MEDICAL PRACTICE

Clinical Problems

Subclinical Brucella Infection in Man

R. J. HENDERSON, D. M. HILL

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Summary

Much subclinical infection with *Brucella abortus* affects the dairy farming community, slaughterhouse workers, and veterinary surgeons. High titres of antibody to *B. abortus* by the saline agglutination, antihuman globulin, or complement fixation test may be shown in subjects from the first two groups and generally there are no symptoms or signs of brucella infection whatever. Veterinary surgeons are prone to subclinical infection and young practitioners frequently display high titres against the usual tests at the same time apparently enjoying good health. Repeated reinfection of this group, however, may result in hypersensitivity to *B. abortus* and bouts of ill health at intervals may be due to this. Infection seems to come more often from contact with infected material than by drinking untreated milk, particularly in the herdsman, slaughterhouse worker, and veterinary surgeon. A doctor investigating illness of a patient from the dairy farming community and allied occupations should not accept a high titre against *B. abortus* as the only clue to diagnosis of the patient's condition.

Introduction

In many bacterial and virus diseases there may be subclinical infection followed by demonstrable antibody development. Widespread subclinical infection with *B. abortus* affects dairy farmers and their families, farm workers, and associated occupational groups—for example, slaughterhouse workers and veterinary surgeons. The resulting antibody may be detected by laboratory tests, and usually the seropositive state develops without any symptoms or signs of disease.

Royal Infirmary, Worcester

R. J. HENDERSON, M.D., Director, Public Health Laboratory
D. M. HILL, B.M., M.R.C.P., Consultant Physician

Results of Studies

In a survey carried out in 1967¹ on 200 dairy farms blood samples were taken from the farmers, members of their families, and farm workers. The results of the agglutination tests are given in Table I. Samples were also taken from slaughterhouse men, meat inspectors, artificial inseminators, veterinary surgeons, and a control group of doctors and Civil Servants who had no connexion with dairy farming. The development of antibodies was found in 31% of the dairy farmers and their families, 22% of the slaughterhouse men, and 92% of the veterinary surgeons.

The results of a more recent survey among dairy farms where milk ring tests became positive for the first time in 1970 or 1971 are shown in Table II. Since previous tests had been negative it

TABLE I—Agglutinins after Subclinical Brucellosis in Dairy Farmers and Associated Groups¹

	Total	Titre of Agglutinins					% with Agglutinins
		20	40	80	160	320 and Over	
Dairy farmers and families	822	72	94	53	27	5	31
Veterinary surgeons	50	3	5	8	11	19	92
Slaughtermen	67	9	1	2	1	2	22
Meat inspectors	35						
Artificial inseminators	29	1	3	1			11
Doctors and Civil Servants	50			1			2

TABLE II—Agglutinins after Subclinical Brucellosis in Dairy Farmers and their Families where Infection in Herd probably broke out during 1969-70

Age (Years)	Total	Titre of Agglutinins					% with Agglutinins
		20	40	80	160	320 and Over	
4-10	13		1				8
11-20	18	2	1	2	1	2	44
21-30	10	2		1	1		40
31-40	18	2	2	3	2		50
41-50	2			1			50
Over 50	8	1	1			1	43

is likely that the herds first became infected in 1969 or early 1970. The percentage of positive sera among the farmers, farm workers, and wives and children again was about 33%, close to the 1967 figure.

In both of these surveys one of us (R.J.H.) personally took all the blood samples, inquiring at the same time about past medical history.

Subclinical infection in brucellosis giving rise to antibody formation has been reported by others. Dooley² described an outbreak of infection in a boys' school in America, where after brucella infection in the herd supplying the school milk two boys became ill with typical undulant fever. Of the remainder of the boys, however, 41% showed agglutinating antibody titres ranging from 1,000 to 12,000 but remained symptom-free. Foley *et al.*³ in an outbreak in a girls' school in Cork, Eire, found, as well as overt cases of the disease, 32 girls in whom antibody had developed and who remained symptomless. Foley and O'Flynn,⁴ investigating brucellosis in an agricultural research establishment, found that 31.5% of the staff had demonstrable antibody but were fit and well. Meade (personal communication), examining sera from 210 patients in his rural practice in Devon, found 17 with positive agglutinating titres, and four of them had high complement fixation titres. These 17 patients had not had symptoms or signs of brucellosis. Cayton⁵ examined sera from young veterinary students and found many who were seropositive but were fit and well. Moreover, the agglutinating titre of the serum actually rose in some of these apparently healthy students during their stay in college.

Duration of Seropositive State

If contact with infection is broken off these humoral antibodies disappear slowly and gradually. In the school described by Dooley virtually all the boys had become seronegative in a year. McDevitt⁶ states that veterinary surgeons usually become seronegative in about 10 years; in our experience the serum often shows a considerable reduction in antibody titre in much less time than this. If, for example, a veterinary surgeon changes from cattle practice to small animal work titres will fall to a low level or disappear in less than five years. Some rates of fall in antibody levels are shown in Table III. Of course, for the antibody to disappear contact with the source of infection must be severed. It is not enough for a veterinary surgeon to start wearing gloves while cleansing. His antibody level may be boosted by infection through aerosols or by accidental inoculation with S.19 vaccine.

TABLE III—Subclinical Brucellosis. Rate at which Antibody Titre Falls

	Age (Years)	Date	S.A.	A.H.G.	C.F.T.	Interval
Veterinary surgeon	25	March 1970	320	320	128	1 year
		March 1971	160	160	8	
Farmer's daughter	20	April 1967	1,280	1,280	64	4 years
		April 1971	320	160	8	
Dairy farmer	30	April 1970	320	320	8	1 year
		April 1971	160	80	8	
Dairy farmer's wife	28	April 1970	1,280	1,280	256	1 year
		April 1971	320	640	64	
Herdsman	26	April 1970	1,280	640	32	1 year
		April 1971	640	80	Neg.	

S.A. = Saline agglutination. A.H.G. = Antihuman globulin (Coombs) test. C.F.T. = Complement fixation test.

Age When Subclinical Infection Begins

The age at onset of subclinical infection is not easy to assess; it is difficult and not conducive to good relations to bleed young children when visiting a farm, nor was it possible to arrange for very young children to come to a paediatric clinic for blood to be taken. During the routine visits 4 years was the youngest age at which a positive titre was found, but there is no reason to suppose that conversion to a seropositive state may not happen earlier. The position in young veterinary surgeons is an inter-

TABLE IV—Subclinical Brucellosis in Veterinary Surgeons recently taking up Practice. Titre of Antibody by saline Agglutination, Antihuman Globulin (Coombs), and Complement Fixation Tests

Case No.	Age (Years)	Saline Agglutination	Coombs	Complement Fixation
1	24	<20	20	<10
2	24	1,280	5,120	160
3	25	1,280	5,120	160
4	26	640	1,280	40
5	26	80	640	16
6	27	320	320	128
7	28	80	80	20
8	29	<20	1,280	40
9	29	40	640	10
10	31	160	1,280	40
11	42	<20	20	10

esting one. We have studied 11 young veterinary surgeons recently established in practice in Worcestershire, and positive titres of varying degree were found in all (Table IV). Apart from one (Case 1) who had a low titre to the saline agglutination test, and another (Case 11) who had been engaged solely in small animal practice for six years, which no doubt would account for his low level of antibody, substantial antibody formation had taken place. Eight of the 11 gave no history of an illness resembling undulant fever in the past that could have accounted for the presence of antibodies, but four had lived in the country from childhood and had drunk untreated milk. Thus their raised titres could have dated from early in life and not necessarily have arisen on entry into practice.

Health of Young Veterinary Surgeons

Of the 11 young veterinary surgeons investigated five were seen by one of us (D.M.H.) and assessed by examination and investigation with regard to evidence of past or present brucella infection; the results are given in Table V. Three appeared healthy but a fourth (Case 3) gave a history compatible with an episode of acute brucellosis in 1964 when he was aged 19. On examination he showed bilateral epitrochlear lymphadenopathy but appeared otherwise normal. The fifth veterinary surgeon (Case 6) complained of pains in his chest, abdomen, and locomotor system for over four years. He appeared normal on examination and the relevance of his symptoms to brucella infection was uncertain. Investigation in each case showed a normal haemoglobin concentration, peripheral white blood cell count, erythrocyte sedimentation rate (Westergren), and chest x-ray picture.

TABLE V—Subclinical Brucellosis. Results of Medical Examination of Five Young Veterinary Surgeons with High Antibody Levels

Case No.	Sex	Age (Years)	Exposure (Years)	No. of Years Qualified	History	Symptoms	Signs
2	M.	24	19	1½	—	—	—
3	M.	25	25	1½	+	—	+
4	M.	26	8	2	—	—	—
5	F.	26	14	2½	—	—	—
6	M.	27	7	1	—	+	—

Exposure: time during which patient was in contact with farm life, including drinking untreated milk.

History: positive where past illness compatible with acute brucellosis was described.

Symptoms: positive where patient did not feel in normal health.

Signs: positive where fever, lymphadenopathy, or hepatosplenomegaly was found on examination.

Source of Infection

The source for many dairy farmers and herdsman and their families is untreated milk. Knowledge, however, of the danger of raw milk is spreading, and it is not so freely consumed in farming families as hitherto. Otherwise farmers are infected by dust or contact with infected animals; many farmers carry out cleansing after a calf has been dropped, and thus handle infected placenta, membranes, and discharges. The usual practice is to bury the products of conception, but while doing this the skin

of the hands and forearms may be contaminated from this highly infectious material. Slaughterhouse men are infected through the skin when handling raw meat or through the eyes or mucous membranes of the respiratory tract from infected aerosols. Many veterinary surgeons have antibodies, going back, no doubt, to childhood on farms or in country districts where they were accustomed to drinking untreated milk; otherwise they are infected by contact through the skin, such as when cleansing and carrying out other intravaginal or intrauterine manipulations in infected animals.

Discussion

There is a good deal of speculation at the moment about the extent of brucella infection in man—for example, the number of acute cases a year, how much undiagnosed disease there is, and how much chronic disease may exist. Equally there appears to be an unawareness of the levels of humoral antibody to *B. abortus* that may be found among dairy farmers, slaughterhouse men, and veterinary surgeons caused by subclinical infection and apparently accompanied by good health. This has undoubtedly led to diverse opinions being held about the amount of morbidity caused by *B. abortus* and in certain circumstances to misdiagnosis—for example, where an individual already having a raised agglutination titre against *B. abortus* takes ill with an entirely different disease and it is unrecognized through too much attention being focused on the brucella antibody titre. Recently one of us saw two patients (dairy farmers) thought to have acute brucellosis because of a high antibody level, disclosed by the direct agglutination, antihuman globulin, and complement fixation tests. Treatment with an antibiotic was begun, but because there was no clinical response further investigations were carried out and both patients were found to be suffering from infectious mononucleosis. Thus an antibody titre against *B. abortus* in one of the occupational groups associated with dairy farming should not be accepted as the only explanation of the patient's condition.

Probably this subclinical state in the dairy farming community actually confers protection. In the experience of one of us undulant fever has never attacked anyone known from a previous survey to have antibody but, of course, it is not possible to say why some subjects develop an acute infection when exposed to *B. abortus*, some a subclinical infection, and most remain unaffected. It is also unknown whether subclinical infection gives rise later to clinical symptoms or so-called chronic brucellosis, as is sometimes believed. One of us followed up patients known to have humoral antibodies for up to

six years, and in no patient did deterioration in health take place. Generally, in the absence of a boost agglutination titres tend to disappear, sometimes within a year. It is accepted, however, that in veterinary surgeons the situation may be different.

In some veterinary surgeons repeated exposure to infection boosts the titre, keeping it at a high level, and in the tests the highest response is often seen in the Coombs antihuman globulin test, showing that "incomplete" antibodies are present, thus indicating that the major immunoglobulin to *B. abortus* in the serum is IgG. Some of these veterinary surgeons develop hypersensitivity, as shown by excessive reaction to accidental inoculation with S.19 vaccine or the intradermal inoculation of brucellin or the appearance of a rash after contact with a brucella-infected animal. This state of affairs may give rise to ill health, particularly so since it appears that in a sensitized subject accidental contact with *B. abortus* or extracts of it may be followed by brief episodes simulating true undulant fever. In addition to stimulating the formation of humoral antibodies *B. abortus* generates cell-mediated immunity, and possibly repeated exposure and experience of the antigen may lead to the development of immune complexes, thus accounting for the ill health, arthritis, and rheumatism-like syndromes from which some veterinary surgeons suffer. The rashes that appear certainly seem to be of the delayed hypersensitivity type of reaction associated with cell-mediated immunity.

One of us (R.J.H.) carried out intradermal passive transfer (Prausnitz-Küstner) tests with sera from veterinary surgeons who were stated to be hypersensitive and to have developed rashes on contact with brucella-infected animals. In each case, however, no tissue fixation of immunoglobulin took place and no reaction followed intradermal inoculation of brucellin into the site. The hypersensitivity, therefore, could not have been associated with immunoglobulin of the IgE type and the rashes could not have been caused by an immediate type of response.

Clearly the hypersensitive state in veterinary surgeons is of interest and we are carrying out further investigations, but the existence of so much subclinical infection without hypersensitivity or ill health in dairy farmers and their families, slaughterhouse workers, and a number of veterinary surgeons is of epidemiological importance and should be recognized.

References

- ¹ Henderson, R. J., *Lancet*, 1967, 2, 353.
- ² Dooley, P., *Archives of Internal Medicine*, 1932, 50, 373.
- ³ Foley, Bridget V., Clay, M. M., and O'Sullivan, D. J., *Irish Journal of Medical Science*, 1970, 3, 457.
- ⁴ Foley, Bridget V., and O'Flynn, J. G. A., *Irish Veterinary Journal*, 1971, 25, 42.
- ⁵ Cayton, H. R., *Lancet*, 1967, 2, 836.
- ⁶ McDavitt, D. G., *Veterinary Record*, 1971, 88, 537.

One Hundred Years Ago

From *The British Medical Journal*, 13 July 1872

DIRECTIONS FOR BATHING

The Royal Humane Society has issued the following instructions. Avoid bathing within two hours after a meal; when exhausted by fatigue or from any other cause; when the body is cooling after perspiration; and altogether in the open air if, after having been a short time in the water, there is a sense of chilliness with numbness of the hands and feet. Bathe when the body is warm, provided no time is lost in getting into the water. Avoid chilling the body by sitting or standing undressed on the banks or in boats after having been in the water. Avoid remaining too long in the water—leave the

water immediately there is the slightest feeling of chilliness. The vigorous and strong may bathe early in the morning on an empty stomach. The young, and those who are weak, had better bathe two or three hours after a meal—the best time for such is from two or three hours after breakfast. Those who are subject to attacks of giddiness or faintness, and those who suffer from palpitation and other sense of discomfort at the heart, should not bathe without first consulting their medical adviser.