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SENIOR THESIS

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INTRODUCTION

The motive for this paper is to review the observations, on Undulant Fever, of the various authors, as to the comparative importance of milk borne infection and infection by direct contact. The answer to this question should be of some help in the diagnosis of Undulant Fever and it should also be of value where a question of the disease as an occupational entity is presented. Throughout the papers which have been read I believe it is safe to say that there is, at present, no controversy as to the pathogenicity for man, of Brucella; this matter having been settled by earlier writers with experimental and clinical proof. There is, however, the question of whether the infection reached its host via raw milk and dairy products or by contact with livestock on the farms and in the meat industries. Some of the authors believe the former to be the dominant factor while others give emphasis to direct contact.

It would be well, at this point, to consider the Brucella organism classification as it is now known. The term Brucella includes the various organisms causing the syndrome in man known as Malta Fever, Undulant Fever, or as it is currently called - "Brucellosis". The specific organisms include three main groups, and under each of these are several numbered strains, which are as

follows:

1. Brucella Melitensis - Caprine Origin (goat)
2. Brucella Abortus - Bovine Origin (cattle)
3. Brucella Abortus - Suis Origin (hogs)

At the present time the last two groups are thought by some to be identical. It should be mentioned also that these groups are very similar and can not be differentiated except by other than ordinary bacteriological methods.

In most of the literature on Undulant Fever the main problem, as I understand it, is to establish where the organism came into the environment of the infected individual. How this situation could be prevented and controlled is of course the underlying question. These considerations are particularly important in this disease since, up to the present time, there is no specific therapy. The unfortunate hosts to this organism must be satisfied with symptomatic measures and their own natural resistance. It is well that this disease has such a comparatively low mortality (8) rate (1-8%) and that its morbidity is so mild at times that there are no subjective complaints. Before proceding further with the details of this presentation I should point out the historical aspects in the development of our present concept of Brucellosis or Undulant Fever.

HISTORY

The history of the disease of Undulant Fever seems to begin back with Hippocrates (72). He describes - "protracted fevers lasting for many months, some with rythmically recurring pyrexial waves" - that easily suggest the term undulant. The modern literature on this disease begins in 1859 when Marston (72) made an accurate description. He was stationed at the Island of Malta and observed many instances of a disease occurring during the spring and summer which was characterized by fever, splenic enlargement and low mortality rate. He also pointed out the difference between this fever and others and particularly differentiated it clinically from Typhoid Fever. In the following decades many papers were written on this disease but little was added to the general concept of the disease except to apply different names to the fever until Bruce (6) identified the "micro-coccus melitensis" in 1887. Bruce (7) lists the following names which were used to describe the same condition: - Mediterranean Fever, Gastric Remittant and Bilious Remittent Fever, la febbre gastrobiliosa, faeco-malarial fever, intermittent typhoid, adeno-typhoid, febris complicata, febris sudoralis and pythogenic septicemia. It was in 1896 that Hughes (8) first suggested the name Undulant Fever.

Sir David Bruce (7 & 6) wrote much about this disease and was the first to identify an organism present in those having the disease. The name Brucellosis, as the disease is now called, is applied in honor of this original work. The article written by

Bruce (6), in 1887, reviews his original observations and the truly scientific approach he made to the search and identification for the causative organism of Undulant Fever is worthy of note. His technic was most meticulous and he was able to observe the organism from smears made from the spleens of fatal cases. He also cultured these organisms through several generations. In his later article (7), written in 1898, Bruce summarizes his observations on Undulant Fever up to that date. His definition of the disease at that time is interesting - "A disease of long duration, characterized clinically by fever, profuse perspiration, constipation, frequent relapses, often accompanied by pains of a rheumatic or neuralgic character, sometimes swelling of joints, or orchitis; anatomically by enlargement and softening of the spleen, congestion of the various organs, no enlargement or ulceration of Peyer's or other intestinal glands, and the constant occurance in various tissues of a species of micro-organisms, the micro-coccus melitensis." He had also carefully studied the bacteriology of the organism and listed the bacteriologic characteristics.

Bruce (7) considered most every aspect of the disease. In regard to its incidence he says that any age is liable but liability is exaggerated in those under 35. He thinks it endemic to the Island of Malta. The theory of his time that the organism gained entrance to humans via the respiratory tract is frowned on by him as difficult to understand and he clearly points out why the theory

is unsound and theorized that the organism is probably transferred by means of drinking water, or other fluids or solid food. Bruce further points out that Malta Fever differs clinically from typhoid by being of longer duration, having constipation generally rather than diarrhea, frequent presence of articular symptoms and the low mortality rate of Malta Fever as compared to typhoid. In his differentiation he includes the serum differentiation tests when - "two fevers difficult to distinguish from each other exist side by side, that the method of serum diagnosis may be expected to give good results".

In regard to immunity Bruce (7) feels, contrary to his contemporaries, that one attack of Malta Fever confers immunity.

For treatment of the condition Bruce (7) offers suggestions such as avoiding Malta and the Mediterranean area during the unhealthy spring and summer season, maintain good general health by adequate rest and diet. He even advises that milk is one of the best diet ingredients, which probably carried more germs.

The next important step in the knowledge of Undulant Fever was made by Bang (4), in 1897, when he identified the organism responsible for contagious abortion in cattle. About this same time Hughes (9) wrote a classical article on Malta Fever. In this article he classified the disease into three groups and first suggested the name Undulant Fever. He groups them as follows:

1. A pernicious type - rare but generally fatal
2. An undulant type - characterixed by exacerbations of

temperature at regular intervals.

3. A continued type - with continuous fever persisting for weeks or months.

It was Craig's article (15), published in 1897, that first described a case of Malta Fever in the United States.

The British Army was vitally interested in the study of Undulant Fever and appointed a commission to investigage the disease and report on it. As a result of their interest and work, and work by other investigators, in 1905, Professor Sir Th. Zammit (53) suggested and fairly well proved that goats were closely associated with human cases of Undulant Fever. In this same year an incident occurred, which is reported by Manson-Bahr (53), which further substantiated this belief. This incident occurred when a boat, the S. S. Joshua Nicholson, sailed from Malta. It carried a herd of sixty-five goats which were to be brought to the United States. During the voyage a number of the officers and crew drank freely of the milk furnished by these goats. All of the men contracted a fever, except four men who either had boiled the milk before using it or had not drunk it at all. On arrival at New York the organism Brucella was recovered from the goat milk and the whole herd was destroyed.

In the following years numerous articles appeared reporting a case here and there in the United States and elsewhere. The early cases in this country were mostly found in the south-western states, including Arigona, Texas and New Mexico. It was not until 1913

that much new information was added to the knowledge of the disease. In that year Larson & Sedgewick (52) studied the agglutination reaction of human serum on bacillus abortus antigen. They suggested, since they found this bacillus in cow's milk and that the agglutination reaction was seemingly specific, that there was probably some relationship. It could be said that they were the first to point out the possibility of human infection with Brucella from cow's milk containing the infecting organism. They also pointed to the frequent association of abortion in farm women with abortus epidemics in cattle and suggested that contact of these women with infected cattle might be a factor.

In 1914, Traum (71), identified the porcine variety of Brucella.

It remained for Alice Evans (20), in 1918, to positively establish the relationship of bacterium metitensis and bacterium abortus. She was the first to bring experimental evidence to support this relationship.

In 1920 Meyer (33) suggested the name Brucella be applied to the organisms causing Undulant Fever. Dr. Walter M. Simpson in his remarks concerning an article by Bierring (8), in 1929, reemphasized the name Undulant Fever for the sake of propriety because some groups resented the term "Malta Fever" since the disease has world wide distribution. At the present time Bruce is honored by naming both the organism and the disease after him. The present term being Brucellosis (2).

In 1924, Keefer (47) described the first case of Undulant

Fever proven to be caused by Brucella Abortus. He isolated this organism repeatedly from the blood of the individual showing the clinical symptoms of Undulant Fever. From this time on many articles have appeared on the subject of Undulant Fever, some stressing the epidemiology, some the clinical aspects, some the bacteriology and still others mainly the treatment. It still remains, however, in spite of much progress in the study of the disease, that little can be done in the way of treatment other than symptomatic measures.

CLINICAL ASPECTS

DEFINITION - Undulant Fever is an acute or chronic infectious disease characterized by the typical onset of fever, chills, profuse sweating, arthritic-like pains and associated with loss of wieght and the persistent undulant type of fever curve. It is caused by a group of organisms known as Brucella which gain entrance to the human host via the skin or alimentary tract. Its duration varies from a few weeks to many months and the morbidity is variable while its mortality is low (1-8%). There is no universally accepted specific treatment.

SYMPTOMATOLOGY - A few generalizations might be stated as to the clinical aspects of Brucellosis as it is considered at the present time. The following descriptions are chosen because they are typical of various papers that include such observations,

Brucellosis contracted from hogs and cattle is not distinguishable clinically from Malta Fever as it is known in the Mediterran-

ean countries. There is a difference, however, in the clinical manifestations of Undulant Fever according to which organism has infected the individual. This will be shown in later remarks in this paper. It is agreed, according to Bierring (8) in 1929, that the bovine and caprine varieties of brucella are so closely related that more than ordinary laboratory methods must be used to differentiate these different species.

The clinical approach to the disease is listed by Baltzan (2), in 1937, when he mentions the triad of fever, rapid loss of weight and sweating as the basis for using the agglutination and culture tests. He also lists the symptoms in their order of importance as follows:- "Fever, sweats, chills, loss of weight, headaches, emesis and abdominal pain, occassionally hemoptysis and vertigo and joint pains."

In observing all of these symptoms Carpenter and Boak (9), in 1928, consider the onset of the disease of special importance listing the character of the onset of rigors, chills with profuse sweating, arthritic pains, loss of weight and the undulating type of fever curve.

Bierring (8), in 1928, wrote an article giving a detailed analysis of the various important symptoms. His observations are unusually clear and conform with other descriptions of the symptoms.

Sweating - is a marked and constant adjuvant of the disease. In all but two of 150 cases reported by Bierring (8) he emphasized

that sweating is one of the most distressing complaints. Concerning its character he says that this symptom is distinctly a night sweat and usually appears in the early morning hours, occassionally equally prominent during the day. Patients describe the sweat as "wringing wet", water runs off, feel water running from side, "wet clean through the mattress", and older writers even call the disease "Febris Sudoralis". The profuse drenching character of the sweat resembles a malarial sweat more than anything else. It is the unusual perspiration, preceded by severe chills and rigors, that differentiates Brucellosis from typhoid. Of course the plasmodia in the blood is the criteria and differential point between Malaria and Brucellosis.

Arthralgia and Muscular Pains. Muscular and joint pains are prominent features of all descriptions of Undulant Fever according to Bierring (8). They are present in Undulant Fever caused by Brucella Abortus as well as Melitensis. These complaints are usually connected with the onset and often present throughout the course of the disease. Patients describe a general ache, joint pains and aching fever and in some cases a severe pain in the calf of the leg. One physician compared the severe headache and backache to the onset of small pox. At any rate the painful condition of the muscles and joints is a very distressing condition. The joint symptoms suggest Rheumatic fever but they are different in that, even though hydrarthrosis and swelling are present, they lack the pain character and redness incident to Rheumatic fever.

Fever - According to Bierring (8) the most distinctive feature of the clinical course is the fever. It has an undulating irregular curve and is of long duration. British Medical Officers considered the fever curve as highly significant but later observers regard it as important but not pathognomonic. The curve is equally significant in either melitensis or abortus type. Many of the patients observed by Bierring continued to work even though they had fever. He noted three types of fever curves. The fulminating malignant type of fever with a temperature rapidly rising to 106°F or higher and rapidly overwhelming the patient in hyperpyrexia. The typical undulating type of curve was not very prominent in the Iowa cases being present in only six of the cases. The long continued, usually intermittent, with occassional spike like curves and of afebrile periods was the predominant type. In charts of fever curves of Undulant Fever, chronic tuberculosis, liver abscess, subacute bacterial endocarditis and typhoid, it was noted that all the curves had points of similarity making it difficult to make a diagnosis from the fever chart alone.

Physical Findings - These are rather scarce but probably the most important is the enlarged spleen, but this too is not always present. The fever, loss of weight, and enlarged spleen, plus the previous symptoms already mentioned, form the basis of a diagnosis but only laboratory findings can make a positive diagnosis.

Laboratory Findings - The work of proving Brucella infections rests with laboratory findings Baltzan (2) believes. Clinical

diagnosis alone is insignificant. An unfortunate thing is the discrepancy that exists in what laboratory workers call a positive reaction. An indisputable laboratory report, in all cases, does not mean the solution of a diagnostic problem because other recognizable disease may cause the discrepancy. Baltzan (2) lists the main laboratory procedures including Blood Cultures, Serum Agglutination tests, Intradermal Skin tests, Rapid Agglutination test, and White Blood Cell Counts. Of these different methods he says that the recovery of the organism from the blood of a patient is positive proof but that this method is not without difficulties as the culture takes ten to thirty days to develop and large percentage of failures can be expected. It is also quite expensive and requires unusual laboratory equipment and practice. The agglutination test is the commonest method used but there is a wide variation of opinion as to the proper dilution for determining a positive reaction. A titer of 1 to 80 is most commonly accepted but as low as 1 to 10 is still recognized. It should also be remembered that, even in severe cases with positive cultures, that agglutinations may still be lacking, and this is even more likely in mild cases. The fact that there is a 16.6% of failures of this test should be recognized but its 85% dependability makes it a preferential test. Baltzan (2) points to Angle's observation that 15% of tularemia patients show cross-agglutination with Undulant Fever as does paratyphoid and typhoid fever and in one case this occurred in a case that later showed a positive culture of hemolytic streptococci. The intra-dermal test requires

one-tenth of a cubic centimeter of a killed brucella culture, standardized and diluted according to the amount of concentrate, and is then injected intracutaneously. Positive skin tests are obtained where the agglutination is 1-20 or even negative in studied controlled cases. The intradermal test is simple and attractive but requires dependable killed concentrates and often causes sloughing. The Rapid Agglutination method has the patient's serum mixed with a dense killed culture concentrate of the organism on a glass slide. It gives a rapid ready reading but it also has the disadvantage that, while positive reactions are significant, negative reactions are of doubtful value.

While Baltzan (2) puts little stock in the white blood count with a relative lymphocytosis because of two cases of equal severity one of which had 25,000 and the other 2,000 cells per cubic milimeter, other observers feel it quite significant. Bierring (8) says the blood changes are rather constant and distinctive, including a hemoglobinemia and an erythrocythemia, with usually a leucopenia but occassionally a leucocytosis. The leucopenia was most constant showing a relative lymphocytosis in almost every case where frequent blood examinations were made. In some of his (Bierring) cases the relative lymphocytosis was noted in early stages of the illness; in one case it reached 79% but usually as the illness progressed the proportion of polymorphonuclear cells decreased as the lymphocytes and mononuclear cells increased, the average percentage ranging between 40 and 60. Bierring (8) quotes Awe and Palmer as

saying that an absolute mononucleosis is a characteristic of Undulant fever. Castellani and Chalmers (8) were also quoted by him as giving pathognomonic importance to the increase of lymphocytes both relative and absolute.

No less an authority than Manson-Bohr (53) thinks that the leucocyte count in both abortus and melitensis is distinct. He says there is usually a slight leucopenia with a relative increase in lymphocytes. The average in seven abortus cases he reports as follows: - leucocytes-6880, polymorphonuclears -43%, lymphocytes-49%; in his melitensis cases the averages were - leucocytes-6500, polymorphonuclears-45%, and lymphocytes-48%.

In regard to the agglutination test Manson-Bahr (53) feels that the titer is of no significance since he reports a case of repeatedly positive blood cultures which never had a higher agglutination titer than 1 to 80. He agrees that blood culture is the best positive diagnosis and specifies the points of technic to avoid failures in its use - namely- to use a fresh blood specimen and inject it into a medium held continuously at body temperature as long as ten to sixty days. He says culture of a blood clot after the serum separates may be very satisfactory. Isolation of the organism from urine and feces should not be disregarded according to Manson-Bahr as it has been reported as successful in melitensis but as yet (1933) not in abortus.

Kemp (48), in 1936 says to consider an agglutination test as positive one must also have a clinical picture of Undulant Fever.

The agglutination test in itself can hardly be considered as diagnostic. He points out that a definite titer for these tests can hardly be established as the clinical picture and the agglutination titers are often very unproportional.

Carpenter and Boak (10) also warn against absolute dependence on agglutination tests because in many cases the anti-bodies remain in the blood stream months and even years after the symptoms have subsided.

A summary of agglutination evidence is given by Heathman (40) in 1934. These figures were derived mostly by analysis of blood sent in for Wassermann tests.

Arnold and Miller, Illinois	7.0% positive reactions
Carpenter and Kind, New York	7.3% positive reactions
Hardenbergh, Minnesota	4.2% positive reactions
McAlpine and Mickle, Connecticut	0.6% positive reactions
Gilbert and Coleman, New York	0.4% positive reactions
Hardy, Iowa	8.6% positive reactions

Heathman concludes, in dealing with persons exposed to Brucella infections, that great care must be exercised in interpreting both positive agglutination and intradermal tests.

Diagnosis - Bierring (8) points out that because of the leucopenia Brucellosis must be classed with typhoid, tuberculosis and influenza. He also says in regard to diagnosis that after the onset of the illness is established and the fever continues, that the differential diagnosis becomes more difficult because the clinical

picture is one of septicemia and generalized infection. Tuberculosis can be discounted by the absence of distinctive physical changes. Spleen enlargement early with lymphodenopathy, particularly in young patients, may suggest tularemia. The character of the rigors, the chills and the sweating are the most confusing clinical symptoms.

Manson-Bahr (53) refers to subclinical cases- those in which there is only slight temperature elevations obtained only by four hourly readings and in which no signs of any sort can be discovered. Only by exhaustive inquiry and by ruling out all other kinds of infection can the diagnosis of Undulant Fever be made. He wonders how many unexplained pyrexias in young people suspected of tuberculosis can be ascribed to Brucellosis. He regards the agglutination test as the best diagnostic aid and feels that with a titer of 1/1000 positive reaction there is little question as to the diagnosis.

Swartout (66), writing in 1929, summarizes the diagnostic problems of Undulant Fever pretty well by saying that the differences in reports on signs and symptoms is probably due to which strain, bovine, porcine, or caprine, is responsible. He also says that Undulant Fever is a markedly protean disease, hard to diagnose clinically but the agglutination test is the most practical diagnostic criterion.

The following chart shows an analysis of the clinical and laboratory aspects of the ten cases of Undulant Fever that have occurred in the University Hospital of the University of Nebraska

College of Medicine, Omaha, Nebraska, from 1932 to January 1, 1938. This chart is included to show the variations in the clinical picture of Undulant Fever cases.

Case #	1	2	3	4	5	6	7	8	9	10	Totals
Joint Pains	+		+		+		+		+		5
Fever	+	+	+	+	+	+	+	+	+	+	10
Sweating		+						+	+		3
Chills		+						+			2
Weakness	+	+		+	+		+	+			6
Loss of Weight	+	+	+	+		+		+	+		7
Spleen Palpability		+	+		+						3
White Blood Count in thousands	10.6	5.0	5.0	10.6	4.7	10.3	10.0	2.9	14.0	2.5	5-↑ 5-↓
Anemia			+	+	+			+	+	+	6
Liver Palpability		+								+	2
Abdominal Distention					+	+	+	+		+	5
Days in Hospital	89	27	47	22	23	25	14	12	39	57	Av.= 35.5

Note: Plus signs are used to indicate the presence of findings and the minus signs the absence of findings.

Prognosis - The prognosis of Undulant Fever is as a rule very favorable when considering the ultimate outcome, as comparatively few fatal cases have been reported. The mortality listed by Bruce (7) was 2%. Bierring (8) says that his cases had a mortality rate of 2% and that published records of Malta Fever give variations from 2-8%

with 14% in epidemics of the disease.

The statements of various writers, in regard to duration of the disease, all support the greatest variability, the durations given are from weeks to years.

Evans (22), writing in 1937, refers to Hughes' Monograph of 1897 in which he considers the duration of the disease. He states, according to her, that in one case "sciatica" continued for 1½ years and that prolonged cases do not return to their original health for 12 to 24 months and in some, years, are required for recovery. Evans also says that since many patients suffering from "chronic Brucellosis" may go undiagnosed for long times; that duration of the disease is really extremely variable.

It is well, in spite of the ultimate recovery, to remember that during the disease that many of the cases show marked debility and still others may have very little, as can be judged from the reports of the many so called "subclinical" cases of Undulant Fever.

Distribution and Incidence - Brucella infections in the United States have been reported from practically every state. The number of cases increases as the literature on the condition has been spread through the various agencies to the practicing physcian.

An article by Hasseltine (38) on the epidemiology of Undulant Fever, written in 1931, gives a very good classification of the epidemiological groups. They are as follows:-

"1. The Milk Group-Those having little or no contact with livestock--198 cases, 108 or 52% of these were males

and the balance, 48% were females.

2. The meat group-Those having contact with livestock and carcasses in the meat packing industry-44 cases, of which 43 or 98% were males and the one female in this group made sausage casing in a packing house.
3. Farm group-Those having contact with livestock on the farm-193 cases, 184 ot 95% of these were males and nine or 5% were females."

In this same article Hasseltine says that there were 1305 cases of Undulant Fever reported in the United States up to 1929, and prior to 1925 only 128 cases had been reported.

When we consider the incidence of this disease we must include both the clinical cases and the large group of cases that fall in the so called subclinical group.

Hardy (33), writing in 1929 says unquestionably all states and almost all countries have cattle infected with brucella melitensis-variety abortus. The brucella organism causing contagious abortion even exceeds bovine tuberculosis in frequency of occurrance and in economic loss.

In a study of 2492 cases analyzed by Baltzan (2) in a 1937 article he says that out of this group of cases who presented themselves because of ill health from various causes, he picked 512 cases on suspicion or routinely for agglutination tests. From these 512 samples he found 57 or 11% gave positive agglutination reactions. He thinks the striking thing is the fact that this result, when

applied to the group from which the facts arose, shows that 2.3% of all sick people had Brucellosis.

Fulton, who investigated 5023 blood samples from an area in Saskatchewan practically identical with Baltzan (2), is referred to by the latter as finding 81 or 1.61% positive agglutination reactions. In 461 blood samples sent in for Brucella Abortus 40 or 8.61% gave positive reactions. He used a titer standard of 1/50 with a trace at 1/100. Baltzan concludes from his own study, and from the writers he refers to, that Brucellosis infection is common. It may be acute or chronic, and even in the acute cases only 43% show general systemic manifestations, while the chronic infections, which are the most common, are very elusive to diagnosis. In any case the diagnosis rests on the laboratory tests plus the clinical observations according to him.

In regard to the chronic cases Evans (22), writing in 1937, says that there is widespread Brucella infection of cattle that appear healthy, and that chronic ill health in humans of unknown etiology is also present. She suggests that since laboratory tests for Brucella are made usually on only the acute cases that many unclassified illnesses belong to the chronic Brucellosis group.

In Iowa Undulant Fever has been studied extensively. The first case was reported in 1926 by Dr. R. L. Woodward according to Bierring (8). Up to June 1, 1929 there had been 230 cases reported to the Iowa Department of Health. These men in Iowa consider Brucellosis to be of state wide incidence.

Giordano (29), writing in January 1929 says that since Abortus disease in cattle is widespread in this country the possibility of human infection has existed for a long time. In this report he had studied 1100 blood serums by the agglutination reaction. 1000 of the serums were from hospitals and clinics where the patients had presented themselves because of acute or chronic symptoms. The 100 specimens were taken from apparently healthy young adults, for comparison. Out of the 1000 specimens fourteen active cases of Undulant fever were identified.

In the 1000 cases the agglutination test was positive fifty-nine times, 5.9%. In the 1100 specimens 63 or 5.7% positive reactions were found. In the 100 "healthy serums" were four positive reactions, 4.0%. Giordano is surprised by the small variation of incidence in the three groups.

Hull and Black (44), in an article in 1927, report on sixty-nine blood specimens from fever patients who consistently gave negative Widal reactions. They found six positive agglutination reactions to the Brucella Abortus (bovine) antigin. Five of these reactions were positive in dilutions of 1 to 200 or greater. They concluded that Undulant Fever is much more common than is ordinarilly suspected.

Out of 998 sera sent in for Wassermann tests, and proving negative, Harrison and Wilson (37) in 1928, ran agglutination tests with Brucella Abortus antigin and found 5.5% gave positive reactions in dilutions of 1 to 10 or higher with an average dilution

of 1 to 64.

In contrast to most writers Cruickshank & Barbour (16), in 1931, report the incidence of Brucella as less than 0.5% in a sample of a general hospital population. They conclude that Brucella is an uncommon infection in this country but that blood agglutinins may develop in individuals closely associated with cattle, without necessarily producing infection.

According to Giordano and Sesenick (31), in 1930, the incidence of Brucella is greater in small communities because of the lack of pasteurization facilities and the more common use of raw milk and exposure to brucella infected herds.

A report concerning the incidence of Brucella among cattle was made by Traum (71), in 1929. He says the serums from thousands of cattle in various parts of the United States were found to have about 20% positive reactions; in 30 to 50% of these reactors or 6 to 10% of the whole group, the organisms were eliminated in the milk. He says, since infection in cattle is so universal while Undulant Fever cases are so few, that cattle may not be such an important factor in the incidence of this disease.

Up to January 1, 1935 Dustin (19) found that 9965 cases of Undulant Fever have been reported in the United States. I think the preponderance of opinions supports the conclusion that Undulant Fever is a fairly common disease in the United States and from the statistics reported it would seem that the disease, in either acute or chronic manifestations, is present in about 5 % of the population.

Incidence According to Age and Sex -

Age - In general it is recognized that there is a difference in incidence amoung the age groups and among the sexes. The factors causing this are suggested to be either an immunity or a greater degree of exposure.

Hardy (35) in his report on Iowa cases, 1936, says that Iowa cases involve adults most heavily. He places the greatest incidence in the ages between 20 and 45 and in these the most of the cases come from farms or country towns. He also says there is a comparatively high rate for men on the farm and for packing house workers.

Fleishchner and Meyer (27), in 1918, recognized the immunity present in infants fed on milk containing Brucella. They used the cutaneous hypersensitivity test.

Bierring (8) in reporting 150 Iowa cases finds 112 of these to be in the age group of 20 to 50, 18 cases were under 20 years of age, and 20 cases were over 50.

Kavanaugh (46), in 1928, observed that children under eight years of age apparently have a high grade immunity to Undulant Fever.

Parker and Dooley (18), in 1931, studied an epidemic of Undulant Fever in a school community which used raw milk, from a single dairy, which was highly contaminated with Brucella. In 15 children under ten years of age, who had been reared on this milk, they could not find a single evidence of brucella agglutinins or infection. They conclude that children are relatively unsusceptible to the disease.

Heathman (40), in 1934, refers to Huddleson and Orr's (41)

report of 500 cases divided equally among males and females, and of all age groups and constantly exposed to organisms through infected milk. In this group only 1.4% gave positive reactions and only 0.8% showed evidence of active infection.

Dustin (19) writing in 1937 says the disease is rarely found in children under 12 years of age, the majority of cases being in young and middle aged men. Occupation plays a definite roll in etiology because of the infective opportunities. He says that the incidence in general is greater in smaller communities because of the greater opportunity for contact with infected animals and because of the more common usage of raw milk in these communities. He is one of the few who mentions the seasonal variation of incidence and states that it seems to be greater in the summer.

Sex - This is a factor probably because of the probability of direct contact being greater among males than females since both males and females drink raw milk in about equal proportions.

Hardy points out in a discussion of Bierrings (8) article that there is some factor which must be overlooked because there are three times as many males have the disease as females. Hardy says in another paper (57) that he is impressed by the fact that very often they find cases on a farm with the man infected and not the woman. He says the proportion of men to women on farms having Undulant Fever is 9 to 1. He states that other investigators support this observation and they believe the difference is due to the greater possibility of direct contact with the organism by the occupation

of the men on the farms.

Bierring (8) reporting 150 Iowa cases finds that 120 were males and 30 were females.

Stone and Bogen (65), writing in 1935, state that no particular sex or age susceptability to this infection has been found. These men seem to be overlooking some very strong evidence.

Hasseltine (38), in 1931, divides his analysis of cases according to source of infection and concludes that the fact that out of 193 cases in farms 184 or 95% were in males and only 8 or 5% of these were in females that direct contact seems to alter the sex incidence.

Hardy (35), in 1936, regards the similarity of rates of incidence among women on farms and among other adults not having occupational contact as evidence that farm women acquire infection mainly by direct contact.

It is correct I believe to say from the above references, that while there is a difference in incidence among males and females that sex only plays a passive role in that both are equally susceptible to infection but occupational differences gives males the added opportunity for exposure by direct contact.

The variations of incidence according to occupation will be brought out in subsequent pages but a chart by Hardy from his article (35) gives the variations in the cases he reports. The following charts on occupational incidence and distributional incidence will be of interest.

Relative Incidence of Undulant Fever in Iowa, - by Occupational Groups.				
Occupation	Population 1930-Census	Reported Cases Undulant Fever 1927-1936	Av. Annual Cases of Undulant Fever with known Occupation	Av. Annual Cases Per 100,000-Pop.
Packing House Employees	8000	103	11.4	142.5
Men on Farms	324,000	422	46.9	14.5
Women on Farms	250,000	80	8.9	3.6
Others 10 yrs. of Age & Above	1,375,000	371	41.2	3.0
Children Under-10	464,000	15	1.7	0.4
Totals	2,471,000	991	110.1	4.5 = Av.

(35)

Distribution by Occupation of Undulant Fever in the U.S. & In 4 Selected Localities										
Occupation	U.S. Total		Iowa		Tenn.		N.Y. State		Dayton, O.	
	#	%	#	%	#	%	#	%	#	%
Farmers	192	28.8	103	46.2	24	47.1	20	14.9	8	14.0
Housewives on Farms	19.0	2.8	11	4.9	5	9.8	1	1.7	0	0
Packing House Employees Butchers, Veterinarians	46.0	6.9	25	11.2	7	13.7	4	3.0	0	0
Business, Professions, Students, Laborers.	263	39.4	48	21.5	15	29.4	78	58.2	27	47.4
Housewives	112	16.8	22	9.9	0	0	25	18.7	22	38.6
Children Invalides	26	3.9	14	6.3	0	0	3	2.2	0	0
Laboratory Workers	9	1.4	0	0	0	0	3	2.2	0	0
Totals	667	100	223	100	51	100	134	100	57	100

(35)

Pathogenicity of Brucella - Hardy (33), in 1929, recognizes the universal distribution of contagous abortion and says that this disease exceeds Bovine tuberculosis in frequency of occurrance and as a cause of economic loss. He says the pathogenicity is variable but that in guinea pigs the porcine type is more pathogenic than the bovine. He quotes Burnett and others who feel that the melitensis variety more readily causes infections in monkeys than the abortus types. He also refers to Huddlesons finding that porcine abortus caused the most severe infections of all, with death usually resulting. Hardy remarks that bovine variety caused only mild infections and he thinks the most common variety causing Undulant Fever in the United States had not yet been established. He does indicate that the porcine type is chiefly concerned but points out that conclusive evidence is lacking as to the relative virulince of the different types of Brucella for man.

In 1931 Carpenter and Boak (11) points to evidence that Brucella has been isolated from cultures of blood, urine, stools, joints, tonsils, ovaries, oviduct and epididymus, as well as, practically all parenchymatous tissues. He also says that because of its manifest affinity for reproductive organs in animals that it probably carries the same affinity for humans and may be the cause of many abortions in women who have the possibility of contact with animal contagious abortion.

Huddleson (42), in 1930, says that for the great majority of people Brucella is not highly pathogenic, but there appears to be a minority group who are infected when exposed to sufficient doses of

infective material. He warns every one to avoid exposure because as yet (1930) there is no means of differentiating the two groups. He refers also to the fact that of the people exposed to infected goats milk in Mediterranean areas, many more fail to get infections than do become infected. The origin of immunity of so many human beings to Brucella is a subject of considerable importance.

McAlpine and Mickle (54), in 1927, report on an analysis of 10,157 human sera sent in for Wasserman tests and tested also for Brucella Abortus by the agglutination method. In this group of sera he found that 0.6% gave positive reactions up through the 1 to 100 dilutions. He also states that these sera were taken from an area where testing of animals had shown 90% of the dairy herds infected with Brucella and only 60% of the milk was pasturized. He concludes that infection of man with the bovine type of Brucella is relatively rare.

As early as 1913 Larson and Sedgewick (52) observed that there seemed to be an association between the cause of abortion in women and contagious abortion in cattle. They discounted Lues and injuries as the cause of these human abortions and were also able to find a large percentage of these women gave positive complement-fixation reactions using Brucella Abortus antigin.

A study of the value of hypersensitivity findings was made by Fleischner and Meyer (27), in 1918, which showed that Brucella Abortus Bovinus and tuberculosis behaved very closely as to character of lesion and cutaneous hypersensitivity.

King and Caldwell (49), in 1929, state that individuals with lowered resistance who drink Brucella infected raw milk may develop agglutinins in their blood either with or without manifestations of clinical symptoms of Undulant Fever. He concludes that the presence of Abortus agglutinins in human serum is evidence of infection with Brucella Abortus and says that these agglutinins may persist in the blood for months or years after recovery of the patient.

Dustin (19) in an article published in May 1937 refers to Hardy's (36) division of cases according to the duration and severity of their symptoms. There are four groups which are as follows:

Group I - Fatal cases - He isolated sius variety from the the three fatal cases and from one of them the abortus variety also.

Group II - Severe or moderately sever cases - includes 28 cases, 23 of which were caused by suis and 5 by abortus

Group III - Mild cases - 7 cases in this group, 4 were caused by suis and 3 by abortus.

Group IV - Ambulatory cases - 8 cases - 3 caused by Suis and 5 by abortus.

Meyer and Eddie (57), in July 1929, said that final conclusions concerning the relationship of the varieties of Brucella to human infection in this country could not be drawn. They thought then that Brucella melitensis variety abortus bovinus was the causative organism in a fairly large percentage of cases.

Traum (71), writing in October 1929, points out that evidence has accumulated since 1924 that proves the goat is not the single animal responsible for Undulant Fever in man but that the cow and the hog must also be considered as sources of this infection. He says that infection with all three varieties have been found in man. He points out also that the variety identified does not necessarily identify the source of infection. Infections of all three varieties have been reported in cattle. Of 96 strains isolated from cattle 86 were bovine, 8 were suis and the balance of 2 were of the variety melitensis.

Fleischner and others (27A) experimented on the pathogenicity of Brucella Abortus and melitensis. They proved them pathogenic for monkeys and observe that melitensis is far more invasive than Brucella Abortus. These experiments show that one or two feedings of one-one thousandths of the amount necessary to cause an infection with abortus is sufficient to parasitize a monkey with melitensis variety.

Hardy (33), in 1929, revealed with caution that he felt that cattle were the chief source of infection in the United States.

Immunity - Regarding this phase of Undulant Fever little is definitely known. I have already referred to it in the comparative freedom of children from Undulant Fever as well as the fact that the great majority of people exposed to Brucella do not show clinical manifestations of the disease.

Jordon (45), in 1931, says that immunity probably plays a

significant role in the epidemiology of Undulant Fever if one judges from the large percentages showing "no agglutination" in the various selected groups. Some of those in this "no agglutination" class have come to have the negative reactions following infection associated with disease; a larger number apparently following infection without disease, others show no agglutination even though exposed to infection. He asks - are there other factors controling this, for instance, natural immunity in children and other age groups.

Coolidge (13), in 1916, says they had no proof of the pathogenicity for man of Brucella Abortus. He said it was possible to develop antibodies in blood serum of adults for Brucella Abortus by feeding milk containing the organism , as well as, Brucella Abortus antibodies. He thought these antibodies represented a passive immunity derived from absorption in the large intestine of the antibodies already present in the infected milk.

There has been much work and many articles published on the bacteriology and immuniological aspects of Brucellosis but they are studies in themselves so I only barely refer to them as I try to limit myself to the problem of Undulant Fever as an occupational disease. I believe that immunity must play an important role else the incidence of the disease would be much greater since the possibility of infection is widespread and potent. What the factors are that control this immunity are not as yet understandable.

Source of Infection - In considering the source of infection of human cases of Undulant Fever we can follow Smith (63) in his division of the possibilities into two groups - those without, and those with direct contact with livestock and carcasses. The first group has for its source dairy products that contain the infective organism. The second group includes the possibilities of the organism causing human infection by exposing an individual through direct contact with excreta of live animals or of handling the carcasses and meat of dead animals.

There is no question now as to the existence of Brucella organisms in cattle, hogs and goats, other domestic animals have also been suggested as containing the organism. The variety of Brucella present in infected animals is not specific as has already been mentioned in this paper since cattle are susceptable to the suis and melitensis varieties, as well as the bovine. It does make a difference which variety infects a human as there is evidence which shows a different degree of virulence for man of these varieties. Melitensis and Suis show the greatest virulence while the bovine type is more variable.

In this paper I think it is possible to consider the source of infection which can be divided into two main groups; milk borne infection, or infection by direct contact.

Again referring to Hasseltine (38) for his classification of Undulant Fever cases into three groups; (1)- the Milk Group, (those having little or no contact with livestock; (2) the Meat

Group (those having contact with livestock or carcasses in the meat packing industries); (3)- the Farm Group (those having contact with livestock on the farm). This grouping is the most practical and should be born in mind in considering the source of infection.

Milk Borne Infection - In considering this group I have made no attempt to differentiate, the degree of virulince or even which variety is the etiologic agent, What I am interested in mainly is how the organism gained entrance to its human host.

Huddleson (43) in considering the source of infection, questions why there are not more cases of this disease in the United States if raw milk was the source of the infection. He answers this question two ways; first- When Brucella Abortus is found in milk it is present in concentrations of about 500 per cubic centimeter, but during the drying up period of the udder on cows it is found in millions per cubic centimeter. Probably it is during the latter time that most infections occur. Second - His second suggestion is that there are many unrecognized and subclinical cases.

Another factor is suggested by Traum (71). He says that when we consider the number of Brucella organisms in infected cow's milk is as a rule small, and that this is usually mixed with milk from non-infected cows and is thereby greatly diluted we must also remember that even in the rare susceptable individual, epidemological studies indicate that large numbers of organisms are required to induce Undulant Fever.

A few of the things that must be considered before raw milk

should be blamed for causing Undulant Fever are listed in Bulletin #50, published by the California State Department of Public Health. They list these requirements:

1. Shedding of Brucella into the milk must be proved by laboratory data.
2. The extent of the infection in the milk herd should be determined by agglutination tests.
3. Positive results from a direct inoculation of Guinea Pigs with centrifugalized specimens of pooled raw milk.
4. History of recent abortions in the herd.
5. History of recent use of live abortus organisms for vaccinating the herd.

According to Stone and Bogen (65), writing in 1935, ingestion of raw milk obtained from cows infected with contagious abortion and showing positive agglutinins to Brucella Abortus in their blood, is responsible for the development of similar agglutinins in the blood of consumers. This has been found to occur in about 8% 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 consumed.

An article by Gordon (45), in 1931, presents some statistics on the source and contact of representative groups of population in Iowa. He says that 80% of the general population group have no contact with livestock and therefore, that the agglutinins found in this group are derived largely from the use of raw dairy products.

He also says that infection with Brucella Melitensis and disease due to ingestion of raw dairy products from infected animals seemed to be largely dependent on the amount consumed, the duration of exposure and the number of organisms ingested.

In studying the elimination of Brucella Abortus in cow's milk Redvers Thompson (68) says the presence of Brucella Abortus in cows was first reported through the United States Bureau of Animal Industry in 1894 by Theobald Smith, who called attention to some experiments by E. C. Shroeder in which he described a peculiar lesion in guinea pigs caused by intra-abdominal injection of milk, and he warned against confusion with tuberculosis. Thompson, in general, supports milk as the main source of Undulant Fever infection and he feels the data he presents further demonstrates that Brucella Abortus may be constantly eliminated with the milk of cows classified as "healthy carriers".

Theordore Thompson (69) of England, in 1928, wrote that of the domesticated animals the cow appears to be the means of transmitting the infection to man in England. Transmission via goat's milk in England has not been proved.

Cornell and De Young (14), in 1929, point out that groups of persons in constant contact with bovine disease and drinking raw milk from such animals for many years have not developed the disease.

Dooley (18) reports an "epidemic" of Undulant Fever where he found the group considered to be using infected raw milk....."of some 300 adolescent boys and adults using this milk 41% showed serum

agglutinins for Brucella Abortus in dilutions over 1 to 20". Several cows of the dairy involved were found to have positive sera and some of these were shedding virulant organisms in their milk.

An outbreak of Undulant Fever was traced to an infected milk supply by Hasseltine and Knight (39) in 1931. Six cases of Undulant Fever occurred in a town of 5387 population between September, 1930 and January, 1931. All six of these cases used milk from the same dairy. A large proportion of the cows in this dairy herd gave laboratory evidence of Brucella infection, and the organism was recovered from the milk of some of them. Pasteurization of this milk, even with the infected animals remaining in the milk line, resulted in cessation of cases among the consumers of this milk.

Strauss and others (64) report five cases that showed direct contact to be impossible but that all of these cases could have gotten Undulant Fever via raw milk. Three of these cases in particular showed strong evidence favoring raw milk as the source.

In a report by Weissman (73), in June, 1937, is an analysis of individuals associated with a tuberculosis sanitarium, where the diagnosis might be questioned. There were 243 patients and employees whose blood contained agglutinins for Brucella in titers varying from 1 to 15 to 1 to 405. These people had been fed in part by raw milk. This check-up was done in 1930. In 1932, having in the mean time enforced pasteurization of all milk, they again checked the serum agglutinins for 312 individuals with the result that

"all were found to be negative in titers ranging from 1-25 to 1-200. Included in this group were 23 patients formerly positive .....conclusions are obvious - Pasteurization is effective in the prevention of infection by milk from cows with contagious abortion."

Redver Thompson (67) in July 1933 reports that Brucella Abortus is transmissable from naturally infected milk or cream to ice cream and remains viable in this product when held at temperatures below the freezing point for a period of at least one month. In ice cream made from ordinary unpasteurized, special, or certified milk may constitute a mode of transmission of Brucella Abortus from the bovine to the human.

Giordano and Sesenick (31) wrote in 1930 what is also true today. They said that while the modes of infection are variable, occurrence of the disease following the ingestion of milk containing Brucella Abortus in cases reported by them and by Carpenter, Huddleson, Evans, Kern, Simpson and others, leaves no doubt as to the possibility of infection from milk.

In regard to certified milk there are several articles and references.

Cornell and De Young (14), in 1929, say that in spite of all the precautions taken by certified milk producers, this product can not, at present, be eliminated as a possible source of infection to Undulant Fever.

Not until July 1930 according to Meyer (56) did California authorities require certified dairies to have only animals free

from Brucella Abortus infection.

It might be interesting to list the requirements of Certification of Cattle that were suggested by Norton and Pless (59) in 1930. They recommend:

1. A blood serum agglutination test with a Brucella Abortus antigen on
   (a) all producing cows - twice a year.
   (b) on all cows 15 to 30 days after freshening.
2. Samples of milk from each quarter of the udder are taken separately from all cows giving a positive reaction in blood serum dilutions of 1 to 100 or higher.
3. Animals showing any agglutinins in the milk serum from any quarter of the udder are immediately excluded from the producing herd.
4. Animals excluded are re-tested one month later and if still positive are isolated from the certified barns.

Huddleson and Orr (41), writing in October, 1937 report sixteen cases of Undulant Fever, all of which had been using unpasteurized milk. In nine of the cases there was evidence of contagious abortion in the milk source. Two cases could give no information as to the milk source and the remaining five had not been completely investigated. They conclude that raw milk from infected cows "is the essential cause of Undulant Fever in man, at lest in Michigan".

In Denmark the percentage of cases, as to their source, is 40% from milk and 60% from contact, according to Madsen who is re-

ferred to by Hasseltine (38). In the contact group he adds the remark that some of this group had been using milk from the infected cattle also.

Away back in 1913 Schroeder (61) warned that infants who must be fed artificially by cow's milk or milk of a foreign species, should receive properly certified, boiled or pasteurized milk to guard against Undulant Fever.

Alice Evans (21) reporting twenty cases in 1927 lists their possible source of infection. Eight cases were not clear on this point but in the twelve left, six gave a definite story of contact possibilities, and six gave raw milk as possible source with no possibility of contact.

In 1929 Dr. Walter Simpson (62), reporting on 63 cases in and about Dayton, Ohio, says that in every case where a source could be established - "the disease occurred in those persons who drank raw milk or ate unpasteurized dairy products". There appears to be no etiologic factor other than the ingestion of raw milk and unpasteurized dairy products in these cases.

Dr. J. C. Ruddock of Los Angeles commenting on Bierring's (9) article reports that in 31 proved cases in California, 90% of these cases showed the use of raw milk from dairys in which there was an active infection of contagious abortion among the milk cows------ Ruddock says....."From observations it is evident that raw milk is on trial as one of the etiologic factors in this disease, and that this disease is a real economic factor that affects us all."

The information mentioned above is all in support of raw milk as a source of Undulant Fever in man. I believe the evidence supports that conclusion and there is no controversy on this point. However, it is not the only possible source of infection. Infection by contact with infected materials from animals is also a possibility and which, if either, plays the dominant role? The next part of this paper points out evidence in support of Direct Contact.

Direct Contact - There are numerous references to the possibility of this factor and there is quite a little evidence to support it. I have read all articles making reference to Direct Contact and will attempt to present the evidence.

Hardy (32), in a report of September, 1928, said that the modes of transfer of Brucella from the infected animal to man is a matter of great importance. In cases where there had been no direct contact with livestock, evidence suggests that the organism was transmitted through raw milk or cream. It may be accepted also that, in the case of packing house workers, the organism was acquired either from infected meat or the excreta and gained entrance through the injuired or broken skin, or by way of the digestive tract. The cases contracted by workers in packing houses require special attention. He says that in these cases it is clearly an occupational disease and to gain compensation, for time losses of 1 to 5 months on the average of cases observed, it must be recognized that Undulant Fever among this group is an occupational disease.

Simpson (62), in 1929, reporting 63 cases, says that while the

great majority of cases of Undulant Fever have resulted from the ingestion of unpasteurized milk and dairy products, the disease also affects packing house workers, meat handlers, farmers and veterinarians as a result of direct contact with animal tissues infected with Brucella.

In support of the importance of infection by contact Hardy (33) reveals that in his study of Iowa cases he has been impressed by the frequency of infection of farm males as against farm women; the ratio being 9 to 1. This observation led him and others to believe that the skin might be a portal of entry. In experiments in Guinea Pigs to prove this point, they found that guinea pigs become infected four times as often via skin infection as by feeding. Dosage has a great deal to do with whether infection will be acquired. They then studied a group of packing house employees-217 blood serums were obtained- 29 or 14% reacted to the agglutination test in a titer of over 1 to 80; the proportion infected varied in proportion to the intimacy of the contact with infected tissues. Less than half of those giving laboratory evidence of infection gave any history of Undulant Fever and only three had had clinical diagnosis. They concluded that the skin, as a portal of entry for Brucella, must be given more consideration.

In a later article Hardy (35) published in August, 1936, he says that he has demonstrated further the significance of direct contact with livestock and carcasses. "Iowa and surrounding states have a demonstrably higher incidence of Undulant Fever than do other areas.

Limited evidence undicates that the porcine type of infection is largely limited to these states and accounts for the unusual incidence. The porcine type was found in 87 out of 147 cases." The Iowa cases involve adult males most heavily. The comparative high rates for men on farms and for packing house workers suggest the risk in occupations involving direct contact with livestock and fresh meats. The similarity in rates of incidence among women on farms and among other adults not having occupational contact, is added evidence that farm women acquire infection chiefly through the use of infected raw dairy products the same as does the general population. He says further that he believes that inocculation through the skin not infrequently follows direct contact with discharges of living animals, including products of abortion and especially through the tissues of those recently slaughtered.

Bierring (8), in 1929, decides - "Undulant Fever can, with propriety, be classed as an occupation disease in Iowa" because of the 150 cases in his series , 108 included farmers, farmers wives, members of farm families, dairy men, stock buyers, and packing house employees. The vocations involved suggest that contact with animals, particularily cattle and hogs, is a prominent factor. "Drinking of raw milk is given special mention in a considerable number of cases, yet the relatively slight number of infections in children, the largest users of milk, precludes its general acceptance of its etiological factor." He says the increasing number of butchers, pig-killers, and packing house employees becoming infected furnishes

strong evidence that skin contact is a very probable portal of entry.

Axel Thompson (70), in an article published October, 1930, tried to correlate occupation and serologic reactions for Brucella Abortus and found- 272 persons whose occupations bring them into contact with cattle, were examined serologically for agglutinins and compliment-fixing bodies for Brucella Abortus. A control group of 61 healthy, non-febrile persons showed no reactions. In the 272 cases, 65 veterinarians in rural practice for one year or more were included and 61 or 94% showed positive reactions. Complement fixation tests were positive much more often than the agglutination reactions.

An entire class of young veterinarians, tested before graduating showed no reaction. Another entire class of 18 tested five months after graduation showed that of these 18, 15 gave reactions in titers equal to those in cases of Undulant Fever but only one had clinical Undulant Fever. A third class of 12 examined about one year after graduation gave similar findings, and also showed that those who were not in contact with cattle gave no reactions.

A group of 16 Bacteriologists, working with Brucella, had 10 or 63% positive reactions. In 21 cattle attendants on farms, 13 or 62% gave positive reactons. In 25 minor farm employees doing some work with cattle, 6 or 24%, gave positive results; in 23 farm owners 9 or 39% were positive; from 20 milk maids on similar farms only 1 showed a positive reaction; no reactions were noted among 10 milk testers of large Copenhagen dairies; 5 or 20% of 25 butchers

gave positive reactions; from 12 inspecting veterinarians working in slaughter houses 4 or 33% gave positive reactions.

From these observations Thompson (70) concludes that contact with infected sick animals is primarily responsible for the incidence among this group. He warns that interpretation of positive results in diagnostic serologic tests for Brucella among those in occupations connected with cattle, or with Brucella, should be made with care, since the serums of healthy persons thus employed may also give positive reactions.

Gordon (45), in 1931 says that veterinarians show agglutinins for Brucella in definitely higher ratios than does the general population, owing chiefly to their contacts with cattle, but the titers do not tend to reach higher dilutions, ordinarilly indicative of high infection, owing possibly to an acquired immunity. He says infection with Brucella and manifest disease due to direct contact are in direct proportion to exposure; this is seen in workers in packing houses who exemplify direct contact with swine and cattle. In this article he gives some figures on the incidence of Brucella infection in the animals. He collected blood specimens of 343 hogs by picking every tenth animal from a total of 3500 killed in a single days operation. He found 64 or 18% of the specimens agglutinated Brucella in titers of 1 to 40, and ten or 3% agglutinated, at from 1/80 to 1/320.

Heathman (40) studied a group of packing plant employees, all from 5 packing plants, 1096 all told. Among the combined force of

four of these plants a number of frank and suspected cases of Undulant Fever had occurred. Intra-dermal and agglutination tests were carried out on representative groups in the various departments. The result in the skin reactions were invariably of the delayed type. The degree of intensity of the allergic phenomena, as well as the number of men in an allergic condition, was found to vary greatly in the different groups, but in general the incidence of the allergic state definitely increased with the length of service while the agglutinins declined. He suggests that the development of the allergic state is due to long continued exposure to small doses of organisms of a low degree of virulence. In a group of workers who had no contact with animals or animal products the incidence of agglutinins was far lower (1.3%) than has been reported by the majority of writers for general population groups.

Messer (55), in 1932, reports three cases of subclinical Undulant Fever giving a history of contact with cattle having had abortus infection. Agglutination tests were positive for two of them in a titer of1/50, and positive for the other one at 1/125. None of these three were ill at the time of the investigation nor did their history point to any previous illness suggesting Undulant Fever. He believes these cases belong to the large subclinical group which is fairly well established.

Gage and Gregory (28) report a single case in 1926 of a patient employed for five years prior to their observations, in the hog killing department of a packing plant. This case reached the Civil

Service Commission because of the question of occupational disease. The decision was at first against the possibility of infection as the result of employment. Their comment added that it would be interesting to see the decision if heard by a Workman's Compensation Commission. The authors think this case was an occupational disease.

Huddleson (43) reports three cases of laboratory workers with Brucella who happened also to be using raw milk from a single dairy. This milk proved stongly positive, on culture, for Brucella Abortus. He lists three possible avenues of infection for those three cases, but seems to prefer the first.

1. Laboratory work with Brucella
2. Ingestion of raw cow's milk.
3. Ingestion of raw goat's milk (this was ruled out definitely)

Hardy (33) points out that as a rule the organisms are present in cow's milk in relatively small numbers but at certain periods are present in vast numbers in the vaginal discharges. Contact with infected animals must frequently result in contamination of the hands and this followed by direct entrance of the organism through the skin has not been given due consideration in the study of the transmission of this disease according to him.

Two unusual but possible sources of infection are mentioned by other authors.

Cornell and De Young (14), in 1929, suggest the possibility of infection via uncooked meat and other products used in sausage as a route from pigs and cattle to humans.

Hasseltine (38) quotes Madsen who suggests that there is a possibility of the transmission of Undulant Fever from one human case to another in the course of an obstetrical practice, and also that since Brucella has been cultured from human feces the transmission from this source is very possible.

In only one place in the available articles was any reference made as to the mode of transfer of Brucella among cattle. This one was by Meyer and Eddie (57) who concur with many others in the opinion that the disease (Brucella Abortus) is transmitted from one cow to another by the bull via seminal route.

Dustin (19), writing in May, 1937, makes the observations which more or less summarize the possibilities of modes of infections and sources of them in humans. He says a study of large groups of cases of Brucellosis would indicate that the drinking of milk from infected herds is a relatively minor source of infection. Apparently the disease is much more frequently acquired by contamination of the abraided skin with blood and excreta from infected animals. Cows, goats, sheep and hogs are known to excrete the organisms from the genitals as well as in milk. Thus there are many sources for easy infection among persons handling domestic animals. He also mentions that elimination of Brucella in human urine for periods as long as two years after onset of infection makes it a possible source. Humans have been found to eliminate Brucella in milk and it also has been isolated from their gall-bladders. He thinks urine is the chief source of elinimation of Brucella in man.

The portal of entry may be the alimentary tract or any mucus membrane as it has been demonstrated that Brucella can penetrate normal mucus menbranes of the nose, eye and genito-urinary tracts of man. He thinks skin abrasions are a common means of entry, even unabraided skin may allow the entrance of Brucella.

SUMMARY

All that can be said in summarizing this paper is to briefly point out the important points in the diagnosis of Brucellosis and to list the observations that can be derived from the various articles in regard to the source of infection with the Brucella organism.

I believe that is possible to conclude from the material presented that the diagnosis of Brucellosis is dependent on a proper analysis and correlation of both clinical and laboratory findings. The clinical observations include the main symptems of fever, chills, sweating, arthralgia and loss of weight, and sometimes splenic enlargement; and the laboratory findings to be considered include (1) the white blood count, which usually, in Brucellosis, shows a leucopenia with a relative lymphocytosis, (2) blood culture- if the laboratory set up is available a positive finding in this test is unquestionable but a negative finding does not entirely over rule a diagnosis, (3) the agglutination test - This is the most practicle test as well as being the most available to practicing physicians. While it is 85% accurate its result must be interpreted with caution.

The titer at which a positive reaction must occur can not, with present knowledge, be arbitrarily established for reasons indicated in the previous pages.

A positive diagnosis of Brucellosis rests on the presence of the clinical syndrome plus the support of the laboratory findings.

The observations brought out in the previous pages shows evidence to support the various possible sources of infection of humans with the Brucella organism. No definite conclusions can be drawn as to the relative importance of the various avenues of infection. It can be said that there are two main avenues - (1) raw dairy products and (2) direct contact with livestock and their excretions either in the handling of live animals or of animal products in the meat packing industries.

Definite proof has been listed supporting both of the above routes. In selected cases, if the dairy product source could be positively over ruled, and direct contact could be demonstrated, then there is little question as to the source. If the question should arise as to whether a case of Brucellosis is an occupational disease, if these conditions existed, I believe it would be possible to conclude that infection was derived from direct contact. In tracing the source of infection with these organisms, however, one must always consider dairy products.

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