BRUCELLOSIS

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FIG. 1.—A Maltese Goat.

History and Aetiology

In 1859, in Malta, Marston differentiated from other prevalent fevers a prolonged illness with undulating pyrexia which he called Mediterranean remittent fever. In 1886 Bruce discovered the causative organism, which he called *Micrococcus melitensis*, and in 1897 Hughes named the disease undulant fever. It was probably the same fever as one described by Hippocrates in his 'Epidemics' and recognized by Cleghorn in Minorca in 1751.

In 1905 it was shown that the disease was conveyed to man from goats by their milk. The disease became widely recognized on the shores and islands of the Mediterranean under different local names such as Malta fever, Gibraltar fever, Rock fever and Neapolitan fever. In 1921 it was discovered that similar undulating fever in man could be caused by *Bacillus abortus*, which had been shown by Bang in 1897 to be the cause of contagious abortion of cattle; and later it was found that human undulant fever could also be contracted from swine infected by a similar

organism named *Bacillus suis*. These three closely related organisms now take their generic name from Bruce and are called *Brucella melitensis*, *Brucella abortus* and *Brucella suis*.

The usual reservoir hosts of *Br. melitensis* are goats and sheep, of *Br. abortus* bovines such as cows and bulls, and of *Br. suis* swine, but all three varieties can infect all these animals, and some of them have also been found in horses, mules, dogs, cats, rats and chickens, and in certain wild animals. The disease is conveyed from some of these animals to man—from goats, sheep and cows by their milk and rarely by milk products such as cream, butter and cheese; and from goats, sheep, cattle, pigs and rarely from horses by direct contact of infected animals or their carcasses with a cut or scratch on the human skin. Hence farmers, herdsmen, dairymen, tanners and veterinarians are especially liable to the disease. It is always conveyed to man from animals, or by laboratory infection. No case of man-to-man infection has ever been proved. All infection from

FIG. 2.—An aborted calf.

milk could be prevented by pasteurization. The native cause in England is *Br. abortus*, derived from cattle of which probably about 10 per cent. are infected. The disease probably often goes undiagnosed, especially in country districts.

Such local names as Malta fever, Neapolitan fever and Gibraltar fever should now be abandoned, and whether the disease is caused by *Br. melitensis*, *Br. abortus* or *Br. suis* it should be called either undulant fever or brucellosis. Brucellosis is the term commonly used in America, and has the advantage of not suggesting that undulating pyrexia need necessarily be present. It has an almost world-wide distribution, being found as far east as China, as far west as California, as far north as Russia, Scandinavia, Scotland and Canada, and as far south as New Zealand, India, South Africa and South America.

The Clinical Picture

It is impossible to state a definite incubation period in a disease which often starts so insidiously, but commonly it is between three days and three weeks. The onset is often gradual or subacute, but may be acute and signalled by rigor. The pyrexia may be undulating, continuous, irregular, remittent, intermittent, recurrent, extreme (hyperpyrexia), slight or absent. The pulse rate usually follows the temperature curve. The disease can occur in many different forms, but with no sharp delineation between them to justify artificial classification into 'types.' Common symptoms are headache, backache (especially low backache), pain in the limbs (especially in the joints), shiver-

ing, sweating, easy mental and physical fatigue, loss of appetite, loss of weight, nausea and constipation and, in women, amenorrhoea. The patient is often irritable and depressed, and at night insomnia and drenching sweats are common. In about half the cases the spleen is palpable and the liver enlarged. In some cases there is gross tremor of the fingers and tongue or tenderness over the vertebral spines. Usually the skin is moist or sweating. Brucellosis due to *Br. melitensis* is on the whole more severe than that due to *Br. abortus* or *Br. suis*.

In a large number of cases there are additional symptoms and signs due to localization of the disease in various organs. These and other complications will be mentioned under appropriate headings.

Bone. Spondylitis occurs frequently, often with marked spur formation, and is especially common in the lumbar spine. Disc degeneration is common and many of the neuralgias found in the disease are due to these two things. Osteitis of the spine may rarely proceed to abscess formation. The pus may discharge anteriorly and compress the cord and so cause paraplegia, or it may track after the fashion of a tuberculous abscess to form a cold (or warm) abscess in the lumbar region or (after spreading along the psoas sheath) in the groin. Long rest on plaster cast may be necessary, or even Albee graft. Osteitis may also occur in the long bones or the skull, ribs, ilium, scapula and carpus.

Joints. Apart from the common joint pain, true polyarthritis can occur, with localized swelling, but not usually redness or warmth, of the joints. Occasionally, usually late in the disease, a single large or small joint may be the site of suppurative and destructive arthritis and *Brucella* organisms may be grown from the pus. Arthritis is probably commoner in cases due to *Br. melitensis*, for Hughes recorded joint effusion in 40% of his *melitensis* cases, although often of short duration.

Nervous System. Meningitis, encephalitis, myelitis, radiculitis, neuritis, or any combination of these, may occur, either in the course of known brucellosis after a number of pyrexial undulations, or at the onset overshadowing all else, or in convalescence, or months or years after recovery from brucellosis has been presumed. In the nervous system the disease has a special affinity for the meninges, and many of the neurological manifestations are thought to be due to involvement of vessels of the brain and cord where they traverse inflamed meninges. There is thus a tendency to recurrences of focal lesions of short duration in the same or different places, so that the patient may at different times have hemipar-

FIG. 3.—Severe brucellosis with paraparesis.

paresis, hemidysthesia, numbness of one arm and the homolateral half-face and half-tongue, aphasia, homonymous hemianopia, or cranial nerve palsies. Any cranial nerve can be affected, and fits and myoclonus may occur, or (rarely) Parkinsonism, chorea, athetosis, cerebellar lesions, internal hydrocephalus, diabetes insipidus or migraine. There is a tendency to late development of paraplegia in neurobrucellosis, due either to myelitis, radiculitis, or rarely to adhesive arachnoiditis or cord compression from hypertrophic pachymeningitis, arachnoid cyst or abscess from spinal osteitis. Brucellar meningitis is usually lymphocytic. It may be the sole manifestation of brucellosis and may resemble tuberculous meningitis.

Psychological illness can occur. Many patients are depressed and irritable and neurasthenic, but some become maniacal, schizoid, paranoid and even suicidal. If in mental illness there are recurring slight fevers with chilly feelings and sweating, brucellosis should be thought of, especially in country districts.

Liver. Hepatitis always occurs, with granulomata in the parenchyma. It is suspected that sometimes it may go on to cirrhosis. Liver abscess is rare.

Reproductive system. Orchitis occurs as a late manifestation in about 5 to 10 per cent. of cases, and can cause testicular atrophy, sterility in rare bilateral cases, and rarely suppuration. It is much

more likely to occur in cases due to *Br. melitensis* than in those due to *Br. abortus* or *suis*. The epididymis may be involved and tuberculous epididymo-orchitis may be simulated. Impotence is common. In the human female abortion is uncommon, but amenorrhoea is common and metrorrhagia may occur.

Urinary System. Febrile albuminuria may occur in the acute stage. Nephritis and cystitis are very rare. In paraplegic cases needing catheterization infection can occur.

Respiratory System. Rarely, bronchitis, pneumonia, pleurisy and empyema have been reported.

Cardio-vascular System. Brucellosis is a rare cause of subacute bacterial endocarditis, pericarditis and of thrombophlebitis.

Nose. Epistaxis.

Eyes. Iritis, choroiditis, retinal lesions and, in neurological cases, papilloedema, optic atrophy, diplopia, ptosis, oculomotor palsies, mydriasis, irregularity, inequality or fixity of the pupils.

Alimentary System. Anorexia and constipation common, diarrhoea uncommon, ulceration and intestinal haemorrhage rare.

Skin. Alopecia has been reported in severe *melitensis* cases. Rarely rashes of various sorts occur—erythematous, urticarial, papular, macular, purpuric and erythema nodosum.

Breasts. In humans, mastitis is uncommon and breast abscess is rare.

Duration of the Disease. Variable, but often

FIG. 4.—*Brucella melitensis*.

three to six months, with sometimes subsequent debility for a year or several years, and sometimes late localizations, for instance in the nervous system.

Mortality. Probably about 2 per cent. before antibiotic treatments were discovered; usually from hyperpyrexia, intestinal haemorrhage, infective endocarditis, encephalomyelitis and urinary infection secondary to unrecovered paraplegia.

Laboratory Findings

Blood

The white cell count is usually normal or low, with relative or absolute increase of lymphocytes. This alone in a case of pyrexia should raise the possibility of brucellosis. Eosinophils are often absent in the acute stage.

Red Blood Corpuscles. In the later stages anaemia often occurs, of varying types, and usually not severe.

Culture. At least 5 ml. of blood are incubated with special media, of which trypticase soy broth is perhaps the best, under increased (10 per cent.) carbon dioxide tension. Frequent subcultures on trypticase soy agar are made from the fourth day for five weeks. With good technique and seven consecutive daily blood cultures, positive blood culture can often be obtained in early pyrexial cases.

Serum agglutination. A titre of 1 in 40 or over is strongly suggestive and of 1 in 100 is diagnostic. A rising titre in serial tests is of special significance. Zonal agglutination tends to occur in which

agglutination takes place with low concentrations of serum whilst no agglutination takes place with high concentrations.

The *complement fixation test* and the *opsonocytophagic test* are more in vogue in America than in England. The former is sometimes positive earlier and persists longer than the agglutination reaction. The *cerebro-spinal fluid* is usually normal in the ordinary case but sometimes shows a slight rise in cell count and protein. When there are neurological complications the cells are usually increased to over 100 and sometimes to over 1,000 per ml. and are usually mainly lymphocytes; the protein is usually considerably raised and may even be xanthochromic, also in such cases the cerebro-spinal fluid often agglutinates brucella in a diagnostic titre of 1 in 100 or over and may give a positive culture.

Intradermal test. 0.1 ml. of brucellin is injected into the skin of the forearm. A positive result is a raised red oedematous and sometimes tender plaque, 2 to 6 cm. in diameter, appearing within 48 hours. It merely indicates past or present brucellosis, being comparable to a tuberculin test, and as it vitiates future agglutination tests it is of little value.

The brucella organisms vary in morphology from very small cocci to delicate rods, depending on the strain and conditions of growth. They are gram-negative, non-motile, non-spore-forming and occasionally encapsulated.

Diagnosis

In a disease with such varying clinical manifestations how is the diagnosis approached? Obviously one cannot wait for undulating pyrexia which, in any case, may not occur. The following steps lead to the diagnosis:

1. **Awareness** of the possibility of the disease and especial alertness in country districts where raw milk is drunk and where the patient's occupation may bring him into contact with the animals mentioned or their carcasses.

2. **Suspicion.** This should especially be aroused:

- (a) In a case of pyrexia with normal or low white blood count, especially if there is backache, headache, sweating or enlarged spleen or liver. The differential diagnosis of such cases must be worked out in each part of the world after consideration of what other local diseases cause a similar picture.

- (b) In cases of headache and backache and joint pains not explained by commoner causes.

- (c) Chronic ill health associated with recurring shivering and sweats or low pyrexia.

- (d) In any case of lymphocytic meningitis.

FIG. 5.—Showing temperature and agglutination curves. There was abrupt termination of the pyrexia after the second dose of vaccine and a rapid recovery.

(e) In neurological diseases with recurring focal symptoms with the same or different localizations or in unexplained paraplegia, especially if there is a history of pyrexial illness months or years previously.

(f) If any of the things mentioned under 'clinical picture' such as cold abscess or infective endocarditis cannot be shown to be due to one of their common causes.

3. *Laboratory tests.* Diagnosis depends on these, although in a typical case those who have seen brucellosis previously may feel fairly sure clinically. The most satisfactory proof is, of course, *blood culture*, but practically the first step will be *agglutination reaction* of the serum, and in neurological cases of the cerebro-spinal fluid also. It is wise to start several cultures and if the agglutination test is negative to repeat it to look for a rising titre. Brucellin intradermal tests have many pitfalls and if used at all should only be used by those with full knowledge of these.

Treatment

1. *Streptomycin with sulphadiazine.* Start sulphadiazine, 1 gm., four-hourly by mouth, and after three days give also streptomycin, 1 gm. b.d., intramuscularly. Continue both for two to six weeks if well tolerated. The disadvantages are drug toxicity and an occasional Herxheimer-like reaction.

2. *Chloramphenicol or aureomycin* often cause

remission but relapses are common and they are probably not as good as early reports suggested.

3. *Terramycin and erythromycin* are under trial. Isonicotinic acid is worth a trial.

The resistance of *Brucella* organisms to chemical and physical agents is comparable to that of other non-spore-formers such as the tubercle and typhoid bacilli.

4. *Brucellin* (a mixed toxic filtrate of the three *Brucella* organisms) injected intramuscularly at intervals of five days, starting with 0.1 ml. and increasing according to condition of patient and reaction to previous dose. In chronic cases which do not clear up on antibiotics this is still worth trying.

5. *Brucella (antibacterial) vaccine*, also worth trying in such cases, starting with 0.5 million intramuscularly and giving increasing doses every five days.

6. *Human Immune Serum.* Some temporary passive immunity may be achieved by injecting 10 to 20 ml. intramuscularly or even intravenously and may help to tide over a fulminating or hyperpyrexial case until antibiotic treatment could become effective. In neurological cases some could also be given intrathecally.

7. Complications.

Spinal Osteitis. Rest on plaster cast may be necessary and, if disintegration of bone should occur, Albee graft.

Paraplegia, if due to spinal abscess, hypertrophic

pachymeningitis, arachnoid cyst or adhesive arachnoiditis, may require laminectomy. In these days intrathecal streptomycin would have to be considered.

8. *Symptoms.* Analgesics for pain and headache, hypnotics for insomnia, aperients or enemata or both for constipation, iron for anaemia and nutritious diet in convalescence.

Prevention

Pasteurization or boiling of milk would eliminate brucellosis except in those whose work brings them in contact with infected animals or their carcasses, and laboratory workers. Complete eradication of the disease in humans depends on its eradication in animals. This has been achieved in Norway as a result of laws which stated that aborting animals must be reported and tested, and that the owner of infected animals must not allow his animals to have a chance of infecting those of other owners. Infected animals were marked and could only leave the farm for slaughter.

Methods of eradication must vary according to

the veterinary problems of the particular country but consist essentially of (i) elimination of infected animals (detected by the agglutination test) and (ii) vaccination of animals. In Great Britain, brucellosis does not occur in pigs, goats or sheep. It occurs only in bovines and is almost entirely due to *Br. abortus*. In bovines, vaccination with an attenuated strain of *Br. abortus* (Strain 19 or S.19) has given valuable results.

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SURGICAL REPLACEMENT THERAPY

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Basic Principles

Whenever important structures are congenitally absent or irreparably damaged by injury or disease, the problem of replacement arises. In many cases no solution can be found; recently, however, surgeons have become increasingly interested in the problem and important advances have been made.

The methods of replacement now being used may be classified under three main headings:

1. *Autotransplantation* (autografting), i.e. transplantation of living tissue from some other site in the same individual.

2. *Homotransplantation* (homografting), i.e. transplantation of living tissue from another individual.

3. *Implantation*, i.e. insertion of inert material. This may consist of:

(a) Dead tissue derived from the same or another individual or from an animal.

(b) Synthetic substances such as acrylic resin.

Heterotransplantation, i.e. transplantation of living tissue from an animal, has also been tried but has now been abandoned as useless.

Transplants may be further subdivided into free transplants, transplants by vascular anastomosis and pedicle transplants. A *free transplant* consists of an isolated piece of tissue which, if it becomes vascularized at all, does so as the result of ingrowth of vessels from the surrounding tissue. In *transplantation by vascular anastomosis*, on the other hand, continuity between the blood vessels of transplant and host is established at the time of operation. In an experimental animal, for example, a kidney may be transplanted to the neck with anastomosis of the renal artery to the carotid and the renal vein to the jugular vein. A *pedicle transplant* remains attached to the donor site until an alternative blood supply has developed. A homotransplant which remains temporarily at