

A New Look at Infectious Diseases

Brucellosis

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Brucella abortus is the one species in the genus *brucella* enzootic in Britain. Its primary host is the cow, and man and several domestic and wild animals are infected directly or indirectly from the cow. Human *Br. melitensis* infection (Malta fever) is rare, only seven of the 681 cases of brucellosis reported to the Public Health Laboratory Service in 1971 being due to this organism. It is usually acquired while living or travelling overseas, but the organism can also be brought here—for example, from Italy or Spain in fresh sheep or goat's milk cheese. In Britain human *Br. suis* infection does not occur.

Pre-eradication surveys have shown that in some areas a third of the herds and more than a third of the cows in some of these herds are infected, proving that bovine brucellosis is highly contagious. In man, as in most other secondary hosts, there is no risk of cross infection although brucellosis has been known to follow transfusion of blood taken in the incubation period.

THE RISK FROM MILK

A clean herd when infected may show a high initial rate of abortion—the so-called abortion storm. But cows with long-standing brucellosis often give birth to healthy calves and the producer/retailer of raw infected milk therefore is usually unaware of his transgressions. Regrettably, the reverse has been true, with collusion from the licensing authority, but even when milk regulations are honestly observed the required random culture tests are unreliable. For the venturesome—there are, after all, other unpleasantries the cow must answer for—raw milk from a herd accredited under the new eradication scheme is *brucella* free, and the chance of breakdown of this protection is low, in one area less than 5%. Tests of acceptance are strict, but when the herd of a licensed producer retailer fails these tests the licensing authority is not told.

Predictably, therefore, a patient has recently presented with brucellosis after drinking milk from a known infected herd, known to the Ministry of Agriculture, Fisheries, and Food but not to the local health department, whose tests on the herd of a licensed producer retailer had been perfunctory and negative. *Br. abortus* is destroyed by pasteurization and the discriminating housewife can recognize pasteurized from raw milk by examining the bottle top—for one is labelled “pasteurized” and the other “untreated.” Cartoned cream is now also properly labelled, but in buns and doughnuts even clotted cream still earns its notoriety.

OCCUPATIONAL BRUCELLOSIS

Though a danger to public health, brucellosis is primarily an occupational disease, now prescribed under the National Insurance (Industrial Injuries) Act, 1965. Immediate contact with the cow is the likeliest cause of infection and farmers and farm workers therefore are more at risk than their wives. Brucellosis occurs in slaughtermen and butchers; veterinary surgeons almost invariably show serological evidence of it, but artificial inseminators—who are fastidious about asepsis—are spared. Agricultural engineers are infected from contaminated implements, and laboratory workers from *brucella* cultures.

Br. abortus will penetrate the abraded skin and can also be absorbed after ingestion, but in the milking parlour and the laboratory the respiratory tract and the eyes are important portals of entry. If the veterinary surgeon injects himself accidentally with the live variant S19 used to inoculate calves the result can be a severe local and general reaction.

Clinical Features

Brucellosis presents as an acute or a chronic illness and the terms “subclinical” and “latent” should be used with care.

ACUTE BRUCELLOSIS

The incubation period is short, two to three weeks or very much longer, and in non-occupational brucellosis the diagnosis then is more likely to be missed. Headache (occipital as well as frontal), intense back pain, and pain in the arms and legs are common, and patients often voice concern because of their extreme unaccustomed fatigue. Sweats occur at any time of day or night; they may be drenching and dramatic, preceded or accompanied by shaking chills, and followed by extreme prostration, but in modern times they are no longer signally offensive. Chest pain worse on breathing, palpitation due to a dysrhythmia, prostration with mental confusion, nightmares with somnambulism, and abdominal pain with constipation are occasional symptoms which can mislead. High fever is usual, the spleen is often enlarged, and the liver may be palpable, but appreciable lymphadenopathy in acute brucellosis is an exceptional and overrated sign.

Untreated, the duration of brucellosis will be many weeks or months, but complete recovery is possible even after a severe long illness and it is made more certain if antibiotics are prescribed. Convalescence is usually slow and many patients pronounced cured even according to their own standards admit long afterwards that somehow they are not the men they were. In Britain life-threatening fulminating infection with *Br. abortus* is rare. It can occur when resistance is low, owing to malnutrition or malignancy or after major surgery. That the illness is sometimes trivial and short, without immediate or late sequelae, need not be emphasized, for this is the favoured slogan of the protagonists of the vendors of raw infected milk.

CHRONIC BRUCELLOSIS

The incidence of chronic brucellosis is unknown. It is missed when the weary smallholder with demanding cows to milk but without help denies ill health or seems inarticulate, unable to describe his symptoms properly. But mistakes are less likely if the diagnosis is kept in mind and if the patient's family is questioned. The onset of chronic brucellosis may be insidious or it may follow an acute attack, untreated or inadequately treated. It may also take the form of an acute relapse long after an assumed cure, and precipitated sometimes by another infection or, interestingly, by trauma. Commonly there is a story of recurring "flu" and four symptoms are almost invariably present: lassitude, headache, pain, and sweats. Lassitude is mild, allowing work, or disablingly severe. Mild lassitude, often described as breathlessness, may not seem undue, but on closer questioning the patient owns that he must rest from time to time, especially after heavy tasks, and that in the evening when work is done he sleeps in his chair. In some a compelling need for sleep after lunch is a significant new related symptom. Headache is frontal or retro-orbital, and it is sometimes wrongly attributed to chronic sinus disease. Low back pain is common, unassociated with radiological evidence of spondylitis, and limb pain or stiffness is more often muscular than articular and more often proximal than distal. Sweats occur especially after effort and also at night, their frequency reflecting the severity of the disease. When the diagnosis seems certain but the patient denies nocturnal sweats his wife must be asked, for it may happen that she alone is disturbed.

True suicidal depression is rare in chronic brucellosis, though anxiety and dejection are understandably common, for the farmer who has chronic brucellosis also has to bear the cost of infection in the herd. Dizziness defies precise description. Patients complain of momentary dizziness with faintness and fatigue after severe sweats but dizziness may occur alone as a strange and frightening presenting symptom when disability otherwise is mild. Weight loss is not invariable and the patient may look deceptively well, though usually his appearance points to the presence of serious disease. As in acute brucellosis, moderate splenomegaly is the only noteworthy sign. It is present in about 10% of patients, not always the most severely ill, and it may remain when symptoms have been cured. When the spleen is very large—more than 4 fingerbreadths below the costal margin—coincidental disease such as cirrhosis, a reticulosis, or leukaemia must be sought.

SPECIAL FEATURES

Brucellosis in Children

The theory that gastric hydrochloric acid may protect against milk-borne brucellosis has fostered the belief that children are immune, but children on farms play with animals and implements and are therefore exposed in other ways. Brucellosis should be included more often in the differential diagnosis of childhood fevers.

Cleansing Rashes of Veterinary Surgeons

Inserting an unprotected arm into the cow's genital tract may give rise to diffuse erythema or a discrete papular or pustular rash and brucella allergy has been blamed, an attractive hypothesis without proof. There is proof that some pustules produced in this way are due to infection with *Salmonella dublin* or *S. typhimurium*, incriminating man as a vector of bovine pathogens—a charge he is loth to admit.

Brucellosis in Pregnancy

The bovine placenta is the perfect culture medium for *Br. abortus*, probably because it contains the carbohydrate erythritol.

It is not found in the human and for the pregnant woman therefore brucellosis has no special risk. An exception to the rule was reported in 1971, in the case of a symptomless young wife of a farmer, who had a spontaneous abortion; *Br. abortus* was isolated from the products of conception.

Complications

The list of recorded complications of acute and chronic brucellosis is long. Among them are thrombophlebitis, epididymo-orchitis, spondylitis, and synovitis of a large joint. Meningitis, meningomyelitis, and thrombotic infarction are probably the commonest neurological complications; uveitis may occur in seronegative brucellosis; and endocarditis, if untreated, will result in death. Other causes of death attributed to brucellosis have been pulmonary embolism, hepatic cirrhosis, and suicide.

Laboratory Tests in Diagnosis

Leucopenia with relative lymphocytosis is not the rule in acute brucellosis, but in some described cases it has been the first diagnostic clue. In chronic brucellosis this finding is rare and has led to a mistaken diagnosis of cyclical neutropenia on one occasion. The erythrocyte sedimentation rate is sometimes raised in acute brucellosis, but is normal in chronic brucellosis.

SERUM ANTIBODY TESTS

There are four tests in common use: (1) phenol saline agglutination test; (2) mercapto-ethanol agglutination test; (3) antihuman globulin test; and, (4) complement fixation test. They are valuable within certain limitations (see table). The results of tests (3) and (4) are more sensitive indices of the presence of brucella antibodies than those of tests (1) and (2) and are therefore more often positive. Tests (2), (3), and (4) mostly show

Some Examples of Serological Tests in Diagnosis

Phenol saline	Mercapto ethanol	Antihuman globulin	Complement fixation	Remarks
160	160	>5,120	>320	Practising veterinary surgeon. Age 75. Never ill
0	0	0	0	Farm boy. Age 13. Acute brucellosis. Splenomegaly with fever and abdominal pain of five weeks' duration. Two weeks later all tests became strongly positive and liver biopsy specimen showed brucella granulomas
5,120	2,560	5,120	80	Head cowman with acute brucellosis, a week after being crushed against an iron gate by a stampeding herd. ? Relapse due to trauma
—	—	320	160	Veterinary surgeon with psittacosis. Fever, headache, and cough productive of purulent sputum
1,280	1,280	>5,120	>320	Farm worker. Age 21. Symptom free. Son of a patient with acute brucellosis
—	—	5,120	80	Girl. Age 9. Acute brucellosis. Splenomegaly with symptoms of six weeks' duration. Later all tests became positive. The daughter of an agricultural engineer, she had played with farm implements
—	—	40	—	Housewife. Age 47. Chronic brucellosis. Six months headache, sweats, lassitude, "pain in every bone," and "tennis elbow." Liver biopsy specimen showed scanty microgranulomas

The reciprocals of the dilutions are shown.

IgG antibodies, but the presence of circulating IgG antibodies does not necessarily indicate active disease. Thus in symptomless veterinary surgeons who are constantly exposed to brucella antigen all the tests are often positive in high dilution. On the other hand, tests can give negative results in patients with active symptomatic disease. Rarely, in acute brucellosis negative results are obtained for several weeks, but in most cases all the tests become unequivocally positive very soon. In chronic brucellosis the results of tests (1) and (2) are often negative and those of (3) and (4) are usually positive, but symptoms may persist long after serological evidence of infection has disappeared. Serological tests therefore are most helpful in the diagnosis of non-occupational brucellosis. In such patients the finding of brucella antibodies, especially in rising titre, is strong confirmatory evidence. Once the diagnosis is made progress in response to treatment cannot always be judged from the results of serial antibody tests, for they may remain positive long after effective cure.

ISOLATION OF ORGANISM

Attempts to isolate *Br. abortus*, even in the acute illness, are more likely to fail than to succeed. Furthermore, the results may not be known for several weeks, by which time treatment should already have been prescribed

LIVER BIOPSY

Brucella granulomas in the liver, though non-specific, are consistently smaller than some of the granulomas common in tuberculosis or sarcoidosis and they never caseate or undergo hyalinization. Finding such granulomas after biopsy can be helpful, especially when the interpretation of antibody tests is uncertain. A negative biopsy result, on the other hand, does not rule out the diagnosis.

Some Points in Clinical Diagnosis

Acute brucellosis may at first be indistinguishable from influenza, especially when salicylates can be blamed for the sweats, but most mild virus infections are ruled out when there is clearly no improvement in the second and subsequent weeks. A rash, a sore throat, symptoms of tracheobronchitis or pneumonia, and jaundice, make the diagnosis of brucellosis unlikely.

The diagnosis of chronic brucellosis is usually beyond reasonable doubt, but it may depend wholly on the interpretation of symptoms—for the spleen is often impalpable, liver biopsy does not always help, and in occupational brucellosis serological tests are inconclusive. When symptoms are atypical and there is an emotional overlay the diagnosis is more likely to be missed and in a few patients psychoneurosis cannot be excluded. It is better then to admit uncertainty, even to the patient, than

to make the conveniently equivocal diagnosis of "neuro-brucellosis." Patients with chronic brucellosis also suffer from intercurrent disease, and dyspepsia with anaemia, for example, is an indication for barium studies.

Treatment

It is commonly supposed that brucellosis is incurable and some patients therefore need reassuring. *Br. abortus* is an intracellular pathogen relatively inaccessible to antibiotics. Prolonged treatment would seem advisable and two drugs are probably better than one. Treatment is also best started early and the temptation not to treat patients diagnosed late who are improving must be resisted. They may deteriorate suddenly while being observed.

Most patients respond to oral tetracycline 0.5 g, six-hourly for six weeks, together with intramuscular streptomycin, 1.0 g daily for the first three weeks, but in a severe illness tetracycline should be prescribed for another six weeks at least. At first there may be a brisk febrile reaction, but true drug intolerance is unusual and in the few patients who complain of mild gastrointestinal symptoms the dose of tetracycline should be halved. Streptomycin should be stopped if there is evidence of hypersensitivity and it must be withheld altogether in the elderly and in patients with severe ear disease.

Co-trimoxazole (Bactrim or Septrin, two tablets twice daily for 6 to 12 weeks) has also proved effective, though in a number of patients recovery has been incomplete. Sensitivity tests using commercially prepared discs on bovine isolations of *Br. abortus* showed that 47% were resistant to co-trimoxazole, 1.1% to tetracycline, and 4.7% to streptomycin—and hence co-trimoxazole may be of value only in infection with certain strains.

Relapse or reinfection, which is indistinguishable, is an indication for a further course of treatment, preferably with tetracycline and streptomycin. Occasionally in chronic brucellosis the response even to prolonged treatment is poor, suggesting that some of its manifestations may be due to immune mechanisms which do not depend on a persisting endogenous focus of infection. But treatment with immunosuppressants and corticosteroids would seem inappropriate, for these drugs sometimes are lethal and chronic brucellosis is not. In acute brucellosis with severe toxæmia corticosteroids may be of value when antibiotics are first prescribed and bleeding due to thrombocytopenia is another rare but urgent indication.

Conclusion

Early progress in the compulsory bovine eradication scheme is encouraging but it has not yet reached the most heavily infected areas, and human occupational brucellosis will long remain a serious hazard. Brucellosis acquired from milk is preventable and the inadequacy of present day public health measures can only be deplored.