

With several cyclotrons being built or already operating in Europe, America, and Japan fast neutrons are no longer an experimental possibility but a future clinical reality. Their place in cancer therapy should be established as soon as possible.

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Brucellosis and Veterinary Surgeons

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Summary

Forty-six veterinary surgeons were given a full clinical examination, serological examination with estimates of immunoglobulins, and supplementary haematological and radiological investigations. Thirty-five complained of one or more symptoms, and eight had abnormal physical signs which might have been caused by infection with *Brucella abortus*, but neither serological test results nor immunoglobulin estimates bore any special relation to the clinical features. The soundest way of assessing ill health which had possibly been caused by brucellosis seemed to be thorough clinical examination and disregard of serological findings. Interpreting results by the usual serological tests in the absence of a clinical examination is probably of doubtful value and may even be misleading.

Introduction

Veterinary surgeons are at risk of infection with *Brucella abortus* because of repeated contact with brucella-infected cattle, and many investigations have been carried out to assess the extent of this infection and its effects on health. No investigation of any size, however, has been based on clinical examination; serological results have been related to information obtained from replies to a questionnaire or from visual appearances and answers to questions put when blood samples were taken. Some recent investigations^{1 2} have related the results of clinical examination to laboratory findings, but the numbers of subjects examined were too small for analysis. In an attempt, therefore, to study the effects of brucella infection more closely we decided to examine

as many as possible of the vets working within a 25-mile radius of Worcester and relate clinical findings to antibody levels as obtained by serological tests.

Methods

Of the 46 vets investigated 36 were engaged actively in cattle practice. Four (cases 12, 19, 31, and 36; table I) were officers in the veterinary service (Agricultural Development Advisory Service) of the Ministry of Agriculture, Fisheries, and Food and were at risk of infection because much of their time was spent investigating brucellosis in the field, which involved handling potentially infected material such as placenta or dead calves and the taking of blood samples. Three (cases 17, 27, and 28) worked in a veterinary investigation centre and were at risk of infection in the laboratory from handling samples and cultures, but since they also investigated brucellosis in the field they were exposed through handling infected animals or infected material. Three (cases 20, 24, and 38) had been engaged in small animal practice for at least two years before being examined but had worked with cattle before going over to small animals.

Almost all the vets in the area were asked to participate and of 49 asked 46 were able to take part in the survey, which was conducted from November 1971 to January 1974. Each vet was examined by a consultant physician who paid particular attention to present and past symptoms; details of veterinary training and practice; exposure to *B. abortus*; past proved or suspected acute brucellosis; occurrence of accidental inoculation with S.19 or 45/20 vaccine; occurrence of local allergy to brucellosis; and whether the vet believed he was suffering from some continuing illness caused by contact with *B. abortus*.

Radiological assessment consisted of straight x-ray examination of the chest, examination of the upper abdomen with the subject in a recumbent supine position to display spleen size, and further examination of bones and joints when there was clinical suspicion of disease. Erythrocyte sedimentation rate, Westergren (E.S.R.); haemoglobin concentration; and white cell count (W.B.C.) were measured. The serological tests used were the saline agglutination test (S.A.T.), the agglutination test with 0.05 M 2-mercaptoethanol in the tubes instead of normal saline (M.E.T.), the antihuman globulin test (A.H.G.),³ and the complement fixation test (C.F.T.).⁴ The sera were also examined for IgM, IgG, and IgA content by immunofluorescence.⁵

Results

Forty-six veterinary surgeons, aged from 23 to 58 years, were examined, and all but one (case 38) were men (table I).

Symptoms.—No form of check list or direct inquiry of particular symptoms was used. Eleven vets felt entirely well with no symptoms.

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TABLE I—Clinical Data on 46 Vets investigated for Brucella Infection

Case No.	Age (Years)	Duration of Exposure (Years)	Years in Practice	Past History of Treated Brucellosis	Vet thought he was Suffering from Brucellosis	Accidental Injection of Vaccine	Cleansing Reaction at Bovine Obstetrics	Abnormal Signs*	Proteinuria	Symptoms†
1	34	25	11	+	-	-	-	-	-	M.
2	46	46	22	-	-	-	-	-	-	A.
3	29	23	7	+	-	+	-	-	-	-
4	57	37	33	+	+	+	-	-	Trace	A.
5	58	58	38	-	+	-	-	J.S.	Trace	A., F.
6	32	11	7	-	-	+	-	-	-	La.
7	45	40	22	-	-	+	-	M.R.	-	S.C., S.P.
8	44	20	21	-	-	+	-	-	-	La., S.P.
9	52	36	31	-	-	+	-	-	-	-
10	27	3	4	+	-	-	-	L.	-	La., F., An., I., C.
11	47	47	22	-	-	+	+	-	-	S.P.
12	49	19	20	-	-	+	+	-	-	A., T.
13	37	32	14	-	-	-	-	-	-	A.P.
14	39	39	14	-	-	-	+	-	-	S.P.
15	25	6	1	-	-	-	-	-	Trace	La., H.
16	50	50	28	-	-	+	-	-	-	S.P., S.
17	54	54	31	-	-	-	-	-	-	D., S.P.
18	37	15	9	-	-	+	-	-	-	-
19	46	46	16	-	+	-	-	-	Trace	La., A.
20	49	26	21	+	-	-	+	J.S.	-	A.
21	38	16	11	+	-	+	+	-	Trace	D., H.
22	47	34	25	+	-	+	+	-	-	A.
23	34	16	11	-	-	-	-	-	-	La., A.
24	33	24	9	-	-	-	-	-	-	D.
25	46	46	25	-	-	+	-	-	-	M.
26	40	40	17	-	-	-	-	-	-	La.
27	39	24	14	-	-	+	-	L.	-	-
28	36	25	15	-	-	-	+	-	Trace	La., H.
29	26	17	1	-	-	-	-	-	-	-
30	25	23	2	-	-	+	+	-	-	-
31	58	58	30	-	-	+	-	-	-	S.P.
32	28	5	4	-	-	-	+	-	-	S.P.
33	38	34	14	-	-	-	-	-	-	M.
34	27	27	3	-	-	+	-	-	-	-
35	40	21	16	-	-	+	+	L.	Trace	F., S., P. I.
36	37	37	13	-	-	-	+	-	-	N.C., A., H.,
37	29	27	5	-	-	-	-	-	-	-
38	26	14	3	-	-	-	-	-	-	N.C.
39	27	27	3	+	-	+	+	-	-	-
40	23	23	1	-	-	-	-	M.R.	-	-
41	26	8	2	-	-	-	-	-	-	La.
42	27	7	4	-	+	+	-	-	-	M., D., F.I.
43	32	9	9	-	-	+	-	-	Trace	-
44	31	23	8	-	-	-	-	-	-	A.P.
45	33	33	9	+	-	-	-	-	-	A., A.P.
46	30	30	8	+	-	-	-	-	-	S.C.

*J.S. = Joint swelling and/or reduced joint movement. M.R. = Maculopapular rash or eczema. L. = Lymphadenopathy.

†M. = Myalgia and/or cramp. A. = Arthralgia. F. = Fever and/or night sweats. La. = Lassitude. S.C. = Skin changes. S.P. = Skeletal pain. An. = Anorexia. I. = Impotence. C. = Cough. T. = Tension. A.P. = Abdominal pain other than dyspepsia. H. = Headache. S. = Sciatica. D. = Dyspepsia. N.C. = Nasal congestion. Fl. = Flatulence.

Five believed they were suffering from brucellosis. Other symptoms mentioned were arthralgia, skeletal pain, lassitude, myalgia, dyspepsia, nasal congestion, impotence, skin changes, flatulence, anorexia, cough, nervous tension, and sciatica.

Possible Exposure to *B. abortus*.—A chronological past history of exposure to dairy cattle, drinking of untreated milk, and other possible contact with brucellosis at an early age when working or playing in the farm environment suggested that 32 vets had possibly been exposed to *B. abortus* before starting their veterinary training; of these eight had been brought up on farms and a further 10 had lived in the country from infancy.

Past History of Proved or Suspected and Treated Acute Brucellosis.—Ten vets had received treatment with tetracyclines or chloramphenicol for illnesses with symptoms suggestive of acute brucellosis during their professional life, from one to 21 years earlier, but none could remember *B. abortus* being cultured from any body fluid though serological titres had often been raised.

Accidental Inoculation with S.19 or 45-20 Vaccine.—Twenty-two vets had accidentally inoculated themselves with S.19 (21) or 45-20 (1) brucella vaccine on 41 occasions before the survey, usually when jogged by an animal during a series of such inoculations.

History of Cleansing Reaction at Bovine Obstetric Procedures.—Eleven vets gave a history of skin changes during bovine obstetric procedures such as cleansing or the handling of infected placentae. Commonly erythema and pruritus of the forearms would develop within 15 minutes and fade over 24 to 48 hours, and one vet stated that he would develop a facial erythema if he were to stand in a cattle yard without making any manual contact with the animals or their products of conception.

Physical Signs.—Examination showed abnormal and possibly significant physical signs in eight vets in three of their body systems: reticuloendothelial (four cases of enlargement of superficial lymphatic glands, three axillary, one epitrochlear); cutaneous (two cases of maculopapular rash or eczematous changes); and locomotor (two cases of periarticular joint swelling, deformity, and reduced joint movement but only in hand joints).

Urine Analysis.—Fresh urine samples were tested for the presence of abnormal concentrations of protein, glucose, ketone bodies, and blood with Labstix (Ames). Eight vets showed a trace (<0.30 g/l) positive reaction for protein, but they had no urinary tract symptoms or past history of renal or lower urinary tract disease.

Haematological Analysis.—Haemoglobin concentration fell within the normal ranges for their sex in 44 vets. Low values of 11.8 g/dl and 12.8 g/dl were recorded in cases 26 and 33 respectively; red blood cell appearances were normal in these vets. Only one vet had an abnormal W.B.C. (case 12); his value was $13 \times 10^9/l$ with 70% neutrophils and 30% lymphocytes. The count remained abnormal without explanation on two retestings during the next four months. E.S.R. values were normal (1-10 mm at one hour) for all.

Analysis of Clinical Findings.—Table II shows that the range of antibody titres was wide in all clinical subgroups of vets, and none of the apparent differences in median titres represented a significant difference at the 5% level. A further analysis showed no apparent association between subgroups. For example, a history of brucellosis did not correlate with symptoms or signs at the time of examination, a history of self-injection with vaccine, or a cleansing reaction. There was, however, an association between age and symptoms (table III). The presence of symptoms increased with age (χ^2 test for trend = 9.0; $P < 0.01$).

The serological results are shown in table IV.

Radiological Findings.—Chest x-ray pictures were obtained for 45 vets and showed no evidence of mediastinal lymph node enlargement or pulmonary consolidations. Abdominal x-ray pictures of the left hypochondrium were obtained for 40 and the spleen identified and measured by planimetry in 20. Splenic area varied from 34.0 to 54.5 cm², which was within the normal limits.⁶ In the remaining 20 cases identification of splenic margins was incomplete but there was no evidence of displacement of adjacent viscera to suggest splenomegaly. Joint x-ray films were obtained for seven of the 10 vets who complained of arthralgia; four were normal, two showed the degenerative changes of osteoarthritis, and one showed an old adjacent fracture. There was no evidence of previous infective arthritis or osteomyelitis.

TABLE II—Median Serum Antibody Levels* on Various Tests in Subgroups of Veterinary Surgeons

Group	No. in Group	S.A.T.	M.E.T.	A.H.G.	C.F.T.	IgM	IgA	IgG
<30 years	13	640	80	1280	40	Nil	10	40
30-39 years	16	40/80	20	1280	40	Nil	Tr. 10	20/40
>40 years	17	160	40	2560	80	Nil	Tr. 10	20
With symptoms	35	80	40	1280	40	Nil	Tr. 10	20
Without symptoms	11	320	80	2560	80	Nil	10	40
Exposure before training	32	80	20	1280	40	Nil	Tr. 10	20
No exposure before training	14	160	40	2560	80	Nil	10	10
History of brucellosis	10	80/160	80	1280	40	Nil	Tr. 10	40
No history of brucellosis	36	160	40	1280	80	Nil	Tr. 10	20
History of accidental self-inoculation	22	160	80	2560	80	Nil	10	20
No self-inoculation	24	80	20	1280	40	Nil	Tr. 10	20
With cleansing reaction	11	160	80	2560	80	Nil	10	40
No cleansing reaction	35	80	40	1280	40	Nil	Tr. 10	20
Believed he had chronic brucellosis	5	80	40	2560	40	Nil	r. 10	10
Did not believe he had chronic brucellosis	41	160	40	1280	80	Nil	Tr. 10	20
With clinical signs	8	160	80	640	40	Nil	Tr. 10	10
No signs	38	80	20	1280	80	Nil	Tr. 10	20
With proteinuria	8	160	40/80	1280	40	Nil	Tr. 10	10
No proteinuria	38	80	40	1280	80	Nil	Tr. 10	20

*Median serum antibody level of group is that which is exceeded by 50% of members of group.
Tr. = trace.

TABLE III—Occurrence of Symptoms and Abnormal Signs according to Age Group

Age Group (Years):	<30	30-39	≥40	Total
With symptoms	6	13	16	35
No symptoms	7	3	1	11
With abnormal signs	3	1	4	8
No abnormal signs	10	15	13	38

Discussion

Our object was to relate clinical findings in a group of vets with brucella antibody levels obtained by the four serological tests commonly used in the investigation of brucellosis. Some years ago Kerr *et al.*^{7, 8} emphasized that positive results with these

tests in vets with symptoms and physical signs would enable a diagnosis of chronic brucellosis to be made with some certainty. Since, however, high titres by any or all of the tests may be found in many vets who are exposed to infection and remain symptomless¹⁻⁹ clearly chronic brucellosis cannot be postulated simply because of the presence of symptoms or signs together with demonstrable serum antibody. Other causes for the symptoms and signs must be considered. McDevitt¹⁰ cautions against overdiagnosis on account of these asymptomatic titres and the lack of specificity of symptoms, and our results support a swing away from blind reliance on such tests.

There were no significant differences between the median antibody levels in any of the groups based on age, symptoms, abnormal physical, or any other factor. Forty-four vets showed antibody to a varying degree, but it seemed to make no difference

TABLE IV—Results of Serological Tests in 46 Vets

Case No.	S.A.T.	M.E.T.	A.H.G.	C.F.T.	IgM	IgA	IgG	Symptoms or Signs of Brucella Infection
1	160	<10	1280	40	<10	Tr. 10	20	+
2	160	160	2560	160	<10	Tr. 10	20	+
3	80	80	640	10	<10	<10	10	-
4	80	40	>5120	80	<10	Tr. 10	10	+
5	320	80	2560	40	<10	Tr. 10	10	+
6	40	40	640	10	<10	<10	10	+
7	320	320	2560	80	<10	<10	10	+
8	20	20	2560	160	<10	40	40	+
9	160	80	>10240	640	<10	<10	20	-
10	80	20	320	10	<10	<10	<10	+
11	160	160	>10240	640	<10	10	80	+
12	20	<10	80	5	<10	<10	<10	+
13	40	<10	80	5	<10	<10	<10	+
14	80	20	2560	80	<10	<10	40	+
15	160	80	1280	40	<10	<10	40	+
16	<10	<10	1280	80	Tr. 10	Tr. 10	40	+
17	<10	<10	<10	<10	<10	<10	<10	+
18	<10	<10	2560	160	<10	<10	40	+
19	<10	<10	160	20	<10	<10	10	+
20	160	80	640	40	<10	Tr. 10	40	+
21	320	320	5120	160	Tr. 10	20	160	+
22	160	80	>2650	320	<10	10	80	+
23	640	640	2560	320	<10	40	640	+
24	<10	<10	<10	<10	<10	<10	<10	+
25	80	90	2560	80	<10	Tr. 10	<10	+
26	160	20	1280	160	<10	<10	20	+
27	160	40	640	20	<10	<10	20	+
28	160	<10	160	10	<10	<10	<10	+
29	1280	320	2560	320	80	20	40	+
30	640	40	2560	320	<10	80	80	+
31	<10	<10	80	<10	<10	<10	Tr. 10	+
32	640	<10	640	160	20	10	10	+
33	<10	20	1280	160	<10	10	40	+
34	320	160	2560	320	<10	10	40	+
35	160	40	640	40	<10	10	10	+
36	80	80	2560	160	<10	10	40	+
37	40	20	80	<10	<10	<10	Tr. 10	+
38	80	40	640	10	<10	<10	<10	-
39	640	160	1280	40	10	40	40	-
40	1280	1280	>5120	160	<10	40	80	-
41	640	160	1280	20	20	40	80	+
42	640	640	2560	320	Tr. 10	10	10	+
43	640	640	5120	80	10	10	160	-
44	<10	<10	640	10	<10	10	20	+
45	20	20	1280	40	<10	10	40	+
46	20	20	160	<10	<10	<10	Tr. 10	+

Tr. = Trace.

whether the vet had symptoms, abnormal physical signs, or a history of brucellosis, believed he had brucellosis at the time, or had accidentally inoculated himself with vaccine in the past because their serological results were not significantly different from those of vets who could not be placed in such categories, and this applied to all four serological tests. We had hoped that an analysis of immunoglobulins by immunofluorescence might produce more conclusive results, but it proved no more helpful. The only statistically significant feature to emerge was that IgM was found less often among the older vets, but this was of no help to diagnosis by clinical examination. Correlation between the various tests was best between the results of the A.H.G. test and those of the C.F.T. (to be reported elsewhere).

We concluded that virtually all vets who work with cattle develop humoral antibody, which seems to persist throughout their working life—at least as long as they maintain contact with infected animals—and if symptoms or abnormal physical signs are present they seem to be unrelated to the amount of serum antibody. Two vets (cases 17 and 24) had no antibody by any test, probably because they had stopped working with cattle some years earlier.

Thirty-five vets complained of one or more symptoms. Frequency of symptoms increased with age, but on the whole the symptoms were mild. Fever and night sweats were complained of by three vets. Four vets had glandular enlargement; this may be expected because brucellosis is a disease in which the reticulo-endothelial system is affected and infection with brucellae would be likely to cause glandular enlargement. Two had swelling and pain with some deformity and reduced joint movement bilaterally in the joints of the hands, and while it is tempting to conclude that brucellosis was the cause of the condition other causes cannot be excluded. The fact that the condition was bilateral suggests that trauma might have played a part. Vets hands are subjected to much physical stress and injury through handling animals. X-ray examination in both cases showed no bone disease and serological tests for rheumatoid factor were negative. Two vets had a maculopapular rash that had an element of eczema, which may have been the result of rinsing hands and arms often in disinfectant solutions.

Many vets admitted to accidental inoculation with S.19 or 45/20 vaccine with a painful swelling appearing within eight

hours of the accident even when the minutest quantity of vaccine had been scratched or jabbed into the skin's surface. Usually the reaction passed off in 48 hours, but in the meantime a shivering attack, headache, or even rise in temperature occurred. These phenomena suggest an allergic cause, so some of the symptoms could be explained by postulating a reaction after reinfection from time to time. This reinfection would act as an antibody boost and while reinforcing humoral antibody might also cause symptoms for brief periods.

Comments have been made elsewhere that serum IgA might be associated with skin changes. In two patients with skin changes (cases 7 and 46) and three with a rash or joint swelling (cases 5, 7, and 20) there was no detectable serum IgA or only traces; the numbers, however, were very small. Of the 11 vets who reported a cleansing reaction eight had IgA levels of ≥ 10 or more, but of the 35 who did not report a cleansing reaction 18 had such levels.

It seems reasonable to suppose that what applies to serological tests in vets should also apply to others who are in constant contact with brucella-infected cattle—for example, dairy farmers and slaughtermen, some of whom⁹ have also been found to show humoral antibody and remain asymptomatic. We should not expect it to apply, however, to members of the public who may by chance become infected with *B. abortus*. In the absence of previous experience of brucella antigen the results of serological tests would be valuable, and the saline agglutination test would be as satisfactory a diagnostic weapon as any.

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Use of Computer Program for Diagnosing Jaundice in District Hospitals and Specialized Liver Unit

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Summary

A computer-assisted model for diagnosing jaundice has been adapted for use on the University of London C.D.C. 7600 computer via an on-line terminal at King's College Hospital to provide a rapid turn-round time. The model

was used prospectively in the diagnosis of 219 patients—135 seen in a specialized liver unit and 84 seen in one of four district hospitals in south-east London—with an overall accuracy in distinguishing among 11 different causes of jaundice of 69% and 62% respectively. These figures rose to 77% and 88% respectively when only those patients in whom the final diagnosis reached a "certain" probability were considered. When used to distinguish between a medical and a surgical cause of jaundice the accuracy was 86% in the liver unit and 77% in the district hospitals, rising to 95% in both series for those with a diagnosis of certain probability. The proposed improvements to the model—namely, the use of two separate data bases and more diagnoses within the matrix—should improve the accuracy even further. In practice the rapid feedback to the clinicians looking after patients provided help in managing difficult cases.

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