DIAGNOSIS AND TREATMENT OF BRUCELLOSIS

(*Undulant Fever*)

CHARLES L. HARTSOCK, M.D.

Not only the treatment but also the diagnosis of undulant fever are far from being satisfactory, although many types of therapy are being tried and critically evaluated. Because of the tremendous scope of the disease, frequent discussions and reappraisals of our ideas about brucellosis will be absolutely essential for some time. Some physicians more or less disregard brucellosis and even scoff at the chronic phase of this new intruder in the realm of human disease. Others are overenthusiastic and attempt to explain many vague and indefinite problems upon the basis of chronic brucellosis without sufficient evidence. Still other physicians have lost their original enthusiasm and have reverted to the first viewpoint, probably because of the great difficulty in coping with the caprices and vagaries of this disease and the marked uncertainties in diagnosis and treatment.

Even though this disease is extremely protean and remarkably bizarre in its manifestations, it is a disease of known causative organism to which the generic term of brucella has been given.

The original infection in man was traced to the drinking of goat's milk on the Island of Malta, and for many years this disease was known as Malta fever. Because of the undulating character of the fever with a tendency for remissions and recurrences, it was later called undulant fever which proved to be a very poor description of the febrile reaction in many instances. Brucellosis is the more specific term derived from the organism causing the disease.

Three strains of the brucella organism have been isolated and named for their respective hosts: b. melitensis for the goat strain; b. bovine for the cattle strain; and b. suis for the swine strain. Many other animals are infected with these strains, and man is subject to all three. The virulence of the organisms differs, the bovine strain being the least malignant. However, cattle are frequently infected with the swine type, and as man usually contracts the disease from cattle, he is afflicted with the more virulent b. suis in spite of the infective source. The infection localizes in the udders of cattle and contaminates the milk which is the chief source of infection to man. The known modes of infection are the following:

(1) *The ingestion of milk and milk products.* Complete pasteurization prevents infection with the brucella organism. The danger lies either in unsuspectingly drinking unpasteurized milk, or in disregarding this potential source of infection because of the effect of pasteurization upon

the quality and taste of milk. This mode of infection is common in rural districts, as on most farms the milk is always used without pasteurization. A patient of mine who owns a dairy in a community which is very adverse to pasteurization told me that he pasteurizes his milk without labeling it as such and has never had one complaint about the taste of the milk since he started to pasteurize it. A very great danger lies in incomplete pasteurization, which is a source of infection extremely difficult to control. Milk products, especially ice cream from unpasteurized milk, are also a potential source of infection. I learned from a patient whose daughter and herself had contracted brucellosis from drinking unpasteurized milk that all the ice cream used at the church socials in her community is made by a neighbor who utterly disregards the fact that his herd is infected. As long as this attitude prevails, the control of this disease will be difficult. Fortunately cheese products are usually made from pasteurized milk. Goat's milk is supposedly beneficial in the treatment of gastrointestinal diseases and is another potential source of infection when used in this way as it is very seldom pasteurized.

(2) *The handling of infected material.* Farmers and veterinarians are especially subject to this mode of infection. The handling of the aborted fetus and membranes is so virulent a source of infection that nearly all veterinarians have contracted this disease. Many of them, however, show very strong immune reactions seemingly without having passed through an active phase, which would suggest that immunity can be built up by contact with the disease without having it in an active phase. Direct contact with infected cattle in milking and in handling the infected milk is another possible source of infection. I also believe that it is possible to contract this disease by handling infected meat, although this is not so likely a source of brucellosis as it is of tularemia. I have one patient, a meat handler, in whom no other contact with the disease could be demonstrated.

(3) *The ingestion of infected material, especially meats, that are likely to be uncooked.* This is probably a rare source of infection and a rather difficult one to trace.

(4) *Contact with humans who have the disease.* Infection from direct contact is unlikely, and with ordinary sanitation in the disposal of excreta one need not fear infection from this source. Laboratory workers, however, are very likely to be exposed in working with human cases and should exercise every precaution.

(5) In many cases it is impossible to trace the source of infection, and probably some other rare and unusual mode will eventually come to light.

The clinical types of brucellosis are extremely variable. However, they fall into three general groups.

(1) The acute febrile type is a clean-cut infectious process usually beginning as an ordinary influenzial type of infection with fever, chills, aches and pains, and pronounced weakness. The most characteristic and best lead-directing clue to the nature of the underlying infection is the presence of very severe sweats especially during the night. Symptoms may be prominently localized in several domains. In the respiratory system a severe and prolonged type of bronchitis leads one to suspect whooping cough. The disease frequently localizes in the central nervous system producing symptoms of meningitis and encephalitis and in this form has the highest mortality rate. It may also produce an acute type of arthritis simulating acute rheumatic fever, although joint pains and aches are much more common in the chronic type of the infection. Various gastrointestinal manifestations are also seen in acute brucellosis.

Although acute brucellosis usually begins as an influenzal type of infection, some other type of infection is suspected after the fever has been sustained for a week or longer. The fever chart may strongly simulate the sustained highly elevated, so-called typhoid type of temperature curve which may last six to seven weeks. It usually subsides gradually and sometimes permanently without any further episodes of this disease; however, it may go into a relapsing type and after two or three relapses eventually subside; or it may go into the undulating type and continue for an indefinite period of time. Aside from the prominent sweating and history of possible exposure to the brucella organism, very little distinguishes this type of acute illness from many other acute infectious diseases.

(2) The intermittent or undulant form either may be residual of acute brucellosis, or occur without passing through the acute phase. Undulating brucellosis assumes all the manifestations and complications of the acute type, but the attacks are usually less severe, do not last so long, and the fever is seldom so high. The attacks may recur once or twice a year, or again they may occur quite frequently. One of the best clues to the diagnosis of this type of infection is that the patient thinks that he is getting the "flu" too often. A history of four or five attacks of influenza, or what the patient thinks is influenza, with fever, aches and pains, and symptoms in various domains should suggest the possibility of the undulant form of brucellosis. The patient may feel reasonably well between these attacks, but as a rule lacks the endurance of the average individual and fatigues more easily.

(3) The chronic or continuous type of brucellosis is a more persistent form which may be either febrile or afebrile. In the febrile type a low grade continuous daily fever rarely exceeds 100 degrees F. but occasionally has a single reading which may reach 102 to 103. Other symptoms are weakness, fatigability, aches and pains, particularly in

the joints, ribs, and spine. The patient may be very nervous and restless, irritable, and in general present the picture of chronic nervous exhaustion or neurasthenia, except for the low grade fever.

The afebrile type presents the same clinical picture except that the temperature is absent. There is a question as to whether the afebrile type, or even the very low grade febrile type, is really a manifestation of active undulant fever, or whether the whole picture is a chronic neurasthenic and fatigue state resulting from exhaustion of the nervous system and inability to maintain thermostatic control of the body. Undoubtedly, many patients present this clinical picture in whom chronic brucellosis or any other infection cannot be demonstrated. The diagnosis of such cases is not easy because of the limitations of diagnostic methods for determining the activity in patients who have reactions indicative of exposure to brucellosis. A very important distinguishing point is the background of the patient. If a patient with a background of good health and good inheritance has had a sudden change in health, and if some of the symptoms and results of diagnostic methods suggest undulant fever, a therapeutic trial is indicated. Whereas, if the patient has a poor constitutional background which might be the basis for his symptoms, the evidence should be weighed more carefully because the severity of the treatment we have to offer at the present time is likely to do more harm than good. Good clinical judgment tells us that even though some of these cases may have brucellosis, it is better to treat them purely as a chronic exhaustion state.

Methods of Diagnosis. In any unexplained disease state manifesting any characteristic of acute infection, or in an undiagnosed chronic disease state, diagnostic methods should be used to detect the presence of chronic brucellosis. The history of exposure should be elicited giving special attention to veterinarians, meat handlers, farmers, users of unpasteurized milk, and laboratory workers. I believe it advisable to check this group of workers routinely in any chronic disease state.

The pathology and objective clinical findings detected by routine physical examination tend to turn the attention away from the real underlying disease as they often serve as false clues and are apt to lead to the diagnosis of a symptomatic disease syndrome.

The only diagnostic methods of any specific value are laboratory studies of which blood culture is the most specific with the isolation of the organism in the acute cases. The organism is rarely found in chronic cases, although a culture of a local focus may make a specific diagnosis. The growth of brucella organisms has been reported from periovarian abscesses, and in one of our cases a culture was obtained from the gallbladder. Similar methods at the autopsy table have frequently made the diagnosis of otherwise undiagnosed cases.

Agglutination tests are very valuable, particularly in acute febrile cases where the titer may run quite high. The highest in my experience was 1/10,000. Early in the course of the disease it is usually negative and becomes positive after one to three weeks. In some cases the agglutinins never develop, and the disease runs a full course without ever having a positive agglutination test. In one case which was repeatedly tested during an acute illness lasting seven weeks the agglutination test was always negative. Twelve weeks later the fever entirely subsided, but the patient was still quite weak and easily exhausted. The agglutination test was negative, but the skin sensitization test was very strongly positive and produced a marked relapse of all the symptoms. During the last summer I saw three cases in which all of the symptoms suggested brucellosis. However, all tests for any type of fever were entirely negative, and the patients eventually recovered. The question arises whether or not we were dealing with brucellosis or some new type of infectious disease. The fact that cases have been reported in which all tests have been negative with the exception of positive blood cultures leads us to believe that both the agglutination test and the skin test can remain negative at all times in this disease. Brucellosis must still be suspected in spite of the fact that all laboratory tests remain negative. Fever of any cause such as from an acute upper respiratory infection may bring out agglutinins in chronic cases which may last for several weeks; these can also be provoked by the use of intravenous typhoid vaccine. I believe that a provocative test with typhoid vaccine should constitute one of our diagnostic methods. Unfortunately a skin test is usually done first, and the instillation of even a small amount of vaccine or brucella allergen may produce antibodies. However, when there is no severe reaction to the skin test making the provocative test desirable, it is unlikely that these immune substances would be stimulated to the point of confusion.

If the agglutinins develop and the agglutination test is positive, the length of time that these remain, after the disease has subsided, varies greatly. In some cases the tests remain positive for a long time in spite of the fact that there is no evidence that the disease has become intermittent or chronic. In other cases the agglutinins disappear rapidly after the acute stage has subsided. In the chronic or intermittent form the agglutination test is most unsatisfactory, as it is usually negative, but in such cases I believe that the provocative test with typhoid vaccine should be a standard test and should be made before the skin test.

The skin test can be performed either with protein of brucella or with the vaccine. At the present time, we use 1/10 cc. of Lederle's vaccine injected intracutaneously and read this test at the end of 24 and 48 hours. Many cases show a local reaction at the end of 24 hours which usually subsides completely at the end of 48 hours in negative cases. If

the test becomes progressively severe during the 24 to 48 hour period, it constitutes an important point of interpretation. The skin test is probably our most valuable single test especially in the chronic state, but it certainly is not infallible. There are definite false positives. The patient may get a fairly severe reaction from sensitivity to the protein, and it is almost impossible to differentiate such reactions from the real positive. There are also false negatives. One patient who passed through an acute stage of brucellosis with marked respiratory symptoms and an agglutination test of 1/10,000 had an entirely negative skin test.

In general the skin test is reliable and should be reserved until all other tests have been completed in order to avoid false immune reactions. In interpreting the positive skin test it is a question of whether the disease is active or whether the positive reaction represents an immunity. I make a definitely positive diagnosis only in those cases which show very strongly positive local reactions and in whom there is also usually a general reaction with lymphangitis, adenitis, a rise in fever, and possibly the reproduction of some of the symptoms of which the patient has complained. When such a reaction is present, I believe that it undoubtedly means active disease. The opsonocytophagic index has been devised to distinguish these conditions, but in my experience is not nearly so efficient as would be desirable.

The opsonocytophagic index which was devised by Huddleson is a test of the power of freshly drawn white corpuscles to phagocytize a suspension of brucella organisms in vitro. Varying degrees of phagocytosis indicate the stages of susceptibility, infection, or immunity. It is not strictly a diagnostic test and should be used especially in conjunction with the skin test to determine the degree of immunity. My chief criticism of this method is its questionable accuracy in determining which cases are immune as it seems to give too high a percentage of immunity. I have observed this in some cases in which the disease undoubtedly continues to be active clinically. This test has also been found wanting in determining the amount of treatment.

The animal inoculation method of diagnosis is very reliable and is comparable to the methods used in animal inoculation for tuberculosis. The chief criticism of this method is that it is rather slow and is a very dangerous source of infection to laboratory workers.

As previously mentioned the order of making diagnostic tests is very important. It is highly advisable not to do a skin test until the agglutination and provocative agglutination tests have been done, because of the danger of producing falsely positive agglutinin reactions which forever make the diagnosis of this disease impossible by present methods.

The differential diagnosis of brucellosis is beyond the scope of this discussion. A list of some of the diseases from which this disease must be differentiated indicates the difficulties in the differential diagnosis.[1]

1. Influenza
2. Pneumonia
3. Typhoid
4. Paratyphoid
5. Malaria
6. Tuberculosis
7. Acute rheumatic fever
8. Subacute bacterial endocarditis
9. Septicemia
10. Tularemia
11. Typhus
12. Kula agar
13. Relapsing fever
14. Infectious mononucleosis
15. Syphilis
16. Lymphoblastoma
17. Bronchitis
18. Bronchiectasis
19. Bronchial asthma
20. Sinusitis
21. Cholelithiasis
22. Cholecystitis
23. Appendicitis
24. Peptic ulcer
25. Ulcerative colitis
26. Nephritis
27. Pyelitis
28. Cystitis
29. Ovarian tumor
30. Menopause
31. Sciatica
32. Low back pain
33. Osteomyelitis
34. Neurasthenia
35. Psychoneurosis
36. Hysteria
37. Insanity
38. Five kinds of skin disease

This sounds very much like the list of diseases in the old ads for patent medicine which could be cured by its magic properties. This list is exaggerated but not far from the truth and is the chief reason for the lack of case reports in this article as so few cases are ever alike. This disease must be considered in general terms, as one does tuberculosis and syphilis, and as affecting any part of the body.

Although the diagnosis of this disease is considerably difficult, the treatment as compared with the diagnosis presents even greater problems.

Methods of Treatment. The expectant and supportive type of treatment is used in many types of infection without known specific cause, or in diseases of known etiology without specific treatment such as typhoid fever and tuberculosis. In acute cases of brucellosis general support of the patient with fluids, adequate food, and the relief of distressing symptoms is often all that is necessary, and many patients completely recover without recurrences. I think a great many cases of this type must occur which are unrecognized and undiagnosed and get entirely well.

If the disease progresses to the intermittent or chronic form, it is rather unlikely that it will subside with time, and if it does, will cause much disability in the process. Accordingly the methods of treatment should be considered more often in the chronic than in the acute form. However, rest and general supportive measures must not be neglected in the chronic form in addition to the more specific types of treatment.

Immune sera, either the prepared type or sera from recovered cases, should be reserved for acute cases, primarily for those which are likely to result fatally, namely, those with involvement of the central nervous system. The reports are not encouraging enough at the present time to advise it in the routine treatment of acute cases. However, we have reason to believe that sera can be greatly improved and will eventually be of very specific value.

Vaccine or brucella protein may be given either in the acute or the chronic stage and, in my opinion, constitute the best form of treatment at the present time. The great objections to it are that it is quite severe in its reactions and local sterile abscesses may ensue. During the period of treatment, the patient is likely to be made much worse from the standpoint of symptoms and feeling-tone. It is particularly contraindicated in cases of central nervous system involvement. However, patients who are able to stand unusually severe reactions get the best results.

I question the use of vaccine or brucella protein in doubtful cases as it brings out the agglutinins in the blood, and makes it impossible ever to determine whether or not the patient really has undulant fever. Some physicians have a rather bad habit of testing the effect of vaccine treatment on many chronic disease states without having made careful diagnostic tests. If the vaccine method had very specific therapeutic effects this method could not be criticized, but the specificity of the treatment is not great enough in my opinion to counteract the serious objection previously mentioned. Also, in mild chronic diseases the treatment makes the patient feel worse than the disease, and general rest and supportive measures give good results.

If this treatment is not effective or only partially effective, nonspecific methods of treatment may be used in recurrent or chronic forms, particularly fever therapy either with typhoid vaccine or artificial fever. This again should not be used in the acute stages. I prefer this type of treatment in doubtful cases rather than vaccine treatment because falsely positive tests are not likely to be produced, and the use of typhoid vaccine and artificial fever frequently brings out high agglutinins in the blood definitely to establish the diagnosis.

In this day of miracles with chemotherapy, one would expect that some of the sulfonamides would produce results as brilliant as they have in other infectious diseases. Some reports in the literature have been encouraging, but in my experience the drugs are useless except when they produce a severe drug reaction, and in these cases the patients have done unusually well. The benefits, however, are not due to the drug but to the general shake-up of the system similar to that produced by the use of vaccine or fever. I believe that the favorable reports in the litera-

ture are the result of false observations and are spontaneous cures or those cases which have a drug reaction. Possibly our best hope is in the development of some new drug, but at this time chemotherapy is not encouraging.

The removal of a local focus of the brucella organism may give good results, such as the drainage of an ovarian abscess or the removal of a gallbladder. The possibility of such a focus should be especially considered in chronic or undulating brucellosis after an acute episode. Since the instillation of brucellergin or vaccine in very small amounts causes a recurrence of symptoms and at times severe reactions, patients should avoid taking brucellergin by mouth. Certain phenomena suggest that even the drinking of pasteurized milk from an infected herd or the ingestion of meat containing the brucellergin may be the exciting factor in a flare-up of symptoms.

The best prophylaxis at the present time in the pasteurization of milk and in avoiding direct contact with infected materials. Vaccination for the control of this disease will probably come into effect much the same as vaccination for typhoid. Certainly the vaccination of persons constantly exposed to this disease should be attempted, and its effects studied. Unfortunately, the morbidity is so much higher than the mortality that adequate measures have not been taken to control it.

The prognosis is good as far as life is concerned. The mortality rate is between 2 and 5 per cent, and most of these cases have central nervous system involvement. The prognosis is also reasonably good for complete recovery in acute cases, but in the intermittent or chronic type, relief of symptoms and partial improvement is all that can be expected. The patient seldom regains his former state of health. Results from treatment in the chronic stage are even more difficult to evaluate because of the greater uncertainty in diagnosis. For this reason I am inclined to favor supportive measures of very chronic cases similar to those used in chronic tuberculosis.

The greatest question to decide in any given case is when to discontinue treatment. In general the subjective well-being of the patient is the best indication for stopping treatment. Vaccine treatment, however, must be intermittent, otherwise the patient will steadily feel worse. Usually patients do not begin to feel better until treatment has been disdiscontinued. As previously indicated I do not believe that opsonocytophagic index study gives us a clue as to the proper time to discontinue therapy.

SUMMARY

The difficulties in the diagnosis and treatment of brucellosis are obvious. The clinical picture is very similar to that of many other

diseases, and the diagnostic tests are subject to error both in a positive and negative way. We lack specific therapy which could be used as a diagnostic method, and the present methods of treatment are far from being satisfactory. A case with a questionable diagnosis, subjected to long severe treatment in which we do not have too much confidence, is discouraging when it is the general lay belief that all that is needed for a cure is the establishment of a correct diagnosis. The disappointment of many of these patients when they learn that the treatment is sorely limited, although their disabling illness has been definitely diagnosed, is certainly shared by their physician.

Until brucellosis is better controlled we should consider this disease as a scourge of mankind which is becoming more and more prevalent. It should be regarded as a major health problem, and certainly will be when the demoralizing effects of the chronic morbidity are more definitely established.

REFERENCES

1. McGinty, A. O. and Gambrell, W. E.: Chronic brucellosis. International Clinics, 1:1-27 (March) 1939.