ABORTUS FEVER

BY

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Brucella abortus infection in cattle is very common. No doubt a good farmer eradicates known cases from his herd, but I have been told that it is an accepted practice in dairy-farming districts to send infected animals to the sales. The danger of infection to man is from mastitis in the cow, when *Brucella* is conveyed in the milk or through an abrasion in the hand of a farm worker. The disease is not notifiable, and it is difficult to estimate its incidence; since its symptoms are often trivial, very variable, and never distinctive, diagnosis depends almost entirely on the agglutination test, and there seems little doubt that the true incidence is several times that of the recognized cases. Subclinical infection is probably very common. Huddleson (1939) refers to a study in school children which disclosed a significant agglutination titre in 40% after all had drunk infected milk, when only two of the children developed symptoms of the disease; agglutination titres in symptomless subjects rose as high as 1:12,000, and many had titres of 1:320. These children were observed over a period of more than a year, and the development of maximum agglutination was often a matter of months. Wilson (1942) estimates that 500 cases per annum occur in England and Wales.

Human cases of the disease were not recognized for many years after it was known that infection in cattle was common; mortality is low, and the disease does not appear to be a cause of abortion in women, for more than one case has been observed in an undisturbed pregnancy. The number of *Brucella* in infected cows' milk is far less than of *Br. melitensis* in goats' milk, and this may account for the relative mildness of abortus fever as compared with undulant fever. The two organisms can only be distinguished serologically, and the clinical course of the infection is very similar.

The general picture of the disease is that of an insidious onset (with uncertain but probably long incubation), a prolonged course of anything up to several months but usually some weeks, with limb pains and sweating as the prominent symptoms, an undulant type of fever, leucopenia, and negligible (possibly no essential) mortality. This is a true account of many cases, making a picture easily kept in mind, and if the blood of every patient presenting it were examined for *Br. abortus* agglutinins the great majority of cases would probably be diagnosed. One might perhaps question the need for laying stress on the importance of correctly diagnosing a disease which is essentially not fatal, which causes no lasting disability, and which is very possibly not amenable to any specific treatment. The importance is twofold: (1) the infection is a cause of a good deal of prolonged invalidism, and if there is no recognition of its prevalence there will be the less energetic search for a cure and for measures to eradicate it; (2) a true diagnosis will often serve greatly to relieve the mind of patient and doctor, and may prevent a long-continued enforced period of medical observation and inactivity for suspected tuberculosis. Abortus fever is a more likely diagnosis than tuberculosis in patients who have sweating as the presenting symptom.

Quite a high proportion of abortus fever cases, however, have bizarre symptoms, and these may present in such a way as to make diagnosis most difficult. Huddleson thinks that "latent" infection may become evident after some intercurrent, perhaps trivial, illness; on the other hand, in one of my cases the onset of the fever was the signal for the development of a streptococcal endocarditis. It seems worth while to give an account of 8 cases which I saw between June, 1938, and June, 1942, because of the extraordinary diversity of their symptoms: so much is this diversity impressed upon one by even such a limited experience of the disease that the diagnosis is automatically considered in every case of fever unexplained

after a few days. In the central laboratory of the area an agglutination for *Br. abortus* is included in every Widal reaction.

The endemic nature of the infection is shown by the time of onset of these 8 cases from one area:

1938	1939	1940	1941	1942
1	1 1 1 1	1	1 1	1

Only one case had direct contact with cows: the others were therefore all due to infected milk. The provisional diagnoses before the finding of positive agglutination were: typhoid (1), pyelitis (1), pulmonary tuberculosis (1), meningitis (2), bronchitis (1), neurosis (1), rheumatism (1)—i.e., in no case was a correct diagnosis made immediately, and most of the patients had been ill for some weeks before the diagnosis was proved.

Case I: Typical Undulant Fever with Psychosis

A married woman, aged 49, with a lifelong history of psychosomatic symptoms. First seen Jan. 3, 1942. Diagnosis of abortus fever on Nov. 16, 1941, when agglutination titre was 1:1,600. History then about 3 weeks, and symptoms: constipation, rigors, sweating, limb pains, and exhaustion. Two attempts to give sustained treatment with a sulphonamide abandoned for lack of co-operation. Three undulations of fever (see Chart).

Condition of Patient in the Eighth or Ninth Week of Illness.—Apathetic, querulous, and discontented. Complete insight into her condition. No lack of emotional control at this stage. Required trained nursing at home and made life difficult for the nurse. Attempted to supervise affairs of house and family. Physical condition good, but tongue dry; fairly heavy sweating, almost entirely at night. No pain on movement of limbs. No albuminuria and no physical signs found in nervous system; no enlargement of liver or spleen. Differential cell count on Dec. 30, 1941: P. 66; L. 29, M. 3,

Temperature chart of Case I (4th to 13th weeks), showing three undulations of fever

B. 1, E. 0.5%. Blood count on Jan. 6, 1942: R.B.C. 4,170,000, Hb 77%, C.I. 0.92, W.B.C. 6,150 (P. 58, L. 40, M. 2). She found it difficult to sleep, and had been given both bromide and barbiturate; a slight tendency to disorientation and to aphasia and to agraphia, which was evident as hesitation in the finding of words, was attributed at this time to the effects of the barbiturate.

She resisted admission to hospital until Jan. 25, by which time both her physical and her mental condition had deteriorated. She had lost weight and refused food. Her attitude to doctors and nurses was critical and resentful, but there was still complete insight and she was quite prepared to accept the fact that her depression and irritability were the result of her illness. The periods of depression did not correspond with periods of temperature. After admission she had an irregular pyrexia, one definite relapse of the undulant type from Jan. 20 to 27, and thereafter no significant rise of temperature. A little later she developed lack of emotional control and strong paranoid tendencies.

On admission to the Royal Northern Infirmary (Jan. 25) agglutination to *Br. abortus* was 1:16,000. An estimate of blood bromide was made on the suspicion that her depression might be due to bromide poisoning, and was 250 mg./100 c.cm. Complete withdrawal of bromide, however, made no impression on the emotional state. There was intermittent albuminuria and the urine sometimes showed pus cells. Her blood culture on Jan. 22 was sterile. The blood count showed a deterioration, and on March 3 was: R.B.C. 2,880,000, Hb 59%, C.I. 1.0.

Comment.—The symptoms in this patient were essentially psychotic, and consisted of depression, apathy, lack of emotional control, slight tendency to aphasia and agraphia, irritability, and suspicion. Throughout there was complete insight into her state

This case can hardly be regarded as a chronic one, because 5 months after the onset she was restored to her usual health. It is notable that the agglutination increased from 1 : 1,600 to 1 : 16,000 between the third and eighth weeks of the illness. There was no notable leucopenia. Sulphonamides were not used effectively because of lack of co-operation, but short trials of 6 g. daily of (a) sulph-anilamide, (b) sulphapyridine, and (c) sulphathiazole had no influence on the temperature.

Case II: Bronchitis with Steatorrhoea: ? Pancreatitis: Intermittent Albuminuria

A rigger in the R.A.F. aged 37. History of recurrent bronchitis for 10 years. Was admitted to a military hospital on Feb. 13, 1940, with cough and sweating, present for some weeks. The onset of this attack was described as influenza. Transferred to Royal Northern Infirmary Feb. 22. Febrile; signs of bronchitis. Treatment with sulphapyridine begun, but discontinued because of persistent nausea and subsidence of temperature. Inconstant albuminuria; centrifuged urine contained red cells. Blood urea, 39 mg./100 c.cm. Standard urea clearance, 118% of normal. Blood culture sterile. From the first he complained of tenderness in the epigastrium and abdominal pain, and showed muscle spasm. Profuse sweats. Hb 75%, W.B.C. 13,000 (P. 69, L. 29, M. 2). Agglutination to *Br. abortus* positive 1 : 8,000. Stools rather frequent, very pale. Total faecal fat, March 4, 44 g. % (60% split, 40% unsplit). Urinary diastase 50 units per c.cm., and total urinary diastase 62,500 units in 24 hours. March 18: total faecal fat 50.3 g. % (63.1% split, 36.9% unsplit). Serum bilirubin 0.4 mg./100 c.cm. By March 11 his symptoms had disappeared except for slight stiffness in the joints and for the signs of bronchitis.

Case III: Meningism, Pyuria, and Urticaria

A schoolgirl aged 11. Onset Nov. 1, 1940, with vertigo and stiff neck. Seen 3 days later by family doctor, who found nuchal rigidity. T. 101.8° F., P. 130. Spinal fluid normal. Given 6 g. of sulph-anilamide daily for 3 days. Seen then by medical specialist, who found slight cyanosis, dilated pupils, diminished tendon-jerks, resistance to palpation of abdomen, furred tongue, and an urticarial rash. Urine showed pus cells, and diagnosis of pyelitis was made. Symptoms, however, continued. On Nov. 25 Widal reaction, because of continued temperature: agglutination to *Br. abortus* 1 : 480, negative to typhoid group. Blood culture sterile. Blood counts: Nov. 6—R.B.C. 5,100,000, Hb 83, C.I. 0.82, W.B.C. 3,500 (P. 43.5, L. 36.5, M. 19.5, B. 0.5); and on Nov. 7—W.B.C. 6,500 (P. 69, L. 20, M. 9.5, B. 0.5).

I saw her on Nov. 25: temperature still raised; sweating not excessive; pain in the back and hands and feet. No physical signs. Sulphanilamide 6 g. a day was given again, and was discontinued after 2 or 3 days: complete subsidence of symptoms, which did not recur.

Case IV: Bacterial Endocarditis

A hotel maid aged 19. Rheumatism at 13; established mitral disease. Seen in hotel July 31, 1939, 12 days after onset of an acute illness with delirium. No headache; no pains in limbs; no dysuria; no diarrhoea; no vomiting. Examination: Flushed; furred tongue; erythematous rash very suggestive of typhoid (about 20 small erythematous spots on trunk and limbs). Agglutination to the typhoid group negative, but positive to *Br. abortus* 1 : 3,000. She was admitted to the fever hospital; on admission, R.B.C. 3,970,000, Hb 68, C.I. 0.85, W.B.C. 7,350. No albuminuria. She was given sulphapyridine 6 g. daily, with short intermissions, for a period of 5 weeks. Temperature showed rises at irregular intervals of a few days and usually persisted for 24 hours; occasionally febrile periods would last 3 days. Temperature never reached a higher level than 101° F. The temperature chart suggested a recrudescence of temperature whenever sulphapyridine was stopped. Erythematous rash reappeared on Oct. 5.

Transferred to Royal Northern Infirmary on Nov. 6, 1939: R.B.C. 2,360,000, Hb 34, C.I. 0.72, W.B.C. 14,150 (P. 77, L. 18, E. 1, M. 3.5). Platelets 123,610 per c.mm. Reticulocytes 2.5%. Blood film showed anisocytosis, poikilocytosis, and polychromasia. Examination: Very pale; furred tongue; tachycardia; B.P. 140/70; albuminuria—centrifuged deposit of urine showed red cells. Blood urea 135 mg./100 c.cm. No embolic phenomena apart from the kidneys. Agglutination to *Br. abortus* 1 : 120. Blood culture: *Str. viridans*. Further attempts were made to treat this patient with sulphapyridine and heparin, but she shortly afterwards died of uraemia. No necropsy was allowed.

Case V: Typical Mild Case with Sweating and Limb Pains

A labourer aged 20. Seen at Royal Northern Infirmary as outpatient on April 15, 1941. He had been off work for 4 weeks with "influenza." The symptoms were of limb pains, headache, and sweating. The sweats occurred about midnight, and he was referred to hospital because of the sweating. During the daytime he had no

symptoms. Had not lost weight. Examination: A thin, nervous man with acne. No physical signs found. Sweats thought to be emotional, but blood sedimentation rate 7 mm. (Westergren), and agglutination to *Br. abortus* positive 1 : 8,000.

Case VI: Mild Case; Onset with Rigors

A bank clerk aged 25. Diagnosis here less certain than for the others. Admitted to Royal Northern Infirmary 2 weeks after onset of illness with slight rigor. An old case of pulmonary tuberculosis with maintained pneumothorax: last refill the day after onset of symptoms. Temperature raised from beginning of symptoms, and a week later pain in limbs and joints and headache, but no joint effusions. R.B.C. 4,350,000, Hb 73, C.I. 0.81, W.B.C. 7,950 (P. 76, L. 21, M. 3). Agglutination to *Br. abortus* negative on July 14, 1941; agglutination positive 1 : 120 on July 21, and positive 1 : 60 on July 27. B.S.R. on July 19, 21 mm. (Westergren). Blood culture sterile; stool culture negative. Treated with sulphathiazole, 1 g. 6-hourly; immediate subsidence of temperature and symptoms.

Case VII: Pleural Pain, Dyspnoea, and Tonsillitis

A soldier aged 44. Sent to hospital Oct. 3, 1939, as suspected case of pulmonary tuberculosis. Easily tired, breathless on exertion; nocturnal cough, pleural pain, sweating; sore throat one week before admission; no gastro-intestinal symptoms; no limb pains. Examination: Not severely ill; signs of bronchitis; no rash; sputum, no T.B.; B.S.R. 3 mm.; W.R. negative; W.B.C. 14,250 (P. 61.5, L. 30.5, M. 7). Agglutination to *Br. abortus* positive 1 : 4,000. Treatment with sulph-anilamide without any spectacular result, and symptoms still present on Nov. 19, 1939.

Case VIII: Meningism and Ocular Palsy

A farm servant aged 15. Admitted to hospital July 30, 1938, three weeks after onset of illness, with rigor, sweating, and exhaustion. Seen by doctor, but no diagnosis made. Improved. Returned to work for one week, when symptoms recurred with severe sweating and frontal headache. Intermittent diplopia from onset. Examination July 30: Flushed, sweating, dilated active pupils, normal fundi, slight nuchal spasm, and positive Kernig's sign. Left sixth nerve palsy. Spinal fluid twice examined; completely normal. Remained febrile for 3 weeks; symptoms and signs then gradually subsided. Sixth nerve weakness observed intermittently. No albuminuria. Agglutination to *Br. abortus* positive 1 : 16,000 on Aug. 6, and positive 1 : 960 on Aug. 17. W.B.C. 6,350 (P. 55, L. 21, M. 20, E. 4). W.R. negative. Blood culture sterile on Aug. 12.

Comments

1. In none of these cases was enlargement of liver and spleen noted.
2. Anaemia was not a feature apart from intercurrent or pre-existing disease, nor did any case show an important loss of weight.
3. *Leucocytes*.—A considerable diminution in the polymorph count and in the monocyte count, without any proportionate increase in the lymphocytes, is considered characteristic of *Br. abortus*. Only one of these patients, however, showed any material reduction in the polymorphs (Case III; total polymorphs 1,505), but the next day this child's polymorph count had increased to 4,485. The monocyte count was certainly rather low in several cases, the lowest figure found being 122. One case (No. VIII) had a total monocyte count of 1,260, which is a high figure—so high, in fact, that mononucleosis was considered as a possible diagnosis, as also in Case III, in which the monocyte count was at one time 19.5%. The leucocyte counts are set out in the following table:

Leucocyte Counts

Case	Age	Total	P. (%)	L. (%)	M. (%)	E. (%)	B. (%)
I	49	6,150	58	40	2	—	—
II	37	13,000	69	29	2	—	—
III	11	3,500	43.5	36.5	19.5	—	0.5
		6,500	69	20	9.5	—	0.5
IV	19	7,350	—	—	—	—	—
V	20	—	—	—	—	—	—
VI	25	7,950	76	21	3	—	—
		10,700	65	32	3	—	—
VII	44	14,250	61.5	30.5	7	—	—
VIII	15	6,350	55	21	20	4	—

4. Blood cultures in 6 cases at various times, and several during the acute phase, were all sterile.

5. Blood sedimentation rate was estimated only 3 times. It was 7 mm. in Case V, 21 mm. in Case VI, 3 mm. in Case VII (Westergren 1 hour). One might perhaps suggest that high

rates are not found because of the absence of any massive inflammatory exudate.

6. *Skin Eruptions*.—Only 2 cases showed rashes which were considered to be due to the disease. Case III had an urticarial type of eruption, and Case IV in the early stages an eruption indistinguishable from typhoid, which was the original clinical diagnosis. According to Huddleson a typhoid-like eruption is frequent.

7. *Agglutination*.—Agglutination titres with the corresponding period of the disease are given below:

Agglutination Titres

Case	I:	At 3 weeks, 1 : 1,600; at 12 weeks, 1 : 16,000
"	II:	At 7 weeks, 1 : 8,000
"	III:	At 4 weeks, 1 : 480
"	IV:	At 2 weeks, 1 : 3,000; at 5 months, 1 : 120
"	V:	At 4 weeks, 1 : 8,000
"	VI:	At 1 week, nil; at 2 weeks, 1 : 120; at 3 weeks, 1 : 60
"	VII:	At 4 weeks, 1 : 4,000
"	VIII:	At 4 weeks, 1 : 16,000; at 6 weeks, 1 : 960

It seems to be agreed that agglutination does not become positive until the second week, probably not until the tenth day from the onset of symptoms, and Huddleson says it may be negative right throughout a chronic case. The minimum diagnostic titre is a little difficult to determine. It will be noted from the above figures that there was no case with a titre less than 1:480, except Case VI, in which diagnosis, apart from the symptomatology, rested upon an increase in the agglutination titre from 0 to 120 during the first two weeks of illness; at the end of the third week it was found to be 1:60. It so happens that this was the only case in which a rather strong impression of the influence of sulphonamide treatment was gained. Harries and Mitman (1940) give 1:100 as the critical level, but consider that in London, where use of pasteurized milk is general and subclinical infections are less common, a titre of 1:80 is suspicious. This figure is also given by Wilson (1942) as significant. Huddleson gives 1:50 as the level for a presumptive diagnosis. Huddleson uses in diagnosis a skin-sensitivity test made from the products of a broth culture in a form which he calls "brucellergen," but the agglutination test seems to provide all that is required for a positive diagnosis.

8. *Unusual Symptoms*.—Meningism is reported by Huddleson as common in Malta. I have found no previous reference to it in abortus fever, nor any reference to ocular palsy. Cases of bacterial endocarditis are reported by Spink and Nelson (1939), who discuss the difficulties of diagnosis, and by Scott and Saphir (1928).

9. *Treatment*.—There is scanty evidence of any positive effects from the use of any special line of treatment. Huddleson claims a shortening of the infective period by the use of a vaccine. An antimony compound, stibophen (traded as "fouadin"), which is used in schistosomiasis, has been claimed as effective, but the positive evidence is slight (Neumann, 1936). An attempt was made to use this drug in one protracted case, but the appearance of albuminuria after the first dose prevented any further administration. There have been no dramatic or even very encouraging results reported with any of the sulphonamide compounds. All except one of the 8 patients here reported were given a sulphonamide, but without any obvious effect. Sulphapyridine was used in 2 patients, sulphanilamide in 4, and sulphathiazole in 1. In Case VI there was an abrupt termination of symptoms after the use of sulphathiazole; such a mild case, however, is clearly not enough to warrant any definite conclusion.

Summary

A description is given of 8 cases of abortus fever, which is endemic in this country. The disease is benign, but gives rise to great difficulties in clinical diagnosis, and it may be the starting-point of more serious disease. Since milk is almost entirely the source of infection, universal pasteurization would eradicate it. The agglutination test is conclusive in diagnosis.

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FOOT-AND-MOUTH DISEASE IN MAN

BY

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With each new epizootic of foot-and-mouth disease (f.a.m.d.) we must consider whether infection of man is possible, and, if so, is it of practical importance? That infection may occur is instanced by the experimental infection of French scientists through drinking infected milk; by similar results among workers in the German research centre on the island of Rügen; and, finally, by positive results obtained in guinea-pig inoculation from certain cases of f.a.m.d. (aphthous fever) in man which have been described in medical journals.

Infection of man is therefore possible, and, although occurrence is rare and characterized by persistent mildness, we consider it to be of no little scientific interest. The rarity of the disease in man (we know of only ten cases prior to the last war, as opposed to many thousands of cases in animals), and its mildness, do not deprive it of interest, as the slightly affected man may start a serious outbreak among valuable live stock. As the disease causes cattle to lose weight and their milk production is lowered the condition is of paramount importance to farmers and exporters. To-day especially, when the need for maximum food production is a major consideration, the early diagnosis of all cases is essential, if only from the purely economic point of view.

I have had the opportunity of observing two cases of f.a.m.d. in man. The first I studied in detail in Poland, in the University Clinic of Lwow. This has been described in *Polska Gazeta Lekarska* (1938, 17, 501). The second case, that of a Polish soldier, was brought to my notice in Scotland in September, 1940.

Case I

A man aged 40 was wounded in the finger by a splinter from a butcher's table. The wound, although slight, healed very slowly. A transitory lymphangitis and lymphadenitis followed in a few days in the affected arm. Two weeks later general weakness, headache, and febrile manifestations developed, the temperature rising in a few hours to 102° F. These symptoms persisted for three days, the patient believing himself to be suffering from "influenza." On the third day painful mastication and salivation ensued; multiple vesicles appeared in the mouth, later giving way to ulcer formation. The following day the ulcerations were found to be larger, and were bleeding. The doctor, reconsidering his original diagnosis of "aphthous stomatitis," suspected an acute leukaemia or agranulocytosis. Blood examination, however, revealed no abnormality. Within the next few days the temperature had risen to 105° F., the mouth symptoms had increased, and the skin around the mouth showed areas of pustulation. The patient at this stage was sent to the University Clinic.

On my examination (at the end of the first week of the illness) I found the temperature to be 103° F., while excessive salivation was a prominent feature. On the skin around the mouth there were vesicles filled with a serous turbid fluid. Some of these were covered with crusts. Multiple vesicles and small polycyclic ulcers with grey bases were found over the inner sides of lips, cheeks, and palate, the surfaces of the tongue, and on the pharynx. There was slight bleeding from the ulcerating surfaces, and the breath was very foul.

The characteristic sweetish-mouldy smell of the patient reminded me of the smell I once sensed near a cow with foot-and-mouth disease. This smell facilitated the diagnosis. On the skin of the trunk there was a group of vesicles resembling herpes zoster. Large erythematous of cherry-red colour were present on the palms, while on the soles there were single polycyclic spots of similar coloration.

On the tenth day the mouth lesions began to heal, but on the palms and around the finger-nails large vesicles appeared. Vesicles appeared also on the soles, but these remained single. During the next few days the mouth lesions had healed, but the vesicles on hands and feet persisted. By the third week of the illness the ulcers of the mouth had healed without cicatrization, and the perioral lesions had disappeared. Finally the vesicles on the hands and feet healed after separation of the epidermis, leaving no cicatrices. There were no sequelae or complications, the temperature gradually returning to normal after the appearance of the vesicles.

Blood examination during the illness revealed no abnormality, but a lymphocytosis was present during convalescence. The red cell