

**Staff Meeting Bulletin  
Hospitals of the » » »  
University of Minnesota**

**Undulant Fever**

STAFF MEETING BULLETIN  
HOSPITALS OF THE . . .  
UNIVERSITY OF MINNESOTA

Volume X

Friday, April 21, 1939

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during the school year, October to May, inclusive.

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William A. O'Brien, M.D.

I. LAST WEEK

Date: April 14, 1939  
Place: Recreation Room  
 Powell Hall  
Time: 12:15 to 1:00 p.m.  
Program: Movie: "Little Hiawatha"

## Case Reports

John Kometani  
 Robert Brochner  
 Robert Mooney  
 Lawrence Berman

## Discussion

Wesley Spink  
 Cecil J. Watson  
 Leo G. Rigler  
 H. A. Carlson  
 F. W. Hoffbauer

Present: 127

Gertrude Gunn  
 Record Librarian

will address the faculty and students in room 15, Medical Sciences' Amphitheatre on Saturday, April 22, at 11:00 a.m. The title of his lecture will be "Pyelonephritis." Dr. Weiss, who has been connected with Harvard for some time, has recently been named Professor of Medicine to succeed Dr. Henry Christian.

3. MINNESOTA STATE MEDICAL ASSOCIATION

Will hold its annual meeting in the Municipal Auditorium, Minneapolis, May 31, June 1 and 2, 1939. Of special interest will be the round table luncheon discussion groups in which 20 interested persons eat lunch with a discussion leader who conducts a meeting following the meal. One subject will be discussed by each group. This is a plan which has been used for some time by various organizations, notably, the Wisconsin State Medical Association.

II. MOVIE

Title: "Donald's Better Self"  
 A Walt Disney Short  
 Released by: R-K-O

4. ANNUAL BANQUET

The Medical Technologists of the University of Minnesota will hold their annual banquet, Thursday, April 27, at 6:00 o'clock. Prior to the dinner there will be "open house" in the laboratories of the University of Minnesota Hospitals for staff, students, parents, and friends. The evening program will consist of introduction of guests, a report of the development of the course, and a few random remarks by the Professor of Obstetrics and Gynecology. The first degree in Medical Technology was granted in March, 1923. Since then there have been more than 300 graduates. A recent survey showed them widely distributed throughout our country (40 of the 48 states). The first banquet was held in the spring of 1929, and the occasion has been an annual event. Tickets are 75 cents and may be secured in the laboratory.

III. ANNOUNCEMENTS1. SPECIAL GUESTS

Welcome to the members of the course in Diseases of the Blood and Blood Forming Organs, who are spending this week at the Center for Continuation Study.

2. SPECIAL LECTURE

Soma Weiss, associate professor of medicine, Harvard Medical School

#### IV. BRUCELLOSIS (UNDULANT FEVER)

W. W. Spink  
F. W. Hoffbauer

Brucellosis, more commonly referred to as Undulant Fever, has probably afflicted mankind for many centuries. Its existence in the Island of Malta was noted throughout the nineteenth century by British medical officers. Establishment of the disease as a definite entity followed the discovery of the etiological agent by Bruce(1) in 1886. With subsequent development of diagnostic laboratory procedures the recognition of cases of brucellosis was facilitated.

The widespread distribution of the disease has only become apparent in the last few years. Several factors account for the previous failure to recognize existing cases. Lack of knowledge of the protean clinical manifestations which human brucellosis may present has perhaps been the most important one. Bacteriologists in this country were among the first to suspect the existence of the disease here and directed attention of clinicians to it. Though doubtless the disease will eventually fall under control either through adequate methods of treating existing cases or through prophylaxis, it remains at the present time a disease of considerable importance. Difficulties encountered in the recognition of brucellosis are manifold but are no more so than are those encountered in its treatment. The purpose of the following review of our knowledge of brucellosis and an analysis of a small series of cases is to clarify some of the factors involved in establishing a diagnosis and to discuss certain aspects of its treatment. Examination of the fairly extensive literature available emphasizes the fact that the diagnosis and treatment is not simple.

##### Nomenclature and Historical Aspects of Brucellosis

The story of the evolution of a satisfactory name for the disease is in itself an historical account of the malady.

It was probably a disease of antiquity for Hippocrates has described fevers which include all the features which we now recognize as characteristic of brucellosis. As mentioned, British officers stationed in Malta described the disease as early as 1800. This early geographical distribution was responsible for the name Malta fever. The occurrence of cases in other Mediterranean areas account for the synonyms, Gibraltar fever, Mediterranean fever, and Mittelmeer fieber. In 1897, the name "Malta Fever" was replaced by one more descriptive, "Undulant Fever." Though this was more desirable in that it removed the geographic restriction, it was not wholly adequate since many of the cases, particularly those now seen in the United States, are not characterized by undulating febrile periods. Evans(2) credits the only amusing incident in the history of this dreary disease to a Lancet pun: "How would you make a Maltese cross?" The answer being: "Associate the name of the island with a disabling fever."

In 1886 David Bruce demonstrated the etiologic agent of the disease by the isolation of a micrococcus from the spleen of a British soldier dying of Malta fever. This organism Bruce termed micrococcus melitensis, a name which remained in usage until recently. Ten years later Wright and Semple(3) devised the specific agglutination test which has since become of great usefulness as a diagnostic aid. The prevalence of the disease among the military and naval forces stationed at the island of Malta led to the establishment, by the British government, of a commission for the study of Malta fever. It was almost by accident that the source of infection was discovered. In the search for experimental animals with which to work, goats were chosen because of the scarcity of the usual laboratory animals. It was found that many of the goats were already infected, and the source of infection for man was goats' milk, a food commonly used on the island. Prohibition of the use of raw goats' milk for the men in the service was followed at once by a very sharp decline in the incidence of the disease.

At about the time Bruce and his co-workers were solving the problem of Malta fever, another contribution was made to the knowledge of this widespread but as yet unrecognized disease. Bang, a Danish investigator, studying the problem of contagious abortion in cattle, called attention to the occurrence of minute cocci in the exudate of the uterine wall of a cow with threatened abortion. Further study then established this as the etiological agent in contagious bovine abortion, known thereafter as the bacillus abortus of Bang. Confirmatory studies were subsequently made in this country by Theobald Smith. Later Traum(5), an American investigator, studying the problem of contagious abortion in hogs, isolated a causative organism which differed but slightly in its characteristics from the one described by Bang. It was recognized that these two organisms were probably varieties of a single species. It was not appreciated, however, that they could produce disease in man, not was their relationship to the causative agent of undulant fever recognized.

In 1918, Evans(4) called attention to the close morphological and cultural similarities of the micrococcus melitensis of Bruce and the two agents responsible for contagious abortion in domestic animals. In her report she stated that "it would seem remarkable that we do not have a disease resembling Malta fever prevalent in this country." The first case in the United States recognized clinically as undulant fever and proven by bacteriological methods to be due to bacillus abortus was reported by Keefer in 1924 (6). A similar case report by Duncan(7) appeared from England the following year. It gradually became apparent then that undulant fever was not limited to the Mediterranean littoral, but was world wide in its distribution. Three causative organisms, all varieties of a single species, were likewise recognized depending on their origin from goats, cows, or hogs. The multiplicity of names awarded to the disease and to its etiological agents has led to some confusion. Meyer(8) in 1920 suggested the generic name Brucella. This term has enjoyed uniform acceptance. A desirable classification would seem to

be that followed by Evans and listed by Hardy(9) as:

### BRUCELLOSIS (UNDULANT FEVER)

#### Nomenclature

Malta Fever	Undulant Fever
Mediterranean Fever	Brucelliasis
Gibraltar Fever	Brucellosis
Mittelmeer Fieber	

<u>Etiological Agent</u>	<u>Origin</u>
Brucella melitensis	
var. melitensis	Goat
Brucella melitensis	
var. abortus	Cow
Brucella melitensis var. suis	Hog

As a consequence of the renaming of the organism with the generic name Brucella, the name undulant fever should be omitted and the disease called Brucelliasis or Brucellosis. The latter appears preferable and is most widely used today.

#### Etiology and Disease Incidence

The Brucellae are small, Gram negative, non-motile organisms. They commonly exhibit pleomorphism, and coccoid forms usually predominate in animal tissues. Growth on artificial media is slow. Strains of bovine origin require an atmosphere of 10% carbon dioxide for growth. Differentiation of the three varieties of brucella is difficult but is accomplished by agglutination tests with specific immune serum, by agglutination absorption tests, by the effects of certain dyes on the growth of the organism when added to culture media, and by the carbon dioxide requirement for growth. Most strains are pathogenic for man, for the common laboratory animals, and for such domestic animals as cattle, hogs, horses, goats, and sheep. The disease is a most serious one for cattle, ranking second only to tuberculosis. Infected animals often exhibit no evidence of the disease,

hence recognition other than by the occurrence of abortions and premature births is difficult. A summary of the

pathological findings and related signs of brucellosis in domestic animals is shown in Table 1.

Table 1

Summary of Pathological Findings and Related Signs  
of Brucellae Infection in Domestic Animals  
(Hardy, et al.)

<u>FINDINGS</u>	<u>RELATED SIGNS</u>
<u>Pregnant Uterus</u>	
Chorinitis	Abortions, Premature births
Placentitis	Retained placentae,
Endometritis	Sterility
	Complete absence of all signs
<u>Udder</u>	<u>Laboratory Signs</u>
Chronic inflammatory foci of microscopic size	Organisms present in the milk
	Increase in milk cell count
	Organisms excreted in the urine in some animals
<u>Other Organs</u>	
No gross lesions	

Figures for the incidence of the disease in the State of Minnesota for the past eleven years are available. This data, prepared by the Division of

Preventable Diseases of the Minnesota Department of Health, is shown in Table 2.

Table 2

Undulant Fever in Minnesota  
(Minnesota Department of Health,  
Division of Preventable Diseases)

	<u>Male</u>		<u>Female</u>		<u>Total</u>	
	<u>Cases</u>	<u>Deaths</u>	<u>Cases</u>	<u>Deaths</u>	<u>Cases</u>	<u>Deaths</u>
1927	6				6	
1928	10		2		12	
1929	33		9		42	
1930	43		19		62	
1931	57	2	15		72	2
1932	50	1	12	2	62	3
1933	56		16		72	
1934	78		24	1	102	1
1935	92	2	22	1	114	3
1936	57	2	20		77	2
1937	65	4	23	1	88	5
1938	<u>71</u>		<u>14</u>		<u>85</u>	
Total	618	11	176	5	794	16

The distribution according to sex shows a preponderance of cases in males, the ratio being about three to one, a figure which is in agreement with most of the available data. An analysis of

the 794 Minnesota cases shows the highest incidence of the disease in the male to occur between the ages of 25 to 34 years. Age distribution is shown in Table 3.

Table 3

Age Distribution of the 794 Minnesota Cases

Age	<u>1 to 9</u>	<u>10 to 14</u>	<u>15 to 19</u>	<u>20 to 24</u>	<u>25 to 34</u>	<u>35 to 44</u>
Male	14	17	47	84	199	137
Female	<u>7</u>	<u>7</u>	<u>7</u>	<u>12</u>	<u>36</u>	<u>39</u>
Age	<u>45 to 54</u>	<u>55 and up</u>	<u>Unknown</u>	<u>Total</u>		
Male	77	38	5	618		
Female	<u>32</u>	<u>28</u>	<u>8</u>	<u>176</u>		

Epidemiological studies of the reported cases indicate a definite relationship between the incidence of the disease and certain occupations, namely, farmers, packing plant employees,

housewives, and domestic help. An occupational analysis of the Minnesota cases is shown in the accompanying Table 4.

Table 4

Occupational Analysis of Minnesota Cases

Farmer	206
Packing Plant Employes	149
Housewife and Domestic	131
Meat Handler	6
Veterinarian	5
Laboratory Worker	2
Cream Tester	6
Unrelated Causes	265
Unknown	24

The determination of the probable sources of infection in cases of brucellosis is difficult because of the often insidious onset of the malady and the relatively late diagnosis. Factual evidence however implicates the

ingestion of raw milk, contact with infected animals, and the handling of infected meat as the most frequent sources. Data as to the probable source of the 794 Minnesota cases is listed in table 5.

Table 5

## Probable Source of Infection in 794 Minnesota Cases

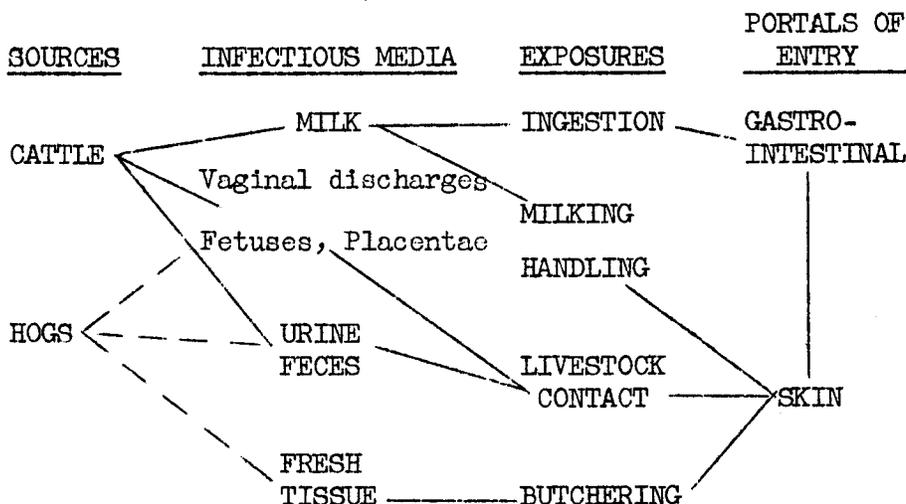
*Raw Milk	512
Handling Meat	160
Handling material from abortion animals	59
Veterinary work	5
Laboratory work	2
No assignable source	52
No data	4

\*Includes 153 farmers who handled abortion material.

In 1936, Kabler and MacLanhan reported that brucella strains isolated from human cases in Minnesota showed twice as many to be of porcine origin as of bovine origin. This would indicate that the hog is the source of more cases of human

brucellosis in Minnesota than cattle. This coincides with the conclusions of Hardy and his associates in Iowa. The suggested modes of transmission of brucella infection to man is shown in Figure 1.

Modes of transmission of *Br. melitensis* var. abortus and suis to man  
(Hardy et al.)



### Signs and Symptoms

In the majority of cases an accurate estimate of the incubation period is difficult because of the multiplicity of exposures and the difficulty in detecting the exact onset of the disease. Most observations place the period of

incubation to be between ten and twenty-one days. Information regarding this point is available from the studies of Otero<sup>11</sup> in experimentally produced infections in human volunteers. In this manner incubation periods were found to vary from ten to sixteen days.

The mode of onset of clinical brucellosis may be sudden or insidious. Clinical symptoms resembling acute respiratory infections are not uncommon, and diagnoses such as "la grippe," "influenza," or "intestinal flu" are often made. Varying degrees of lassitude and weakness are present early in the course of the ill-

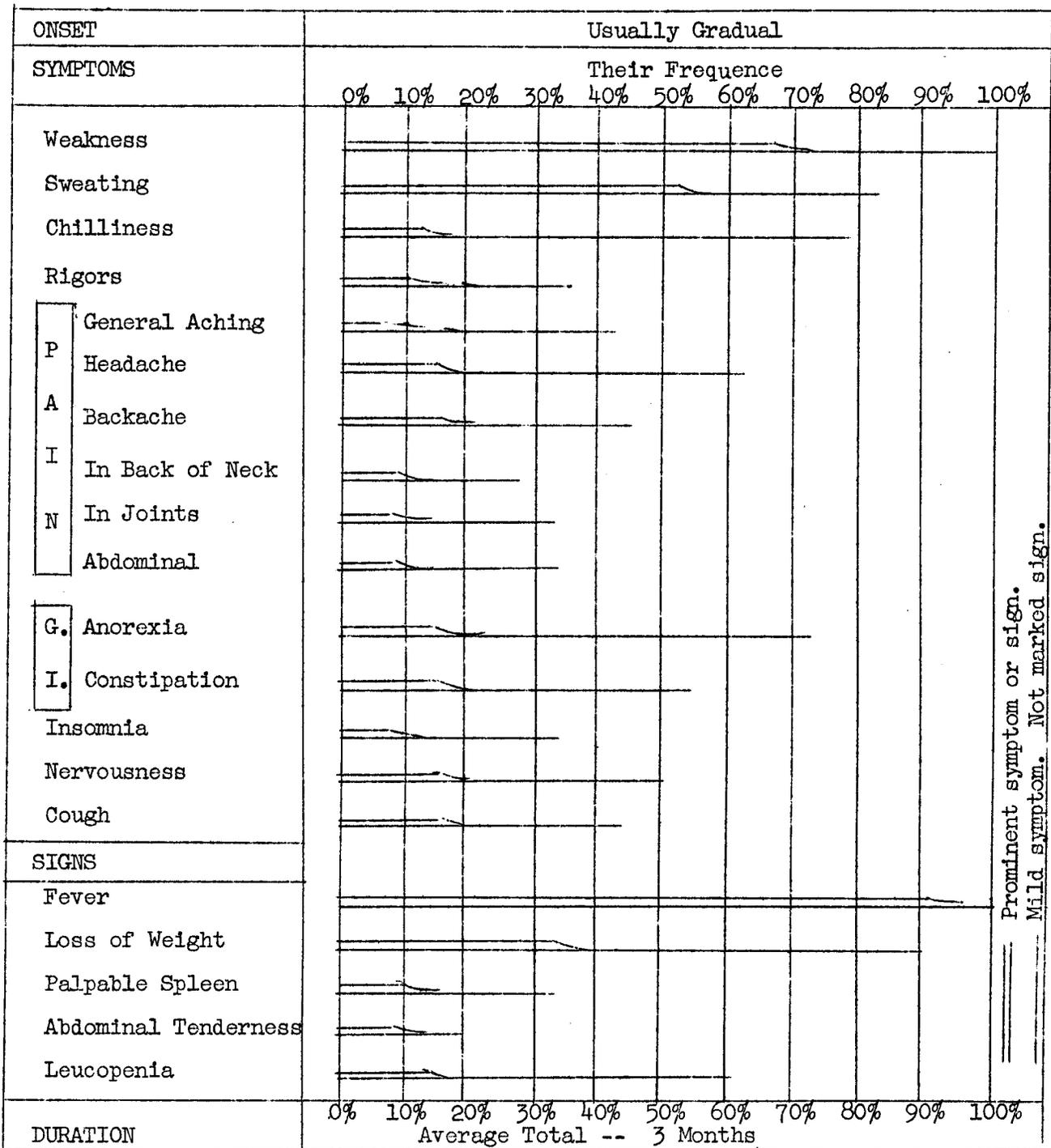
ness in at least one half of the cases.

The common symptoms and signs together with the relative frequency is excellently summarized in the concise table from Hardy. This data, shown graphically in Figure 2, is based on an analysis of 300 case studies in Iowa.

Figure 2

Common Clinical Characteristics of Br. melitensis var. abortus and suis Infections (Data prepared from analysis of the Iowa cases).\*

\*Undulant Fever - National Institute of Health Bull. #58, Hardy et al.



Outstanding in all cases is weakness, which in the mild cases may frequently be the only subjective complaint. Sweating, moderate to profuse, is experienced by a majority of individuals who contract the disease. A peculiar sweetish fetid odor to the perspiration has been reported by some observers. Chilliness, often a symptom observed during the period of invasion, frequently persists and ushers in the daily rise of temperature seen in the more severe cases. Pain usually takes the form of a generalized malaise and tends to persist in the ambulatory patient and to be aggravated by exercise. The pain when it is localized, is generally manifested by headache, arthralgia, lumbar pain, or abdominal pain. The latter may be prominent and has on more than one instance led to erroneous surgical diagnoses. Gastrointestinal disturbances usually take the form of anorexia and constipation. Diarrhea is rare. Of the exhibited neurological disorders, insomnia, restlessness, and irritability are most common, while delirium and coma are rare. Cough, often productive of mucopurulent sputum, is present in about one third of the cases.

#### Physical Observations

The general appearance of patients ill with brucellosis is variable. Many of the patients do not appear acutely or even chronically ill. Even the acutely ill remain mentally alert and lack the dullness so frequently seen in typhoid fever. There is a remarkable absence of physical signs for an infection so widely disseminated throughout the body. Pallor, abdominal tenderness, and splenomegaly are the most frequently reported positive findings. Skin eruptions are usually confined to early cases and are seldom characteristic. Fever, present in all cases at some time, is frequently out of proportion to the degree of prostration. The pulse rate is often relatively slow in proportion to the fever. Low blood pressure is not an infrequent finding, especially late in the disease.

#### Clinical Types of Human Brucellosis

The variable febrile responses exhibited by patients ill with brucellosis permits classification on a clinical basis. The types usually listed are the intermittent, the undulatory, the malignant, the ambulatory, the subclinical and the chronic forms. The latter three are of particular interest because of the ease with which they may escape detection or may simulate some other condition. The chronic form deserves special mention because appreciation of its existence has developed only within recent years. Such cases may emerge from typical febrile forms of the disease but frequently the initial illness is atypical in character. Asthenia, nervousness, lack of emotional control, and melancholia are characteristically present in this form. Temperature elevations are frequently low grade, and there may be long intervening afebrile periods.

#### Diagnosis

##### A. Clinical

Recognition of typical cases is not difficult. Frequently, however, the clinical picture is atypical in nature. The disease should be considered in any patient with fever of obscure origin; in patients with unexplained splenomegaly; in individuals exhibiting weakness, vague muscle and joint pains unaccounted for by demonstrable pathology; and in persons with neurasthenia. Among the diseases with which brucellosis is confused are tuberculosis, typhoid fever, malaria, influenza, subacute bacterial endocarditis, and arthritis. The diagnosis of acute appendicitis or cholecystitis has been erroneously made in cases where abdominal tenderness was manifested.

##### B. Laboratory diagnosis

There is probably no other infection of man at present in which laboratory aid is so necessary to

establish the diagnosis as in brucellosis (Butler - 12). The absence of a leucocytic response in practically all cases of brucellosis is a constant and characteristic feature. True leucopenia is encountered in a half or more of the cases and an absolute lymphocytosis is frequently observed. The sedimentation rate of the erythrocytes is usually normal, a finding exceptional among infectious diseases (Curschmann - quoted from Rieman - 13). An anemia of mild degree is present in many cases, particularly those of long standing.

### Serological Procedures

Two serological tests devised for use in the detection of brucella infection are the agglutination reaction and the complement fixation test. The latter has, however, proved to be of no advantage over the simpler agglutination test and has consequently fallen into disuse. Exhaustive studies both in North America and abroad have established the usefulness and limitations of the agglutination method. It is probably the most reliable single diagnostic aid available for the detection of brucellosis. Blood specimens may be collected from human beings by using the same technique and containers as are used for the Wassermann and Kahn test for syphilis. As in any laboratory procedure, limitation of its value must be kept in mind in interpreting the results. In general, a positive agglutination in a dilution of 1 to 80 or higher has clinical significance. The following must, however, be kept in mind: (1) mild or subclinical brucellosis does occur and may at times be associated with other diseases; (2) specific agglutinins may persist in the blood, though the tendency is toward disappearance coincident with clinical recovery; (3) infection may occur without the production of any demonstrable agglutinins. Such cases, proven by isolating the organisms from the blood stream of patients, are sufficiently common to warrant careful interpretation of negative agglutination tests if the clinical picture is at all suggestive of brucellosis. Cross agglutination reactions with *B. tularensis* are occasionally seen in sera having high agglutina-

tion titres for *Br. melitensis*. Such cross reactions occur in low dilutions only and are seldom confusing (Francis and Evans - 14).

The agglutination reaction in brucellosis may become positive by the fifth day and is usually positive by the fifteenth day of the disease. Rarely positive agglutinations are not evident until the third or fourth week of the disease (Simpson 15). Active tissue invasion by the bacteria is required for the development of agglutinins in humans. Passive absorption of such agglutinins through the gastrointestinal tract does not occur. (Carpenter, Boak and Chapman - 16). Two methods for testing the agglutinating power of serum are the test tube method and the rapid method of Huddleson (17). The latter is performed on a ruled off glass plate resting upon a dark field illumination box. An antigen made from a strain of *Br. melitensis* var. *abortus* (S strain) is said to be satisfactory (Huddleson and Gould - 18). Higginbotham and Heathman (19) have shown the need for the employment of a polyvalent antigen including strains of organisms endemic to the locality.

### Blood Culture in the Diagnosis of Brucellosis

While the agglutination test has the advantage of simplicity and rapidity, it offers evidence that infection either past or present has occurred, but gives no indication as to the type of the offending organism. It suffers the added disadvantage that early in the disease agglutinins are not formed and, more important still, that in some cases they may never appear. The isolation of the organism from the blood stream enables its exact nature to be determined and leaves no doubt that the patient's illness is due to the organism. The absence of bacteremia in some cases limits the usefulness of the method. Butler, an authoritative student of the blood culture method, believes that 80% of patients infected with *brucella melitensis* will yield

positive cultures if the sample is taken at the optimal time during the course of the illness. That such a high percentage of positive results can be obtained in the infections due to the abortus strains of bovine and swine origin, such as are seen in this country, is uncertain. It is probable that some of the failure to demonstrate organisms in cases described in the United States have been due to faulty technique rather than the absence of bacteremia. Three factors are important from a technical standpoint: (1) blood should be drawn when the temperature is high or when a pyrexial wave is beginning; (2) specimens must be incubated for a long time,; and (3) two incubation methods must be used. An atmosphere of 10% carbon dioxide is needed for the growth of *Brucella abortus* var. *abortus*. The growth of the other two strains appears to be inhibited by such atmospheric conditions. Therefore, both methods should be used in the attempt to isolate organisms from the blood stream.

#### Animal Inoculation

Blood, milk, or extract of tissues suspected of harboring the organism may be injected into guinea pigs either subcutaneously or intraperitoneally. After six weeks the animals are killed. An agglutination test for brucella is done with the blood, and the viscera are examined for the characteristic lesions. Specimens of spleen, liver, and lymph nodes are placed in culture media in an attempt to isolate brucellae.

#### Cultures of Urine and Feces

Brucellae have been cultured but very few times from the urine of infected human beings. Very few workers have been successful in isolating the organisms from the feces though Amoss and Paston (20) with the employment of a special technique have on occasions been able to do so. Isolation of brucellae from the gall bladder, the spinal fluid, and the brain of infected human beings have been reported.

#### Skin Test as a Diagnostic Aid

Skin tests as a means of detecting brucella infection in cattle using an antigenic agent prepared like mallein and tuberculin were first used by McFadyean and Stockman in 1909 (21). Many workers have since studied the value of various intradermal tests in humans. The intradermal injection of .1 cc. of a suspensoid of nucleoprotein (1 : 2000) isolated from brucella organisms has been extensively employed by Huddleson. An injection of .05 cc. of a suspension of heat-killed brucella abortus has been found to be satisfactory as a routine procedure. The side of the injection is examined 48 hours later in interpreting the test. The reaction may be graded as in the tuberculin test. Doubt as to the value of the test has been raised because of the finding of positive reactors among people without evidence of the disease. Heathman and her associates (22) found 8.7% positive reactors among a group of 161 healthy hospital employees, all of whom had negative agglutination reactions. On the basis of an extensive survey for evidence of brucella infection using both the intradermal and agglutination test, Heathman was led to conclude that perhaps a negative skin test was more valuable as a diagnostic aid than was a positive one. This view is shared by other writers on the subject. All concede that the test is the most delicate indicator of previous infection or exposure and the presence of a negative reaction will serve to rule out brucellosis in nearly all cases.

#### Opsono-cytophagic Test

Using a modification of the Leishman-Weitch technique, Huddleson (18) has devised a method for determining the Opsono-cytophagic power of blood for brucella. The test is performed by incubating a mixture of a live 48 hour old culture of brucella abortus and the patient's citrated blood for 30 minutes at a temperature of 37 degrees C. A smear of the mixture is then made and

stained. Twenty-five polymorphonuclear leucocytes are examined and their opsonic power classified according to the number of brucella organisms counted within each cell. The classification suggested is as follows:

negative - no phagocytized bacteria  
 slight - from 1 to 20 per cell  
 moderate - from 21 to 40 per cell  
 marked - over 40 per cell

Attempts have been made to correlate this test with the skin test reaction and the agglutination titre to determine whether or not a given patient is immune, susceptible, or infected. Insufficient data is available as yet to make a final evaluation of this diagnostic aid. Certain disadvantages inherent in the test, chief among them being the requirement of young living cultures, limits its scope of usefulness.

#### Treatment of Brucellosis

The evaluation of the effectiveness of therapeutic agents used in any disease is unsatisfactory because of the difficulties inherent in the analysis of clinical data. For several reasons this is particularly true in brucellosis. The frequent occurrence of spontaneous remission or recovery is well known. Then, too, the diagnosis in any given case must be critically analyzed since it may rest only upon the presence of a positive agglutination reaction without due consideration being given to the fact that this may be the residual of some past subclinical infection. A comprehensive review of therapeutic methods was published by Carpenter and Bonk (23) in 1936. Critically analyzing the entire literature available on the subject, they concluded that no therapeutic agent had been developed up to that time, which proved to alter the natural course of the disease to any significant degree. A survey of many reports revealed the rather noteworthy agreement as to the duration of the disease. The average figure reported was three months, an average which appeared fairly constant in treated and untreated cases alike. The multiplicity

of agents and methods so far employed in the treatment of brucellosis attests to the ineffectuality of them.

#### Vaccine Therapy

The use of a stock or autogenous vaccine has been the most widely employed form of treatment. Interval injections, using graduated dosages has been reported by many but with irregular results. Best results appear to have been obtained when a systemic reaction followed the injection. The intravenous administration of such preparations is followed by marked systemic reaction and defervescence is said to occur with coincident clinical improvement. Carpenter concluded that beneficial results were in all probability related to the production of "shock" and that considerable danger existed in the employment of such measures.

#### Serum Therapy

Human convalescent serum and various animal antisera have been fairly extensively employed but the majority of reports are based on a small series of cases. Wherry and his associates (28) were favorably impressed with the results of the administration of a serum prepared from goats. Because of the apparent lack of potency of this preparation, they have suggested the preparation of a horse serum. The administration of human convalescent serum has been reported as being of beneficial, though sometimes temporary, effect. Poston (24) has recently reported successful treatment of 3 cases by this method.

#### Toxic Filtrates used as Therapeutic Agents

Filtrates prepared from broth cultures have been used by a few investigators. Here again beneficial results were noted only when the patient exhibited a marked systemic reaction. In view of the occasional severe local reaction from such preparation when used

as a diagnostic skin test, their employment as a therapeutic agent seems unjustifiable.

### Foreign Protein Therapy

Many non-specific foreign proteins, designed to produce "shock" have been used in the treatment of brucellosis. Most extensively employed are vaccines prepared from the typhoid group of bacilli. Administration by the intravenous, intravascular, and subcutaneous routes have been reported by Budtz-Olsen (25), Simpson (15), Miller (26), and others. The results, dramatic in some cases, appear most favorable in patients manifesting marked constitutional reactions. Benefit can apparently be expected in about one-half of the cases. Less satisfactory results are reported following the injection of sterile milk (Awe and Palmer - 27) (Simpson - 15).

### Therapy with Artificially Induced Fever

This method has been resorted to in a relatively small number of cases. The fact that cures are reported supports the contention that the febrile reaction is an important one in combatting brucellosis. It has been suggested that in the chronic form of the disease, the body has lost the power to respond to the infecting agent by the development of an adequate fever. An encouraging report as to the value of artificially induced fever has recently come from the Mayo Clinic. Prickman, Bennet, and Krusen (29) have reviewed the results obtained in a series of 18 cases. The Kettering hypertherm was employed for the production of fever. Cures were reported in 15 of the 18 patients. Prickman considered this type of therapy is indicated and most efficacious in the acute or subacute febrile stage of the disease.

### Chemotherapy

Carpenter and Boak found reports of chemotherapy used in 75 cases of brucellosis prior to 1926. Among the substances

used because of their supposed bacteriostatic results were methylene blue, mercurochrome, acriflavine, and methyl violet. The routes of administration were variable but the results uniformly poor. The administration of neocarsphenamine has been reported by many European investigators. Wainwright (30) in this country, has recently reported favorably on its use in a small group of patients. Prior to the introduction of sulfanilamide as an agent in the treatment of brucellosis, no drug or chemical had been found which appeared to alter favorably the course of the disease with any degree of consistency.

First reports indicating favorable results in the treatment of brucellosis with compounds of the sulfanilamide group of drugs appeared in 1936 from French sources. Similar reports appeared the following year from Germany. (References Blumgart - 31). Early in 1938 results of five cases of brucellosis successfully treated with sulfanilamide appeared in the British medical literature. (Lloyd - 32, Richardson - 33, Francis - 34). In vitro studies by one of these British investigators (Francis - 34) it was revealed that the drug was bacteriostatic for brucella. Similar results were noted by Chinn (35) when he observed the drug in a concentration of 1 to 1000 killed the organisms. In higher dilutions the drug was found to be bacteriostatic but not bacteriocidal. Guinea pigs receiving the drug were found to be protected against infecting doses which caused the disease in the untreated controls.

Sulfanilamide as an agent in both the treatment and the diagnosis of brucellosis has been recommended by Welch and his associates (36). They found that the drug increased the opsono-cytophagic activity for brucella both in infected animals and in human cases of brucellosis. Clinical reports, indicating that cures can be obtained in this disease by the use of sulfanilamide, have recently appeared from many sources in the United States (Stern and Blake - 37, Blumgart - 31,

Traut and Logan - 38, Toone and Jenkins - 39, Bartels - 40, and others). It has been demonstrated that under this form of therapy bacteremia will disappear, fever will abate, and clinical improvement will occur. While the number of cases reported is small the results so far are encouraging. It would appear that maximal dosages (as judged by present day standards) are necessary to elicit results. Final evaluation of the effectiveness of the drug must, of course, await more widespread clinical trial. At the present time, a trial of the drug in cases of human brucellosis appears justifiable.

of brucellosis have been studied at this hospital. Data from the records of these cases has been arranged for analysis as shown in the following tables. The distribution as to sex, age, and occupation, the probable source of infection, (Table 6); as well as the observed signs and symptoms (Table 7); laboratory findings (Table 8); agree fairly well with those reported for more extensive investigations.

Table 9, showing the various diseases considered in the process of arriving at a correct diagnosis, presents an impressive list of clinical disorders. It serves to emphasize the atypical character of many of the cases.

#### Review of Cases Observed at this Hospital

In the past ten years, 25 proven cases

Table 6

An analysis of 25 cases observed at the University of Minnesota Hospitals for a ten-year period (1929-1939).

1. Sex Distribution:
 

Females	6
Males	19
  
2. Age Distribution:
 

Average	33 years
Range	12 to 62 years
  
3. Symptom Duration Prior to Admission:
 

Average	4 months (approximately)
Range	2 days to 7 years
  
4. Length of Hospital Stay:
 

Average	35 days (23 cases)
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5. Probable Source of Infection:
 

Raw milk ingestion	10 cases
Contact with aborting cows	6 cases
Not determined	9 cases
  
6. Occupation
 

Farmer	11 cases
Laborer	5 "
Student	2 "
Nurse	2 "
Housewife	2 "
Salesman	1 case
Physician	1 "
Child	1 "

Table 7

An analysis of 25 cases observed at the University of  
Minnesota Hospitals for a ten-year period  
(1929 to 1939)

1. Symptoms Observed: In order of their frequency	2. Signs Observed:	
1. Weakness	1. Fever	20 cases
2. Chilliness	2. Splenomegaly	12 "
3. Sweating	3. Weight Loss	6 "
4. General Aching	4. Pallor	5 "
5. Headache	5. Cardiac Diseases	2 "
6. Cough	6. Abdominal tenderness	1 case
7. Anorexia		
8. Constipation		
9. Nervousness		
10. Backache		
11. Arthralgia		

Table 8

An analysis of 25 cases observed at the University  
of Minnesota Hospitals for ten-year period.  
(1929 to 1939)

## Laboratory Studies:

1. Anemia:		
Hemoglobin below 70%		3 cases
Hemoglobin 70 to 80%		7 "
2. Leucopenia:		
Leucocyte count below 5,000		12 cases
3. Lymphocytosis:		
Absolute		3 cases
Relative		11 "
4. Agglutination Studies:		
Positive at one time		24 cases
Negative at one time		7 "
a. Early		5 "
b. After recovery		1 case
c. Persistently negative		1 "
5. Skin Test:		
Positive		16 cases
Not performed		6 "
Negative		3 "
a. Endocarditis		2 "
b. Early case		1 case
6. Blood Culture:		
Positive		1 case
Negative		18 cases

Table 9

An analysis of 25 cases observed at the University of  
Minnesota Hospitals for a ten-year period  
(1929 to 1939)

## 1. Diseases considered in establishing the diagnosis:

1. Tuberculosis	8 cases	15. Unresolved	
2. Typhoid Fever	6 "	Pneumonia	1 Case
3. Hodgkin's Disease	5 "	16. Lung Abscess	1 "
4. Subacute Bacterial Endocarditis	3 "	17. Pleurisy	1 "
5. Tularemia	2 "	18. Psychoneurosis	1 "
6. Malaria	2 "	19. Infectious Mononucleosis	1 "
7. Pyelonephritis	2 "	20. Bronchitis	1 "
8. Influenza	2 "	21. Chronic Arthritis	1 "
9. Tuberculous Peritonitis	1 "	22. Bronchiectasis	1 "
10. Banti's Disease	1 "	23. Appendicitis	1 "
11. Felty's Disease	1 "	24. Cholecystitis	1 "
12. Chronic Sinusitis	1 "	25. Diaphragmatic Pleurisy	1 "
13. Septicemia	1 "	26. Liver Abscess	1 "
14. Empyema	1 "		

Evaluation of the effects of treatment, as may be seen from the results in 23 cases, is difficult. Of 12 cases receiving only symptomatic therapy, 9 improved; of 11 receiving measures thought to be more or less specific for the disease, 7 showed improvement, 4 did not.

One death is recorded in the series, that of a male presenting the clinical picture of brucellosis and bacterial endocarditis. Autopsy studies confirmed the clinical impression. Pure cultures of brucellae were obtained from the cardiac valve vegetations, the spleen, and the lungs.

Treatment and Results in 23 cases

<u>Type</u>	<u>Number</u>	<u>Improved</u>	<u>Not Improved</u>
a. Symptomatic	12	9	3
b. Brucella Vaccine	4	4	
c. Sulfanilamide	3	1	2
d. Typhoid Vaccine	1		1
e. Convalescent Serum and Typhoid	1	1	
f. Typhoid and Brucella Vaccine	1	1	
g. Sulfanilamide and Brucella Vaccine	1		1

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V. GOSSIP

Special interest groups automatically form about leaders. The interest in hematology at the University of Minnesota is the direct result of the presence of Professor Hal Downey in our midst. For many years he has been recognized in this country and abroad as one of the leading blood morphologists. As editor of the four volume "Handbook of Hematology" and his interest in folia, he is known to all persons interested in this subject. His students, now well-established in their own rights, have been the backbone of the faculty for the postgraduate course offered at the Center for Continuation Study this week. Dr. Waugensteen's interest in bowel physiology, Dr. Bell in the kidney, Dr. Watson in the liver, Dr. McQuarrie in convulsive disorders, and many others are the familiar reasons for our special interests in these subjects..... The "J" in Pathologist Benjamin J. Clawson was inserted by Ben after he had been called "Junior" for some time....Internist S. Marx White also compounded his own name....Solon Marx White is said to have been plain "Sam White" back in the good old days before he went to college....Anatomist Clarence Martin Jackson, altho usually classed with the Missourians, is a native of Iowa. He hails from What Cheer, also the birthplace of chiropractor B. J. Palmer.....Bacteriologist Robert G. Green has deserted his north woods cabin for a river boat. Last year, after the season was over, someone made up his mind for him by burning his lake house. A brand new boat with accommodations for four people is the result....Pathologist John Franklin Noble of the Ancker Hospital staff is a graduate of the University of Pittsburgh. In his student days, he was quite a wrestler, which may account for his keen athletic interest....Former pharmacologist Edgar D. Brown is now making his home at Paynesville, Minnesota. He spends his summers at the lake and his winters in town. Very few people know that his avocation is repairing and reconditioning old clocks. He has 56 clocks in his home, including some very unusual types. He also has a large collection of plants and a garden which

is the wonder of the countryside. Ed has made one of the best adjustments of our retired faculty group.... Head physiologist Maurice B. Visscher has been head of his own department since graduating from the University of Minnesota. He received his B.A. degree from Hope College in 1922; from the University of Minnesota the following degrees: M.S., 1924; Ph.D., 1925; and M.D., 1931. He was head of the Department of Physiology at the University of Tennessee, Southern California, the University of Illinois and the University of Minnesota in that order....Professor Gaylord W. Anderson of the Department of Preventive Medicine and Public Health is named "W" for West in honor of Historian West, who was Dr. Anderson's father's superior when he was on the University of Minnesota faculty....Professor J. Arthur Myers again leads the medical faculty in the length of his list of publications. For years he has occupied first position in this regard.....Internist Henry L. Ulrich, following his graduation from Johns Hopkins, headed the Department of Pathology at Baylor in Texas before entering practice....Internist Wesley W. Spink, a former Carleton "great" in athletics, was in charge of coaching in Doane College, Nebraska for a few years after graduation. This is the college which was used by Life to show the similarity of athletic program and student reaction in our colleges (large and small).....Internist Alfonse E. Walch is a son-in-law of Internist John P. "Jack" Snyder, now retired from active service. Dr. Snyder was a famed teacher at Minnesota, with diseases of the blood as his special interest. He belonged to that period when skill in administering transfusions to patients with pernicious anemia was very necessary. When hemoglobin levels were dangerously low, blood was systematically given until a natural remission took place. The majority of patients with this disease progressed to a fatal ending, usually the result of advanced nervous system changes.....Internist Joseph P. Spano comes from a large family. I have just had the pleasure of having the fourth Spano in my class. The family resemblance is so striking that it is not difficult

to find them out there....First honors for unusual names are usually divided between Herman Ertresvaag Hilleboe and Ejvind Palmer Kirketerp Fenger. The former, the director of medical activities for the State Board of Control, is of Norwegian descent, and the latter now occupying a responsible staff position at Glen Lake, is a Dane....Medical fellow John LaDue has paper number one in the medical section at the annual meeting of the American Medical Association to be held in St. Louis in May....Neuropsychiatrist J. Charnley McKinley skipped the first six grades of public school. His instruction was carried on by his parents. ...Neuropsychiatrist Royal C. Gray started housekeeping with a rare collection of antique furniture when he finally decided to make the fatal break....Neuropsychiatrist S. Allan Challman is on leave of absence in the East, said to be for the purpose of being psychoanalyzed....Dermatologist Sam E. Sweitzer, in spite of his cadaverous appearance, is our most enthusiastic faculty member on the subject of food. When a meal is over, his plate looks like a Scotch family has been at work.....Obstetrician and gynecologist Lee W. Barry was the first graduate student in medical sciences in a clinical subject at the University of Minnesota. He was also the first clinical student to receive his Doctor of Philosophy degree.....Obstetrician and gynecologist Everett C. Hartley has again organized a splendid set of courses in obstetrics and pediatrics to be given in Minnesota during May. The programs will be identical in all the centers. They will start at 8:00 A.M. and close at 5:00 P.M. Four staff men will give eight lectures. The meetings will be held at Pine City, Winona, Fergus Falls, Little Falls, Willmar, Virginia, Worthington, Grand Rapids, Albert Lea, and Crookston.....Drs. John McKelvey and Irvine McQuarrie head the special committees for the courses....Ophthalmologist Frank E. Burch and John S. Macnie both have sons who have finished in medicine and are specializing in Ophthalmology. Both have had unusual educational opportunities and both show great promise for the future.....Ophthalmologist Erling W. Hansen is the faculty's leading Scandinavian dialect comedian.

When in costume and butchering his ancestors' speech, he has been known to go unrecognized even by his close associates....Former state senator from North Dakota, Otolaryngologist Fritz D. Hurd, who was located in Colorado, is now practicing in Montana....Pediatrician Woodard L. Colby is the member of our staff who has the greatest number of inventions to his credit. He has a modification of the safety pin which is said to be very effective....Former Pediatrician Willis H. Thompson, now director of the postgraduate course in Pediatrics in the state of Tennessee, writes that he enjoys his new work very much. As a one-man show, he gives a lecture, clinic, speech before a ladies' organization and acts as a consultant in pediatrics for all the physicians in the community for the day. The next day he is in a new community for the same purpose. This continues from Monday to Friday when the performance is repeated. After 8 weeks in a territory, he moves on to the next one, taking his family with him....Radiologist Curtis Nessa is from Osseo, Wisconsin. He has difficulty convincing people that he does not mean Osseo, Minnesota....Surgeon George R. Dunn has a stock expression for everyone when he greets them. To all in his deep voice he asks "How's the boy doing?" A physician who is more than 20 years his senior insists that he likes to have George call him "My boy.".....Surgeon Alexander R. Colvin, who has been chief of staff at Ancker Hospital for many years is most active in arranging teaching programs for postgraduate courses. He has a special flare for doing this sort of thing....Proctologist Walter A. Fansler, is now a proud grandfather. When the Fanslers departed for Oklahoma for the big event, they are said to have gutted one of our department stores of half its stock in baby things. ...Surgeon Martin Nordland has a sophomore pre-medic son who is just as handsome as his father....Surgeon Charles E. Rea is providing competition for desk man Charles Hayden for the unclaimed boxes of plabum.....