° F. On the third day of hospitalization sulfadiazine was prescribed, 2 tablets every four hours. Five days after treatment commenced, his temperature became normal and remained so; he was discharged, afebrile, on October 1, 1942.

This patient was followed up in the Outpatient Department and, on October 18, 1942, found in fairly good condition. On November 2, he was seen again, at which time he stated that he had had fever since October 28. Examination revealed a temperature of 100° F. The same dosage of sulfadiazine was prescribed again and, on November 6, when he returned to the dispensary, his temperature was down to 99° F. The patient stated that his fever had practically disappeared with the sulfadiazine, but he had had a slight rise in the afternoons for the past three days. Since then, he has returned repeatedly to the Outpatient Department and his condition has been found very good, except for a slight febrile reaction on certain occasions, lasting one or two days.

5. E.L.M., age 30 (Case A–3382 U.H.). A white Puerto Rican male was admitted to the University Hospital on October 9, 1942. He informed us that on September 29, 1942, at about 6:00 P.M., he had felt sick and that about two hours afterwards, shaking chills lasting about six hours had developed; that after the chills subsided, he had felt warm all over and had perspired profusely; that since then, his fever had been continuous. The patient added that he had had three to five chills since being taken sick. He added that there had been pains over the kidneys, splitting headaches, gastric discomfort, oliguria, anorexia, and constipation; that his sleeping had suffered since his illness. Atabrin had imparted a yellow color to the patient's skin. After visiting a physician, agglutinations tests for typhoid and typhus fever had been made, both of them proving negative; this physician had prescribed quinine hydrochloride, intramuscularly. The patient revealed that he had drunk goat milk off and on.

Physical examination showed a well-developed and well-nourished Puerto Rican, lying quietly in bed but acutely ill, apparently, and perspiring profusely; he seemed mentally alert and cooperative, however. The examination was essentially normal, except for an enlarged spleen felt three fingers' breadth below the left costal margin at the anterior axillary line. The edge of the liver was found 1½ cm. below the right costal margin at the mid-clavicular line.

Laboratory Findings

Hemoglobin	13.9 g. (Hellige-Wintrobe)
R.B.C.	4,570,000 per cmm.
W.B.C.	6,850 per cmm.
Differential count: Neutrophils	72%
Eosinophils	2%
Lymphocytes	26%
Urinalysis	Heavy traces of albumin and a few coarse and fine granular casts
Kahn	Negative
Stools	Negative
Blood culture	Negative

Agglutination tests for typhoid and typhus fever: Negative
Agglutination tests for brucellosis: Positive (1:12,800)
Skin test for brucellosis: Negative

Gastric analysis	No free acid in residue

Course in hospital. On admission, the patient's temperature was up to 100.6° F. and of the intermittent variety, going up in the mornings and down in the afternoons. On the seventh hospital day, or the 16th of his illness, it came down to normal and stayed so, thereafter. Acetylsalicylic acid and codeine sulphate were administered orally, when needed. The patient was discharged on October 24. At the Outpatient Department on November 27, he complained of a slight weakness; he had had no more fever. On July 2, 1943, he was seen again and stated that the sensation of weakness had continued; the examination, however, revealed nothing abnormal. On January 28, 1944, he was seen for the last time and found in excellent health.

6. A.P.L., age 37 (Case A–921 U.H.). A white Puerto Rican male was admitted to the University Hospital (service of Dr. Ramón M. Suárez) on February 2, 1941, stating that on Friday, January 24, he had been suddenly taken sick, with a sensation of general malaise, exquisite pain in the muscles of the calves, nausea, anorexia, headache, and throbbing pain in the eyeballs. Next day his headache was more intense; the pain in his calves more severe; he also had a low backache. Nausea became more pronounced and

Urinalysis	Occasional granular casts and abundant red blood cells in the sediment
Kahn	Negative
Agglutination test for *B. abortus*	Positive (dilution, 1: 12,800)
Skin test with purified *Brucella* protein	Negative

Further urinalysis revealed the presence of hyaline casts in the sediment, but the red blood cells had disappeared. On September 28, 1942, another W.B.C. count gave 4,500 per cmm., with 66% of lymphocytes and 34% of neutrophils. Gastric analysis revealed a histamine-resistant anachlorhydria.

Course in hospital. On admission, the patient had recorded a temperature of 100.4° E., but it had followed a remittent course, going down in the mornings and up in the afternoons to about 105.4° F. On the third day of hospitalization sulfadiazine was prescribed, 2 tablets every four hours. Five days after treatment commenced, his temperature became normal and remained so; he was discharged, afebrile, on October 1, 1942.

This patient was followed up in the Outpatient Department and, on October 18, 1942, found in fairly good condition. On November 2, he was seen again, at which time he stated that he had had fever since October 28. Examination revealed a temperature of 100° F. The same dosage of sulfadiazine was prescribed again and, on November 6, when he returned to the dispensary, his temperature was down to 99° F. The patient stated that his fever had practically disappeared with the sulfadiazine, but he had had a slight rise in the afternoons for the past three days. Since then, he has returned repeatedly to the Outpatient Department and his condition has been found very good, except for a slight febrile reaction on certain occasions, lasting one or two days.

5. E.L.M., age 30 (Case A–3382 U.H.). A white Puerto Rican male was admitted to the University Hospital on October 9, 1942. He informed us that on September 29, 1942, at about 6:00 P.M., he had felt sick and that about two hours afterwards, shaking chills lasting about six hours had developed; that after the chills subsided, he had felt warm all over and had perspired profusely; that since then, his fever had been continuous. The patient added that he had had three to five chills since being taken sick. He added that there had been pains over the kidneys, splitting headaches, gastric discomfort, oliguria, anorexia, and constipation; that his sleeping had suffered since his illness. Atabrin had imparted a yellow color to the patient's skin. After visiting a physician, agglutinations tests for typhoid and typhus fever had been made, both of them proving negative; this physician had prescribed quinine hydrochloride, intramuscularly. The patient revealed that he had drunk goat milk off and on.

Physical examination showed a well-developed and well-nourished Puerto Rican, lying quietly in bed but acutely ill, apparently, and perspiring profusely; he seemed mentally alert and cooperative, however. The examination was essentially normal, except for an enlarged spleen felt three fingers' breadth below the left costal margin at the anterior axillary line. The edge of the liver was found 1½ cm. below the right costal margin at the mid-clavicular line.

Laboratory Findings

Hemoglobin	13.9 g. (Hellige-Wintrobe)
R.B.C.	4,570,000 per cmm.
W.B.C.	6,850 per cmm.
Differential count: Neutrophils	72%
Eosinophils	2%
Lymphocytes	26%
Urinalysis	Heavy traces of albumin and a few coarse and fine granular casts
Kahn	Negative
Stools	Negative
Blood culture	Negative
Agglutination tests for typhoid and typhus fever	Negative
Agglutination tests for brucellosis	Positive (1:12,800)
Skin test for brucellosis	Negative
Gastric analysis	No free acid in residue

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Kahn	Negative
Stools	Negative
Blood culture	Negative
Agglutination tests for typhoid and typhus fever: Negative	
Agglutination tests for brucellosis: Positive (1:12,800)	
Skin test for brucellosis: Negative	
Gastric analysis	No free acid in residue

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salivation profuse. His temperature, which had been around 37.5° C., went up to 39° C. On January 26, he still felt very badly and took some aspirin and codeine prescribed by a physician. That day he was severely sick at his stomach and vomited some liquid material, yellowish in color: his temperature went up to 40° C. at 9:00 P.M. Feeling somewhat constipated, he took a purgative of magnesium sulfate and felt better afterwards. On Monday, January 27, his temperature fluctuated between 38.6° C. and 39.8° C.; he felt miserable; nausea was very marked and salivation profuse. On January 28, his temperature ranged between 37.7° and 39.1° C., his other symptoms remaining unchanged. On the 29th, his temperature was 37.7° C. in the morning, but 38.8° C. in the afternoon; it continued more or less the same until he was hospitalized. The patient stated that he had been mentally clear but physically weak. There was no history of chills or chilliness, only a slight cough with some expectoration of phlegm. He added that he had had schistosomiasis *Mansoni* for about 20 years and had received three courses of fuadin, the last one about two months previous to his present illness; also previous to this condition, he had been working in the Department of Bacteriology of the School of Tropical Medicine engaged in the study of *Brucella* organisms.

Physical examination revealed a well-developed and well-nourished male, appearing quite ill, somewhat listless but cooperative. There was a slight injection of the pharynx, a slight postnasal drip, and a palpable spastic sigmoid colon. The liver and spleen were not enlarged.

Laboratory Findings

Hemoglobin	13.7 g. (Hellige-Wintrobe)
R.B.C.	4,840,000 per cmm.
W.B.C.	9,900 per cmm.
Differential count: Neutrophils	73%
Eosinophils	1%
Lymphocytes	24%
Monocytes	2%
Smears for malaria	Negative
Kahn	Negative
Sedimentation rate	40 mm. per hr. (Wintrobe's technique)
Urinalysis	Faint traces of albumin and occasional granular casts.
Stools	Negative
Agglutination tests for typhoid, typhus fever and brucellosis:	Negative

Blood culture	Positive for Gram-negative organisms similar to *B. melitensis*
X-ray of the lungs	Negative

Repeated W.B.C. counts revealed a tendency towards an increase in lymphocytes; the highest percentage obtained was 48.

Course in hospital. On admission, the patient recorded a temperature of 101° F., the curve being of the remittent variety with the temperature going down in the mornings and up in the afternoons, accompanied by a corresponding rise in the pulse rate. Sulfanilamide was prescribed on February 6, 1941, 3 tablets every 4 hours. On February 7, the patient's temperature went up to only 99.8° F. (it had been up to 103° F. three days previous); on February 8, he was afebrile and remained so thereafter. He was discharged on February 21, 1941. During the following two months, he complained of feeling below normal, but gradually his state of health improved until he was practically back to normal again except for the occurrence of muscular pains, especially in the lower extremities. About one year after being discharged, the patient was taken sick again with a high fever of 38° and 39° C., occurring always late in the afternoons. This attack subsided spontaneously at the end of two weeks, approximately, and he was able to return to work. Several months later, he had another febrile episode lasting for about two days only. Since then, the patient has felt fairly well, though at times he has diffuse muscular pains with a minimal febrile reaction. Previous to his illness, the patient had been working with a *melitensis* strain; he is of the opinion that the infection was contracted through the skin.

7. A.S.Q., age 60 (CASE A–4477 U.H.). A white Puerto Rican widow was seen for the first time on August 20, 1943, in the Outpatient Department of the University Hospital, when she stated that she had had a fever for two months, her illness having commenced after a Sunday on the beach. Two or three days afterwards, a series of small vesicles, which looked like "rice," appeared on her back, and she started to have a daily fever with mild chills on three occasions. The fever would occur at any time of the day; sometimes she had none. There had been abundant perspiration at night. The patient revealed no history of joint pains, weakness, nausea, or vomiting, but informed us that she had drunk raw milk for many years, though during a period of fifteen days preceding her illness, she had had only boiled milk. In the beginning, a physician diagnosed her case as malaria and had prescribed atabrin, but since the fever did not subside with this treatment, other medicines had been ordered. The patient then visited another physician on three different occasions and he, in turn, prescribed other drugs, but to no avail. She therefore went to still another physician, who prescribed some injections. The first one made her so sick that she did not con-

tinue them. Her past history revealed the usual childhood diseases; she had had repeated asthmatic attacks up to the age of ten, and typhoid fever at fourteen.

Physical examination revealed a well-developed and nourished white female, not looking at all sick but only a bit pale.

Temperature	99.2° F.
Pulse	120 per min.
Blood pressure expressed in mm. of mercury	128/90

The examination, however, was essentially normal.

Laboratory Findings

Hemoglobin		12.6 g. (Hellige-Wintrobe)
R.B.C.		4,410,000 per cmm.
W.B.C.		6,700 per cmm.
Differential count:	Neutrophils	48%
	Eosinophils	2%
	Lymphocytes	49%
	Monocytes	1%
Kahn		Negative
Urinalysis		Negative
Gastric analysis		Histamine-resistant anachlorhydria
Brucella agglutination test		Positive (dilution, 1:6400)

Course in hospital. The patient was instructed to take her temperature four times a day and to bring the record to the Outpatient Department on her next visit. She was seen again on August 27, when the chart showed no fever at 8:00 A.M., with but a slight rise to 37.4° C. at 12, 4:00, and 8:00 P.M. There had been no fever since August 25. On September 3, the patient returned to the Outpatient Department; the temperature chart demonstrated the same notations as before. She stated, furthermore, that there had been no night perspiration, and that she was feeling much better. On September 10, the patient informed us that there had been no fever at all for one week and that she continued to improve. On September 24, she told us that she had had a slight fever for about one week, but that this had disappeared during the last four or five days. Thereafter, the patient remained afebrile and has gained 20 pounds in weight.

ACUTE RECURRENT BRUCELLOSIS

8. A.S.B., age 27 (CASE A–6454 U.H.). A white Puerto Rican married woman was admitted to the Outpatient Department of the University Hospital on March 13, 1945. In January 1944, while pregnant, she developed pains in the lumbar regions and in both knees, with frequent headaches. Fever, preceded by chills, developed at the same time, rising to 41° C. for two or three hours, after which it commenced to decline coincident with the onset of profuse perspiration. This fever used to come on daily, usually at one or two in the afternoon. However, the patient remembers having also had it in the mornings on some occasions. At night she perspired abundantly, especially around midnight, and frequently had to change her gown as well as her bed linen; she did not notice any bad odor to the perspiration, however. This fever lasted for about three months and disappeared three days after she gave birth to a normal girl baby. During these three months of illness, the patient had been treated with sulfathiazole and intravenous glucose solution, given her because of lack of appetite, frequent nausea, and vomiting. She was also constipated, so was instructed to take about three liters of water daily. The patient remained in bed practically all of the time that she had fever, having lost about nine pounds; after the child's birth, however, she seemed in good health until October 1944, when she started running a temperature again every three or four days; later, the fever had come on more frequently. The patient's father was the owner of a dairy, and the patient informed us that she had taken raw milk all of her life, two or three glasses daily. No other member of the family had been similarly sick. Her baby was breast-fed for three months and then weaned, and had never been sick except for mild colds.

Family history: Father living, age 53, good health except for high blood pressure; Mother living and well, age 46. Seven sisters all in good health.

Past history: Usual childhood diseases; tonsillectomy and adenoidectomy at the age of 16; menstrual history irrelevant.

Marital history: Husband in good health.

Physical examination: A well-developed, slightly undernourished white Puerto Rican married woman, not looking sick, cooperative, well oriented, and ambulatory.

Temperature	99.6° F.
Respirations	18 per min.
Pulse rate	84 per min.
Blood pressure expressed in mm. of mercury	118/82

The examination was essentially normal.

Laboratory Findings

Hemoglobin	72% (10.4 g.) Hellige-Wintrobe
R.B.C.	3,700,000 per cmm.
W.B.C.	5,400 per cmm.
Urinalysis	Negative
Kahn	Negative
Blood culture	Sterile

Agglutination test with *B. abortus* antigen	Positive (dilution, 1: 200)
Skin test with purified *Brucella* protein	Negative
Gastric analysis	No free HCl in residue; good response to histamine injection

On March 23, 1945, the patient was seen again. The temperature record, which she had been asked to keep, revealed but a slight rise on March 20 and 21 at 4:00 P.M. The perspiration at night had disappeared.

CHRONIC BRUCELLOSIS

9. J.M.Z. (CASE A–542 U.H.). This patient came to our private office in May 1943, complaining of body aches—especially around the waist—daily rise in temperature in the afternoons, general weakness—felt principally in the knees—drenching night sweats, and lack of initiative. He informed us that he had been suffering from the above symptoms for several years, but that they had become more persistent lately; on being questioned, he did not remember having had high fever for several days at any time. In 1940, because of the presence of calculi and recurrent attacks of acute cholecystitis, his gallbladder had been removed in a New York Hospital. In September 1940, he was admitted to the University Hospital with pain in the left renal region; a calculus was found in the left ureter but it was expelled spontaneously. The patient informed us that he and his wife drank raw milk on several occasions.

Physical examination revealed nothing outstanding.

Laboratory Findings

W.B.C.	4,380. per cmm.
Differential count: Lymphocytes	62%
Neutrophils	38%
Basal metabolism rate	—17
Agglutination test with *B. abortus* antigen	Positive (dilution, 1:12,000)

Treatment was commenced with subcutaneous injections of *Brucella* vaccine (Lederle); due to pronounced local and systemic reactions the amount injected had to be increased very gradually. Treatment continued for about six months, at the end of which the drenching sweats, the apathy, the bodyaches, and the rise in temperature in the afternoons disappeared completely. The patient was seen recently and found in good health; occasionally, he feels somewhat feverish and tired.

10. H.A.S., age 36 (CASE A–4783 U.H.). A young Puerto Rican woman came to our private office complaining of general weakness, lack of pep, somnolence, and a slight rise in temperature during the afternoons. The patient informed us that, for about a year, she had suffered from the above

symptoms which had forced her to stop work, as she tired so easily that she could not accomplish all she was supposed to do. Her bodyaches were more pronounced in the groins and periarticular regions; she stated that she had taken raw milk at various times.

Physical examination was essentially normal.

Laboratory Findings

Hemoglobin	16.6 g. (Hellige-Wintrobe)
R.B.C.	5,740,000 per cmm.
W.B.C.	12,400 per cmm.
Differential count: Neutrophils	78%
Lymphocytes	22%
Kahn	Negative
Urinalysis	Negative
Gastric analysis: Histamine-resistant anachlorhydria	
Basal metabolism rate	—19.5
Agglutination test with *B. abortus* antigen	Positive (dilution, 1:200)
X-rays of the lungs	Normal
Vaginal and rectoscopic examinations	Normal

Brucella vaccine (Lederle) was administered for a period of two months, three injections per week. There was a slight systemic reaction after each injection and when 1 cc. was administered, there was some local reaction, but after this treatment, the patient felt much improved and was able to return to work.

11. J.P.K., age 53 (CASE A–2974 U.H.). A white continental American was admitted to the University Hospital (service of Dr. Ramón M. Suárez) on July 2, 1942. The patient informed us that a cold had come upon him about eight weeks previously and that two weeks after this, he had begun having daily headaches, involving the right side of his head, usually about 3 to 4:00 P.M. Aspirins had relieved him at the beginning, but towards the end, had offered little help. By June 6, the headaches had become constant. A specialist had seen him but had not found anything wrong with his eyes, ears, nose or throat; an X-ray of the teeth had revealed no lesions. For about four years, he had been feeling a stinging sensation after each bath, which had bothered him so that it made him hesitate to bathe. The patient also complained of an excessive amount of perspiration, especially at night, for about the past six months; this perspiration had a very unpleasant odor.

Physical examination showed only normal findings.

Laboratory Findings

Hemoglobin	13.9 g. (Hellige-Wintrobe)

R.B.C.	4,830,000 per cmm.
W.B.C.	4,200 per cmm.
Differential count: Neutrophils	60%
Lymphocytes	37%
Monocytes	3%
Urinalysis	Negative
Stool	Negative
Blood chemistry	Normal
Agglutination for brucellosis	Negative
Skin test with purified *Brucella* protein	Positive
Opsonocytophagic test	Positive

X-ray of the paranasal sinuses revealed a slight opacity of the right maxillary antrum.

There was no follow-up.

CHRONIC BRUCELLOSIS AND PULMONARY TUBERCULOSIS

12. A.L.F., age 50 (CASE A–3764 U.H.). A white Puerto Rican male, admitted to the University Hospital on February 4, 1943, stated that he had been taken sick on January 30, 1943, with general malaise and chillness, headaches, pain in the knees, cough with some expectoration, and night sweats. He was seen by a physician who prescribed quinine, the chillness disappearing with this treatment. However, he continued to cough with expectoration; he was not sure whether or not he had run a temperature. He further stated that, for two to three months previous to admission, he had been suffering from frequent nausea and had vomited on several occasions a light yellow, watery, but not bloody, material; that he had lost about sixty pounds in weight during the last twelve months. He had worked for several years in a dairy and used to drink raw milk almost entirely. On several occasions he had had to extract the placenta from the wombs of cows.

Physical examination showed the patient to be undernourished and looking older than his age, but nothing abnormal was encountered except for subcrepitant rales over the right upper lung.

Laboratory Findings

Hemoglobin	14.1 g. (Hellige-Wintrobe)
R.B.C.	4,790,000 per cmm.
W.B.C.	5,300 per cmm.
Differential count: Neutrophils	60%
Eosinophils	2%
Lymphocytes	38%
Kahn	Negative

Blood Chemistry:

Non-protein nitrogen	37.9 mg.
Blood sugar	302. 8 mg. per 100 cc. of blood
Urinalysis	Slight traces of albumin 19 g. of sugar per 1000 cc.
Feces	Negative
Agglutination test for brucellosis	Positive (dilution, 1:600)
Sputum	Positive for acid-fast organisms.

X-rays of the lungs revealed pulmonary tuberculosis of the right upper lung field with cavitation; gastric analysis showed histamine-resistant anachlorhydria.

The patient was transferred to a tuberculosis sanatorium; there was no follow-up.

COMMENTS

Brucellosis seems to be of rather common occurrence in Puerto Rico, hence it is indeed unfortunate that more accurate statistics are not available. This must be due, in part, to the fact that physicians are not reporting such cases to the proper sources of the Department of Health. In discussing this condition with colleagues, one realizes only then the true incidence of brucellosis in Puerto Rico.

The modern electric refrigerator may have some part in the rising incidence of the disease here. Our grandfathers had to boil their milk before drinking it so as to prevent its souring, and in this way unwittingly combatted the disease. Today, however, milk can be easily preserved raw for a long time; then, too, raw milk is cheaper than pasteurized, and is therefore served practically everywhere, especially in restaurants. It is also utilized in the elaboration of cheese. No law forbids its use unpasteurized.

It is surely fortunate that the organism producing brucellosis has a low virulence in Puerto Rico for, otherwise, the disease would be rampant. Notwithstanding, in the opinion of the writer, brucellosis is now frequent among island people and, unless preventive measures are established, the disease will become widespread. Some prophylactic measures might be:

1. A campaign to familiarize the public with the effects and consequence of the disease.

2. Forced pasteurization of all milk sold in restaurants and in the preparation of cheese.

3. Elimination of diseased animals.

4. The medical profession must play its role in the extermination of the disease. Its etiologic agent, or agents, must be classified and all possible vectors studied.

SUMMARY

A review of the salient clinical features of brucellosis has been presented here. In Puerto Rico the disease is usually produced by the ingestion of raw milk.

Of twelve patients observed by the writer, eight were suffering from the acute type of the disease, and four were chronic cases. Study of the gastric acidity in seven revealed absence of free hydrochloric acid in the gastric residue in three and histamine-free resistant anachlorhydria in four. Inference has therefore been made to the effect that the absence of free hydrochloric acid in the gastric contents seems to have some bearing on the production of brucellosis in humans. It is suggested that investigations along these lines be carried out by those working in areas where the disease is more prevalent.

Whenever tried in the treatment of acute brucellosis, sulpha drugs were used with success. In chronic brucellosis, vaccine therapy brought about a disappearance of the symptoms.

It is the experience of the author that injections should be placed deep in the muscle and not subcutaneously, as heretofore recommended, so as to avoid the formation of large tender nodules, or abscesses, at times.