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Undulant fever, with special reference to its spread

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UNDULANT FEVER, WITH SPECIAL REFERENCE TO ITS SPREAD

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TABLE OF CONTENTS

INTRODUCTION

Although contagious abortion of cattle and other animals has long been known to be a serious economic problem, and the possibility of human infections with the causal organism has been long in the minds of investigators, it is less than fifteen years ago since the first human case of infection with this organism was recognized.

The disease of man contracted from cattle and hogs is indistinguishable clinically from that prevalent in Mediterranean countries, and known as Undulant Fever. In Mediterranean countries it is contracted from goats by consuming infected milk or cheese, or by handling infected goats or infected goat meat, or from contaminated soil or dust. In this country, although the animal host is not the same, the same channels for the transmission of the disease from animal to man are to be expected.

HISTORY

Malta fever has been known to the people of the Mediterranean basin for many centuries, and if the cases of protracted fever described by Hippocrates refer, as is possible, to Undulant Fever, it may be said that the condition was already known as long as 400 B.C., and perhaps earlier. At the end of the 18th century attention was drawn to the large number of cases occuring in Malta, and the name Malta Fever was applied at that time.

Marson (35) who suffered from the fever himself was the first author to give an accurate description of it in 1859. He differentiated it clinically and pathologically from both typhus and typhoid, and suggested that it should be called either "Mediterranean remittent" or "gastric remittent" fever.

Many and various were the opinions held by observers as to the etiological factors in the production of Malta Fever, but nothing more definite was discovered until 1886, when Bruce isolated the organism from the blood and spleen of soldiers dying from the disease. He called this organism Micrococcus melitensis and succeeded in reproducing the disease in monkeys by inoculating pure cultures of the organisms.

The modern era in the history of abortion disease

began with the discovery of the causative organism in cattle, by Bang, in 1897. This organism he called the Bacillus abortus of Bang.

The link lacking in the information regarding the relationship of the two diseases began to take form when in 1918 Alice Evans revealed the fact that Brucella abortus and Brucella melitensis were very closely related, in fact, indistinguishable culturally and morphologically, and the only means of differentiation being melitensis serum agglutinating Brucella melitensis in higher dilutions than Brucella abortus. Because of the close relationship of the two organisms, Brucella melitensis, variety melitensis, and Brucella melitensis, variety abortus, Alice Evans suggested the possibility of human infection with the abortus strain from bovine sources.

In 1904 (35) a commission was sent out by the British admiralty and War office to study the disease in Malta in cooperation with the Civil government of the island. This body sat until 1907 and issued an exhaustive REPORT on which all present ideas of Undulant Fever was based. Among other points it elucidated the fact that the germ leaves through the medium of the urine and that it continues to live some considerable time after evacuation: that Brucella melitensis may frequently be found in the blood of apparently healthy goats and that in such cases the

milk of the goat agglutinates the organism, and that infected goats, whose milk is able to transmit the fever to man suffer no inconvenience from the presence of the germ in their blood. Much of this knowledge is due to Bassett-Smith, one of the leading investigators of the Commission.

In 1905 (56) the steamship Joshua Nicholson brought 61 milch goats and 4 billy goats from the island of Malta to this country into which they were being introduced on account of their fleece. Milk was used by the crew during the voyage and a number suffered from febrile attacks identical with those of Malta Fever.

The first case of Undulant Fever in the United States was reported by Craig (11) in 1905. In 1911, 12 cases occurring in southwest Texas, along the Rio Grand river, were reported. All the patients had consumed raw goat milk.

In 1912 (17) 5 cases were reported from Prescott, Arizona. During the following 10 years scattered cases of Undulant Fever appeared in the southwest. In 1922 a severe epidemic broke out in Phoenix,Arizona, 83 known cases being reported. There was undoubtedly more since the infected milk was sold at soda fountains and it was impossible to trace all purchasers.

Although the cases which have been reported from the southwest had become infected from goats, it is thought that the disease existed among the cattle 25 years ago under the name of "Rio Grande" or "Mountain" fever.

In 1921 (38) Bevan reported some cases of Undulant Fever in patients in whom the only means of infection was contact with infected cattle.

In 1924 (38) Keefer of Baltimore reported a case of human infection by Brucella melitensis, variety abortus, in the United States. The patient was a laboratory assistant who made frequent visits to the slaughter house for histological material. He had also been drinking raw cow's milk and an organism that answered all agglutinative criteria of Brucella melitensis, variety abortus, was isolated from his blood and urine. At about the same time De Korte recognized a case in South Africa: a man infected while attending an aborting cow.

The following year, 1925, Alice Evans (15) of the United States Public Health Service, reported further work on the laboratory phase of the subject, and in 1927 gave brief histories of 20 cases which had occurred in the United States. She had an opportunity to perform agglutination tests and blood cultures on all of these cases.

Since then numerous instances of infection from bovine sources have been recognized in various parts of the world. In this country many cases have been recognized and reported, and particularly the last 2 years it is being recongized in nearly all parts of the country as one of the common diseases which must be considered in cases of prolonged illness. The widespread use of raw milk from infected cattle makes it conceivable that the disease will probably reach epidemic, and at times, epidemic proportions in this country.

SPREAD OF THE INFECTION

The normal habitat of the Brucella organisms in the non-pregnant cow is in the udder, where it does not produce harmful results. It is the habitat provided by nature for perpetuation of the infection during those intervals when conditions are unfavorable for growth of the bacteria in the uterus, which is the normal habitat for the organisms in the pregnant cow.

Smith (46) states the invasion of the udder by Brucella abortus means its presence and multiplication in the milk in the acini and ducts, and not the connective tissue. This he has shown by sections of udders of known-infected cows. Andrews (1) has also proved this by experimental subcutaneous inoculation of cows with living Brucella abortus.

Carpenter and Boak (6) in histological studies of udders in 15 cases found degeneration and desquamation of the parenchyma, and cell exudation into the acini of the gland, the degree depending on the acuteness of the process.

So it can be seen that the predilection of this organism for glandular tissue facilitates it's perpetuation in man thru a medium that serves as man's best food.

Thompson (49) examined the milk of ten high producing cows which never manifested clinical symptoms

of infectious abortion but whose blood serum serum showed agglutinins for Brucella abortus in dilutions of from 1:50 to 1:500, at intervals of 30 days over an entire lactation period, and results demonstrate that Brucella abortus may be constantly eliminated with the milk of cows classified as "healthy carriers."

The age distribution of persons who contract Undulant Fever is wide. In their series of cases, Huddleson and Orr (31), the age range was 9 to 63, the average being between 30 and 40. They found more farmers than individuals of any other occupation or profession.

INCIDENCE BY AGE AND SEX of 463 CASES - HASSELTINE(29)

Age group	Males	Females	Total
below 5 years	3	2	5
5-9 years	5	3	8
10-14	17	6	23
15-19	28	6	34
20-24	48	7	55
25-29	42	15	57
30-34	35	14	49
35-39	60	11	71
40-44	42	16	58
45-49	26	7	33
50-54	20	11	31
55-59	4	9	13
60-64	7	5	12
65-69	3	5	8
70 and over	2	4	6
	342	121	463

Some rather extensive work has been done by Cameron (5) on the viability of the Brucella organism. He found that the organism lived 4 1/2 hours when exposed to direct sunlight, 5 days when dried in burlap sacking on the laboratory table, 37 days in soil that dried slowly in test tubes in the laboratory cupboard, 66 days after having been in wet soil stored in an unheated cellar, 4 days in normal bovine urine at room temperature, 120 days in bovine feces in the laboratory and dried slowly, 77 days in the presence of putrefaction, 77 days in tap water which was sterilized before the organism was introduced and kept at room temperature, 114 days in tap water, at -4°C.

Since the organism is so resistant to drying it would seem that infection could be spread very easily by dust which is prevalent in many barns.

In the light of present day knowledge of the subject it appears that actual infections are out of all proportions to the infection opportunities. Man does not readily contract the disease and even if more or less continually exposed may escape with sensitization only, unless special secondary factors, as yet unknown, enter into the case. McAlpine and Nickle (36) submitted 10,157 samples of human sera to the agglutination reaction using Bacterium abortus as the antigen. Of this number approxi-

mately 0.6 percent gave reactions up through the 1-100 dilution. These results, obtained in a state where preliminary testing has shown at least 90 percent of the dairy herds to be infected with Brucella abortus and approximately 60 percent of the milk only is pasteurized, indicates that infection of man with the bovine type of Brucella abortus is relatively rare, provided any significance can be attached to the agglutination test.

Stone and Bogen (47) feel that the ingestion of raw milk obtained from cows infected with contagious abortion and showing positive tests for agglutinins to Brucella abortus in their blood, is responsible for the development of similar agglutinins in the blood in some consumers. This has been found to occur in about 8 percent of those continuously exposed to the ingestion of heavily infected raw milk, but varies with the duration of exposure, the amount of infection in the herd, and the amount of raw milk so consumed. No particular sex or age susceptibility to this infection has been found. More than half of the patients developing agglutinins to Brucella abortus give no other manifestation of the infection and form a purely serological brucelliasis.

Stone and Bogen (47) compiled the following table showing the duration of exposure to raw milk and titre development.

DURATION OF EXPOSURE	TOTAL CASES	TOTAL POSITIVES	PERCENT POSITIVE	MAXIMUM TITRES 1/20	1/40	1/80	1/160	1/320	1/640	1/1600
over 2 years	91	13	14	2	3	3	3	2	..	..
over 1 year	120	16	14	1	2	3	6	2	2	..
6 months - 1 year	178	13	8	3	1	1	3	..	4	1
employees	12	1	8	..	..	..	1	..	..	..
under 6 months	250	19	7	1	6	3	6	3	..	..
during study	203	4	2	1	..	..	2	1	..	..
TOTAL	854	66		8	12	10	21	8	6	1

Traum (52) esimated that approximately 20 percent of our cows are affected with abortus infection, 30-50 percent of the animals that react to the agglutination test will eliminate this organism, or about 6-10 percent of our cattle. Take into consideration that the number of Brucella organisms in infected cow's milk is, as a rule, small, that this is greatly diluted with milks from non-eliminating cows, and that even in the rare susceptible individual, large number of organisms must be present to induce Undulant Fever. It can be said, I believe, that raw milk can be produced on a commercial scale which will not cause Undulant Fever in man.

The modes of infection of humans with the abortion disease of cattle are believed to be manifold, however, it was not until the last 10 years that extensive work has been done along this line with reference to means of spread other than through milk.

Hardy (24) differentiates the groups and includes them under three heads:

1. Those without direct contact with livestock or carcasses. This group is made equally of males and females and persons of all ages, professional and business men and students. Infection is due to the ingestion of milk or dairy products. Hasseltine (29), in his classification, calls this

the Milk Group.

2. Rural cases having direct contact with live-stock. This group includes farmers, their wives and children, and veterinarians. Information indicated the sources were equally divided between cattle and hogs - those from cattle by ingestion and from hogs by direct or indirect contact, the portal of entry being the skin.

3. Urban cases having direct contact with live-stock or carcasses. This included packing house employees and butchers. The organism isolated was of the suis variety, and seemed to confirm epidemiological impressions, which indicate that contact with fresh tissues of diseased hogs not infrequently results in infection, while similar contact with the carcasses of cattle is rarely followed by Undulant Fever.

Cruickshank and Barbour (12) examined blood sera of 112 cases - 71 males and 41 females. All worked in byre or came in contact with animals. Ten showed agglutination of Brucella abortus in dilution of serum of 1:25 or higher. He concluded that direct contact with infected cattle was more likely to cause agglutinin formation, and presumably infection, among the human population

than is the drinking of unsterilized infected cow's milk.

Many papers have been published showing that men employed in handling domestic animals show a higher incidence of agglutinins for Brucella abortus than do normal males (46). Everson, Poelma, Brucknea, and Pickens (19) attempted to show that there are other important channels by which the organism may gain entrance to the human body, for at one time it was thought that the digestive tract was the most vulnerable portal of entry for this organism.

These four men found that the porcine had greater power to penetrate the skin than the bovine strain, however the bovine strain was more effective when taken into the digestive tract. The results are as follows:

1. Feeding of porcine and bovine strains of Brucella abortus resulted in infection in 4 of the 5 guinea pigs used in each group.
2. After placing the bovine strain of Brucella abortus in the eye, 7 out of 8 guinea pigs used became infected. Of those pigs which received the porcine strain, 4 of the 5 developed agglutinins for Brucella abortus.
3. In the experiment in which wound exposure was employed, all of the guinea pigs in the 2 groups which received the bovine strain developed infection.

4. Infection was produced in 9 of 11 guinea pigs which received the bovine strain of Brucella abortus on scarified skin. Nine pigs received the porcine strain in the same manner and they all became infected.

5. A total of 23 pigs received a drop of suspension of bovine strain of Brucella Abortus on the bald spots back of the ears. Only 1 became infected. Each of 22 guinea pigs likewise received a drop of suspension of the porcine strain of Brucella abortus on the bald spots of the ear. Eleven developed ag lutinins for Brucella abortus antigen.

6. All of the experimental animals exposed to Brucella abortus in the nose, urethra, vagina, and rectum became infected.

Their conclusions were as follows: The following may serve as portals of entry in establishing infection in guinea pigs with the bovine and porcine strains of Brucella abortus: mouth, eye, nose, urethra, vagina, rectum, incisions, scarified and unabraded skin.

Experimental Brucella infections have been produced in man (56). Volunteers drank contaiminated milk or were inoculated through the abraded or non-abraded skin with different strains. Out of 40 inoculated

by various methods with various strains only 10 contracted the infection. Of these, 6 were infected through the abraded skin, and 4 through the gastro-intestinal tract Of the 6 infected through the abraded skin 3 were inoculated with bovine strains, 2 with porcine strains and 1 with a melitensis strain. Single dose produced infection in these cases. Of the 4 cases infected through the gastro-intestinal tract, 2 were inoculated with porcine strains, 1 with melitensis strain and 1 with bovine. Two or more doses were required to produce a milk case with a virulent bovine strain. From these experiments it seems that smaller doses are necessary to produce infection through the abraded skin than through the gastro-intestinal tract. Relatively large doses produced infection through abraded skin with organisms that had been isolated for some time. These same organisms when fed repeatedly in large doses did not produce infection.

The mode of infection is fairly well agreed upon by observers and investigators. Contact with aborting or abortus infected animals, and the consumption of raw milk and milk products from such animals are the most frequent factors in the transmission of the disease. It is also generally accepted that the specific organisms may be taken in through wounds and abrasions as well as through the alimentary organs.

Hardy (25) states that transmission through diary products must be assumed, but that is is evident that people working arcund stock are exposed more dangerously than those using the dairy products, but not working with stock.

McAlpine and Mickle (36) look upon milk and milk-products as the probable sources of Undulant Fever infection, but admit that it is difficult to explain the conditions which are necessary to bring it about.

That milk and its by-products have furnished a medium of transmission of the infection to humans has been investigated by many, however authoritative and complete information as to the presence of Brucella abortus in milk products, is not yet available.

Carpenter and Boak (17) found that when butter was inoculated with the organism and stored at 8°C the organism remained viable for 142 days. They also found that Brucella abortus lived 2 months in cheese, especially roquefort, and in ice cream for a period of at least 1 month when held at temperatures below the freezing point.

Van der Hoeden (20) collected cream from cows known to be shedding Brucella abortus. While still sweet it was made into butter. Half of the butter was salted (3 percent) and half was not. Brucella abortus was isolated from the buttermilk, salted and unsalted butter.

Lerche in 1931 (46) found living Brucella abortus in 1 out of 4 samples of country butter.

Carieu and Lafenetre (46) found an epidemic was traced to cheese sold by a traveling vendor, for it was possible to tell where he had been peddling his wares by the result among his customers.

Thompson (49) arrived at conclusions similar to Carpenter and Boak, namely, Brucella abortus can remain viable in ice cream at temperatures below freezing-point when made from naturally infected milk.

Hasley (28) took samples of milk from each quarter of the udder of 465 animals in 5 certified herds and examined them bacteriologically and serologically in an effort to determine if animals which give negative serological tests excrete Brucella abortus in their milk. In this series of animals Brucella abortus was not detected in the milk from any animal in which agglutinins were not also found, and present in at least a 1-100 dilution.

Herd	No. of animals	Milk negative for Brucella abortus and agglutinins	Milk showing agglutinins	Milk showing agglutinins & Brucella abortus
A	36	32	4	3
B	83	74	9	4
C	76	71	5	3
D	220	219	1	0
E	50	50	0	0
	465	446	19	10

Messer (39) reports the agglutination of the serum of 3 of 4 healthy farm workers. On inquiry it was found that (a) the three workers all belonged to the same farm, (b) at the time the inquiry was made a cow was recovering from 'picking calf', (c) some years ago there was a epidemic of abortion amongst the herd in which a great number of cows aborted, and, (d), all 3 workers had been employed on the farm at and since that time. None of them were ill at the time of the investigation, nor was there anything in their recent medical history to suggest a condition which might have been Undulant Fever.

Messer concluded the article by the following statement: "It seems reasonable to suppose that these 3 cases exemplify the now fairly well established group in which the presence of abortus agglutinins is to be explained as a result of subclinical infection acquired through living in close contact with an infective environment."

The following table as compiled by Hardy, Jordan and Berts (26) shows Undulant Fever in Iowa by occupation.

	Reported Cases 1927-1929 No.	Percent	1930-1935 No.	Percent	Total No.	Percent
Farmers, including sons and farm laborers	162	44.8	260	41.3	442	42.6
Women on farms	24	6.6	56	8.9	80	8.1
Packing house employees	37	10.2	66	10.5	103	10.4
Stock buyers	5	1.4	3	0.5	8	0.8
Butchers	2	0.6	11	1.7	13	1.3
Housewives (not farmer's wives)	37	10.2	64	10.2	101	10.2
Students	18	5	35	5.6	53	5.3
Children	19	5.2	16	2.5	35	3.25
Business persons	58	16	118	18.8	176	17.8
	362	100.0	629	100.0	991	100.0

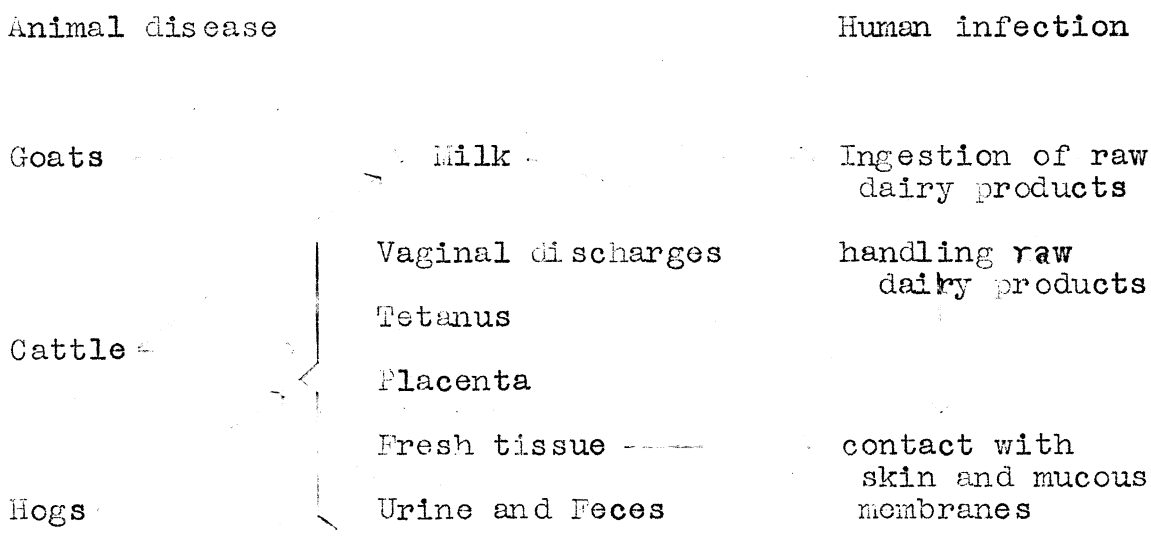
The comparatively high rates for men on the farm and the excessive rates for packing house workers strongly emphasize the risk in occupations involving direct contact with livestock and fresh meats. The similarity in rates among women on farms and among other adults not having occupational contact with livestock is added evidence that farm women acquire infection chiefly

through the use of raw dairy products.

The pasteurization of milk has been mentioned as the most effective means in the prevention of the spread of Undulant Fever, and has been proposed as a specific measure. It was employed by Graham and Torrey (23) in 5 different types of pasteurizers and effectively destroyed Brucella in 31 milk samples.

Their work has shown that the results of heating in the range of pasteurization temperature suggested that the number of Brucella in milk influenced the thermal death time. Two strains of Brucella suis (500,000,000 per cc.) were non-viable after 20 minutes at 140°F., after 15 minutes at 142°F., and after 7 minutes at 144°F. If this work is correct, the pasteurization of all milk sold should completely eliminate the spread of the Brucella organisms by the milk route, as Alice Evans (17) found there are usually about 20 to 440 organisms per cc., and the highest she found was 145,000 per cc.

TRANSMISSION OF BRUCELLA INFECTIONS TO MAN (56)



Gay and his associates have compiled the above chart to express the channels in the spread of the animal disease to the human.

It is, however, quite doubtful that one can determine with any degree of certainty, that a Brucella abortus found in man belongs to a pig or a cow strain, and hence, statements of this kind can be accepted only with reservations. As would be expected, direct contact with aborting animals or their body wastes is regarded as the most ready means by which humans may infect themselves. In people exposed to such contact, like farmers, veterinarians, and butchers, the disease can be regarded as an occupational one.

The consensus of opinion seems to support the view that where direct contact infection can be eliminated, the consumption of raw milk must be regarded as the principal means by which Brucella abortus is introduced into the human body.

On farms, furthermore, contact infections are apt to play a more prominent part in the spread of the disease. Most farm cases and packing house cases could not possibly benefit from pasteurization. The latter may be useful in urban populations, may find desultory application in rural homes, but if an Undulant Fever problem has at some time to be solved, it could not be done by this method alone.

Contact infection can be guarded against by antisepsis on the part of those who have occupational contacts with abortus infected animals. This would tend to reduce incidence of morbidity and sensitization as much as pasteurization.

Especial attention should be given to wounds and abrasions which are apt to serve as ports of entrance to the infection. People handling infected cattle and hogs should protect themselves by suitable garments and should not handle foodstuffs until after thorough cleansing.

What must be emphasized, however, is the fact that actual cases are relatively rare and surprisingly so if the infection chances are properly evaluated. Man does not readily

contract the disease, and if more or less continuously exposed may escape with sensitization only, or develop a subclinical infection, which undoubtedly must exist. However, an organism that is resistant to drying, freezing, and sunshine and can enter the body through the digestive tract, mucous membrane and unabraded skin, and can be spread by milk and all its products, or by direct contact, is indeed a matter of public health importance.

After the completion of this thesis my attention was called to a recent article (57) which shows the horse may be a more significant source of infection for man and cattle than is usually recognized.

Serum of 347 horses showed 49 per cent had a titre of 1:25 or higher. Serum of 2 of 5 horses with fistulous withers reacted at titres of 1:200 and 1:100. A bovine strain of Brucella abortus was isolated by guinea pig inoculation from the purulent exudate of 1 of these horses. Two children who had contact with this horse developed sericus Undulant Fever.

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