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900 Sherbrooke St. W.

CHRONIC BRUCELLOSIS: DIAGNOSIS AND TREATMENT*

E. P. Scarlett, M.B.

Calgary Associate Clinic, Calgary, Alta.

MEDICAL observations on the human incidence of brucellosis on this continent represent in the main the work of the past twenty-five years. The conception of the disease as a self-limited condition with a tendency to a prolonged course, in which the diagnosis is determined by the agglutination reaction, has delayed the recognition of the true nature of the disease. We are now coming to realize that the acute severe form represents only a fraction of the cases and that the majority occur in the form of an endemic chronic infection. In such cases the epidemiological history is obscure, the course is intermittent or continuous, the symptoms protean to an extraordinary degree, there are frequently marked psychasthenic reactions, fever may not be evident, and there are no arresting physical signs. When there is added to these features inadequate laboratory diagnostic techniques and the absence of any satisfactory therapeutic agent there emerges the elusive and difficult clinical picture of chronic brucellosis as it exists at the present time.

The increasing numbers of clinical reports and surveys leave no doubt that an unrecognized chronic form of brucellosis is widely prevalent. It must now be regarded as the most common disease transmitted from animal to man.¹ The usual story follows a pattern familiar to all students of the disease. The individual has a mild infection, there is later a flare-up or several obscure febrile episodes. There follow one or more years of ill health, no adequate

diagnosis is made, the patient becomes either partially or in some instances wholly incapacitated. In those districts where physicians have become aware of the condition numerous cases have been found. In the Province of Alberta there has been a steady increase in the number of reported cases since 1942 due to the increasing awareness of the disease.² Because of these facts there is need for a periodic appraisal of the problem and particularly for a survey of the diagnostic criteria of the disease.

Incidence.—Despite the scepticism in some quarters regarding the prevalence of chronic brucellosis, a review of the surveys which have been made in endemic areas indicates beyond any doubt the wide extent of the disease. In 4,000 individuals tested in Rhode Island (1940) 441 or 10% showed clinical and laboratory evidence supporting a diagnosis of chronic brucellosis.³ This parallels the results of most studies which indicate that approximately 10% of the population in endemic areas has been invaded by *Brucella*. A varying percentage of this group has the disease in some degree of activity. Admittedly such conclusions rest upon a still imperfect understanding of the clinical aspects of the disease and shortcomings in the use and interpretation of laboratory procedures.

At the same time it should be pointed out that brucellosis has a tendency to become chronic in every species of animal in which it has been studied, and that in cattle, for example, veterinarians find that only from one-third to one-half of those becoming infected ever recover fully.⁴ This chronicity of the disease in comparative animal studies is a striking fact. Furthermore a most important feature of brucellosis is the actual invasion of *Brucella* followed by latency of infection. Latent infection from a single exposure has been known to develop into frank disease without intervening symptoms as late as eight years after the initial infection.⁵ This phenomenon is also probably responsible for the recrudescence that occurs in patients who have made spontaneous or therapeutic recoveries from manifest and proved disease, coming in some instances after an interval of five years or more of perfect health. This immunological observation is vital to an understanding of chronic brucellosis.

With respect to the use of non-cultural laboratory methods in establishing the index of the incidence of the disease, while inade-

* This paper was presented at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Ottawa, November 29, 1947.

quacies in the interpretation of these results exist, there is no longer any reason to doubt that the tests—intradermal and agglutination—are specific for brucellosis. Thus the considerable number of reactors which are being found in surveys represents a relatively true situation in indicating the large percentage of the population which has been infected with *Brucella*. In this connection, the analogy with tuberculosis is striking.

With these points in mind we wish to review our experience with a group of 100 cases of chronic brucellosis which have been under treatment for the past two years. All have been subjected to honest scrutiny and have been under observation a sufficient time to enable us to check our conclusions closely and repeatedly.

It is not proposed to discuss the *epidemiology* involved in these cases. This is a very real and complex problem which concerns clinicians, veterinarians and public health authorities acting in co-operation. Our only interest in this particular centres on the fact that the distribution of cases as we have noted them is related to certain areas of this Province where there has been close contact with infected animals or no pasteurization of dairy products. The invading organism in those cases in which it has been recovered has been the *B. abortus*, the bovine strain. There are no complete records to indicate the percentage of *Brucella* infection in cattle and swine in the Province of Alberta but it is recognized as being of considerable extent. As an indication, in 1946, of 4,105 bovine blood samples tested there were 701 positive reactors (positive agglutination reaction in dilution of 1:100 or higher) or 12%.⁸ A notable feature of the disease in this Province is the relative absence of cases of infection among abattoir workers. With the large number of people in this stock-raising part of the country employed in handling animals which must be infected, this is puzzling particularly when contrasted with the reports of the incidence among abattoir workers in Iowa and the middle States. To date no explanation of this phenomenon has been forthcoming.

CLINICAL DATA

This series comprises 100 cases of chronic brucellosis accepted after careful clinical study because of the combination of findings and by

virtue of the clinical course before and after specific vaccine therapy. Nine of these cases either received inadequate treatment or were lost sight of after some treatment and are not included in the major items of this report. All cases have been under treatment from at least 3 up to 20 months. There was 1 death, a woman 56 years of age under treatment for 13 months with a severe relapsing form of the disease, who as well had recurrent metastatic malignant involvement from a carcinoma of the breast removed some years before.

Sex and age.—There were 36 males and 55 females. Ages ranged from 5 to 65 years. The age groups were as follows: children (15 and under) 4; 16 to 30, 30 cases; 30 to 40, 25 cases; 40 to 50, 23 cases; over 50, 9 cases.

Environment.—City residents, 31; residents of rural towns or villages, 27; resident on farms, 33. There were 2 packing-house workers, 1 veterinarian, 1 cattle buyer. Two cases had been internees in a Japanese prison camp.

SYMPTOMATOLOGY

All these patients were ill and had sought medical care. The duration of symptoms prior to treatment ranged from six months to five years. The more common symptoms are indicated in Table I. The cardinal complaints were weakness (100%) and aching pains (95%). Two characteristics of the complaint of weakness should be noted. It was described as an overmastering tiredness as a result of which

TABLE I.
 SYMPTOMS IN CHRONIC BRUCELLOSIS

Fatigue, weakness	_____
Aching pains	_____
Fever	_____
Nervousness	_____
Headache	_____
Gastro-intestinal	_____
symptoms	_____
“Rheumatism”	_____
Weight loss	_____
“Black-outs”	_____
Sweating	_____
Cough	_____

the patient was unable to carry on with work. There were as well episodic attacks of extreme weakness characterized by many of the patients as “black-outs”. The aches and pains followed no pattern and involved both muscles and joints as soreness and stiffness. The nervous symptoms were mainly irritability and emotional instability, with a curious mental depression in

many of the cases. Gastro-intestinal disturbances usually took the form of epigastric burning, flatulence and constipation.

It will be apparent from this list of symptoms why all observers have stressed the difficulty of distinguishing chronic brucellosis from so-called neurasthenia or "constitutional inadequacy". On the one hand Alice Evans after bitter personal experience has pointed out the necessity of excluding the possibility of chronic brucellosis before making a diagnosis of neurasthenia.⁷ Conversely it is equally important that the patient with neurasthenia be not regarded as having chronic brucellosis on the basis of the symptomatology and inconclusive laboratory data and observation.

Physical examination.—The physical findings generally speaking were not significant. A peculiar pallor was evident in 10 of the cases. Splenomegaly was noted in 3 cases only.

CLINICAL FEATURES

Brucellosis is now recognized as a disease which may masquerade under many guises. In addition the greatest single obstacle to complete cure of the infection in chronic cases is the tendency of the *Brucella* organism to live on in a focus which keeps up the infection in a low-grade form. Such focal sites are the spleen, the biliary tract and retroperitoneal and other lymph nodes. Certain comments with regard to the localizing character of brucellosis in this group of cases may be made.

Biliary tract.—In four cases of chronic brucellosis to the writer's knowledge positive cultures of *Brucella* have been obtained from the gall bladder, and cholecystectomy in these cases has resulted in a complete remission.

CASE 1

Male aged 46. For two years there had been flatulent indigestion and epigastric discomfort. Concurrent with these symptoms he noticed periodic evening fever and thought he was subject to "influenza" attacks. On hospital admission cholecystograms showed a non-functioning gallbladder with at least one gallstone. Agglutination reaction for *B. abortus* was positive in a titre 1:1,280; the intradermal test was strongly positive. For a month after admission he ran intermittent fever which finally responded to sulfathiazole therapy. Seven weeks after admission cholecystectomy was done, the gallbladder being grossly thickened and adherent to surrounding structures. Bile culture was negative. In the deeper part of the gallbladder mucosa and in the muscle coat there was a chronic granulomatous process containing foci of pus cells and eosinophile leucocytes together with lymphocytes. This picture was highly suggestive of *Brucella* infection and *B. abortus* organisms were isolated from the culture of this material. The patient has shown progressive improvement since the operation.

Joint manifestations.—Of the 100 cases 10 had what may be described as atypical arthritis and 5 of these had received treatment for their disability which had been diagnosed as arthritis. The involvement in these cases was bizarre, the joints swollen and tender. In every instance they have responded to specific vaccine therapy. Although low back pain was a common symptom there were no proved cases of spondylitis. The following case illustrates the arthritic type of the disease.

CASE 2

Male aged 45. For four years he had complained of marked fatigue and stiffness and soreness in most of the joints. He was finally obliged to stop work. The pain in the knees, hands and back became worse and he was treated for months at an institution specializing in arthritis where he failed to improve. He was first seen in October, 1946. The knees and fingers showed very slight swelling. Agglutination reaction for *Brucella* was positive in a titre 1:160, the skin test was strongly positive, the opsonocytaphagic index was moderately positive. Treatment for chronic brucellosis was begun and in four months' time his fatigue had cleared and the joints were giving very little trouble. He was able to shovel snow and was working regularly. At present, after one year of treatment he is well and is being maintained on a maintenance dosage of *Brucella* vaccine (T 50 strength) 0.2 to 0.4 c.c. twice a week.

Pulmonary manifestations.—One patient of this group had been in a sanatorium under observation for tuberculosis. There were no cases showing an atypical form of pneumonia.

Marked neurosis.—Illustrating the degree of neurosis which may exist and its response to treatment is the following case.

CASE 3

Married female aged 27. For years she had suffered from extreme fatigue, headache and aching pains throughout the body. She had become completely prostrated and was emotional and depressed. She was regarded as a hopelessly unstable neurotic individual by all who had seen her. On examination there were no localized physical signs. Agglutination reaction for *Brucella* was positive in a titre 1:40, the skin test was strongly positive. Specific vaccine treatment was begun in May, 1947, at first with difficulty because of the patient's extreme nervous instability. After six months of treatment the improvement has been remarkable. She writes, "I am catching up on things I had let slip when I felt so poorly". "I am coming ahead much faster than those that baby themselves."

Neurasthenia.—The following case illustrates the degree of extreme physical and mental fatigue which may afflict patients with chronic brucellosis.

CASE 4

Single female aged 24. For three years she had suffered from increasing weakness, aching pains in the body and joints and extreme lethargy. She had lost 10 pounds in weight and had fever 99 to 100° every day or so. She finally was obliged to resign from her teaching post for a year. For three months she had

been confined to bed most of the time. Physical examination showed nothing significant. The agglutination tests for *Brucella* were negative, the skin test was moderately positive. Specific vaccine treatment was begun in December, 1946, and in three months she was able to return to teaching. With the exception of an occasional flare-up at first she has steadily improved and is now practically well on a maintenance dosage of *Brucella* vaccine twice a week.

Skin lesions.—Various types of skin lesions have been described. In this series one patient showed a macular eruption and two an erythema of the limbs which was aptly described by one observer as a “mercuochrome flush”.

LABORATORY PROCEDURES

A clear understanding of the significance and limitations of the laboratory tests in chronic brucellosis is necessary to avoid the confusion and false conceptions which exist at present with regard to such tests. The chief points in this connection are summarized in the following observations based upon our own experience and the investigations of others. In respect to the present group of cases the main findings were as follows (Table II).

TABLE II.
 REACTION TO LABORATORY TESTS

Intradermal test:	
Marked	25
Moderate	63
No reaction	3
Serum agglutination test:	
Positive reaction	25
Titre 1:20, 2 cases; 1:40, 6 cases.	
1:80, 10 cases; 1:160 or over, 7 cases.	
Negative reaction	66
Opsonocytophagic index (Huddleson) at onset:	
Moderate	11
Slight	5
Negative	75

The intradermal tests were carried out with a 1:10 dilution of Lederle's treatment vaccine (equal parts bovine and porcine strains) giving a suspension of 2,000,000,000 organisms per c.c., 0.1 was injected and the test read in 48 hours up to one week. For the agglutination test Huddleson's rapid plate method was employed using a commercial antigen. The phagocytic test was carried out with a 24 hour culture strain of *B. abortus* organisms. No attempt was made to secure blood cultures in these chronic cases of the disease.

Intradermal test.—This test failed to give a positive response in only 3% of our group of cases. A positive reaction merely indicates previous *Brucella* invasion. Its numerical accuracy is generally agreed to be about 92% in proved cases of the disease. It should be interpreted

in the same light as the tuberculin reaction. Hence the intradermal test does not distinguish past from present disease, nor inactive from active infection. It is thus indefensible to make the diagnosis of brucellosis on the basis of a positive intradermal test.

Agglutination test.—In this series of chronic cases the agglutination test was negative in 72%. This is in line with the reports of most observers. It follows that this test cannot be relied upon to confirm the clinical diagnosis, nor, which is worse, does a negative agglutination test exclude the possibility of brucellosis. Furthermore there has been shown to be a difference in the agglutination response with different antigens,⁸ agglutinins may appear intermittently at uncertain intervals, and occasionally cross agglutination may occur. In view of the poor agglutination response in chronic brucellosis and the features above noted, there would seem to be little advantage in establishing an arbitrary critical titre level as being diagnostic. The important point is that the test is not a reliable diagnostic aid and that it cannot be used to exclude *Brucella* infection.

Opsonocytophagic index.—The phagocytic study introduced by Huddleson is of small relative value in diagnosis and then only when used in conjunction with other procedures. A strongly positive skin test with a low phagocytic index may indicate that the patient has active infection. We have found it of greatest value in following the course of a patient under treatment when a progressive increase in the phagocytic index is usually commensurate with clinical improvement. Like other observers we have noted aberrant findings so that the procedure must be accepted with reservations.

Blood count.—We have not found that the pattern outlined by Calder and his associates⁹—relative lymphocytosis, leukopenia and a mild macrocytic anæmia—has applied in a sufficient number of our patients for it to be of any particular diagnostic value.

Sedimentation rate.—Like other observers we have found that the sedimentation rate in brucellosis usually remains normal throughout the course of the disease. This is frequently an important aid in differential diagnosis.

Summary note.—Since all the laboratory aids to diagnosis have serious limitations, it seems that the reasonable thing to do is to carry out

all the non-cultural tests and then to relate them critically to the clinical findings. Isolated laboratory findings are worthless.

DIAGNOSIS

The diagnosis of chronic brucellosis is admittedly difficult. In any survey of chronic cases from the clinical standpoint one is impressed by the fact that the subjective findings are conspicuous by their varied range while the objective findings are conspicuous by their absence.¹⁰ From the laboratory standpoint diagnostic tests are limited. In the face of this dilemma, until better criteria are devised, diagnosis must be based upon investigation of all aspects of the case and the final decision rest upon clinical judgment. There must first of all be a lively clinical sense of the possibility that chronic brucellosis may exist in a given case. This should be balanced by the realization that brucellosis is not an acute general infectious illness with a positive agglutination test. The two symptoms which dominate the clinical picture are fatigue and muscle and joint pains. A positive skin test indicates *Brucella* sensitization and serves as a broad guide. This should be set alongside the other laboratory findings and the results considered in relation to the clinical findings, endeavouring to rule out all other diagnostic possibilities. The close resemblance between brucellosis and a psychogenic illness such as neurasthenia must be regarded from both points of view.

As the clinician becomes more familiar with the disease, we feel sure that he will recognize several clinical syndromes which, in spite of the variable nature of the disease, he will come to associate with chronic brucellosis. Only in this way will sound clinical judgment ever develop. As Foshay says:¹¹ "Better diagnosis of this deceptive disease during the next twenty years will depend chiefly upon a better grasp and understanding of its clinical manifestations and less upon laboratory developments".

TREATMENT

The treatment of chronic brucellosis is most difficult and relatively unsatisfactory. Two factors must be borne in mind in evaluating treatment under any circumstances—the great difficulty in establishing the diagnosis, and the occurrence of spontaneous remissions of varying degree.

The *sulfonamides* in our experience are of little value in the chronic form of the disease except to control acute exacerbations. *Chemotherapy* has no real effect. Although the results of the use of streptomycin in experimental animals have been encouraging, its use in human cases, while inducing a temporary remission in some instances, does not materially affect the course of the illness. *Fever therapy* has given good results in the spondylitis and salpingitis manifestations of the disease, but we have not had occasion to use it.

Specific vaccine therapy constitutes the main attack upon the chronic case. The aims in treatment are desensitization to the *Brucella* protein and the production of antibodies. These ends are best accomplished by the use of killed organisms in a concentration avoiding anything but mild local and systemic reactions. The intramuscular route rather than the subcutaneous is more likely to avoid such reactions. Brucellin of Huddleson which is a filtrate of all three strains of *Brucella* and commercial vaccines we have found to give too great a reaction. Harris reports a vaccine from a *B. abortus* strain of greatest value in his experience.¹²

We have used the detoxified vaccine prepared by Dr. Lee Foshay of the University of Cincinnati. This is a nitrous acid treated *Brucella* vaccine from the *B. suis* strain. We have found it possible to start with a T25 strength as a rule giving 0.05 c.c. in daily injections, gradually increasing the dosage, keeping below the reaction point. Treatment is continued for months, nine to twelve months usually or longer. In the later stages a maintenance dosage is given two or three times a week. The reasons for this prolonged treatment are that the incidence of recurrences is high in cases in which inadequate immunization is obtained, and because of the low antigenicity of the *Brucella* organism, prolonged immune response to vaccine is essential to prevent relapses.

We have found that the first relief of symptoms is apparent in from six to twelve weeks after vaccine treatment is begun. The criteria of improvement are disappearance of the subjective symptoms, ability to perform work, absence of fever, increase in weight and increase in the phagocytic index. It is freely admitted that this vaccine method of treatment is tedious and makes a great demand upon the patient. The answer is that, until better meas-

ures of treatment are discovered, this remains the only attack upon the chronic entrenched form of the disease which offers any hope of success or improvement. Furthermore it has been our experience that patients need little urging to continue the laborious vaccine treatment after the initial stages because the improvement which occurs is sufficient encouragement to persist.

The duration of treatment to date in the cases of chronic brucellosis under review is as follows: 3 to 6 months, 29; 6 to 12 months, 44; 12 to 18 months, 16; over 18 months, 2. Table III records the results of treatment.

TABLE III.

RESULTS OF TREATMENT	
Excellent (arrested cases off treatment)	8
Very good (on maintenance treatment)	29
Good	31
Improvement	18
Slight or no improvement	4
Deaths	1

Of the cases showing marked improvement and on a maintenance dosage of vaccine once or twice a week, 21 had been on continuous treatment for 12 months or more, and 8 for 6 to 12 months. Of 52 cases showing improvement 35% reported a gain in weight, in some cases up to 20 lb.

At the present time about 75% of cases may be expected to obtain a complete arrest of chronic brucellosis with persistent vaccine therapy. In this disease one cannot safely talk about "cures". The disease is not a self-limited one and a relapse may occur after years. In those cases which do not respond to treatment and go on in a chronic relapsing state, it seems likely that the disease smoulders in a focus which keeps up the infection in a low-grade form. We have already referred to such focal sites which act as a reservoir of the disease. In such cases if supported by clinical data, removal of such a focus is warranted. In four chronic cases to my knowledge cholecystectomy in the presence of biliary tract infection has resulted in a complete arrest of the disease. In a few cases in which splenic involvement was suspected, removal of the spleen has given a similar satisfactory result. I have seen one such case recently in which after four years of continuous illness splenectomy produced a complete remission.

In conclusion it may be said that since Hughes's classical communication, *Mediterranean, Malta or Undulant Fever* written in 1897, the perplexities concerning diagnostic and therapeutic problems of the disease have persisted and are now becoming more pointed as the incidence of the disease increases.

ranean, Malta or Undulant Fever written in 1897, the perplexities concerning diagnostic and therapeutic problems of the disease have persisted and are now becoming more pointed as the incidence of the disease increases.

SUMMARY

The diagnostic and therapeutic problems of chronic brucellosis are considered in the light of a review of a series of 100 cases.

The disease is widely prevalent. The diagnosis is surrounded with difficulties. In the absence of positive cultures it cannot be established either on clinical criteria alone or on laboratory findings alone but rests on clinical judgment taking into account all factors involved.

The treatment is with specific vaccine therapy over a long period of time, and good results may be expected in 75% of cases.

Better handling of the disease in the future will depend upon a better understanding of its clinical manifestations.

The assistance given by Mrs. Lillian Martin of the Calgary Associate Clinic during the course of this study is gratefully acknowledged. Our thanks are also due Dr. A. P. C. Clark and officials of the Colonel Belcher Hospital for permission to include cases under treatment in the hospital.

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It is almost certain that part of the recorded increase in the death rate from leukaemia is spurious, and reflects the more frequent recognition and reporting of the disease. In the past quarter century, physicians have become better qualified to diagnose leukaemia and are more alert to recognize its symptoms. In addition, the development and more widespread use of improved laboratory techniques of blood testing have facilitated the discovery of cases.