Diagnosis and treatment of undulant fever

James W. Martin
University of Nebraska Medical Center

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THE DIAGNOSIS AND TREATMENT

OF

UNDULANT FEVER

BY

JAMES W. MARTIN, B.Sc., M.Sc.

A Thesis
Presented to the University of Nebraska
College of Medicine
In partial fulfillment of the requirements
of the senior year for the degree of
Doctor of Medicine
1934
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INTRODUCTION

During 1929 and 1930, while working as a Research Fellow in the Department of Pathology and Bacteriology at the University of Nebraska College of Medicine, my work was directed along the lines of blood studies in Undulant Fever which constituted the work for the degree of Master of Science. At this time I developed an interest in the treatment of the disease and since then have been following the cases I have had opportunity to contact and have induced the Doctors in charge to try an autogenous vaccine.

This thesis deals with the diagnosis and treatment of Undulant Fever only. The literature is reviewed on diagnosis and treatment and a series of cases observed in Omaha is presented. An idea of whether or not autogenous vaccines are of therapeutic value may be judged from the results of the cases presented which were so treated.

James W. Martin.
DEFINITION

Undulant Fever is a specific infectious disease, due to Brucella abortus, Brucella suis, or Brucella melitensis. It is characterized usually by a fever of long but varying duration, an irregular course, with a tendency to relapses and remissions, and varying concomitant symptoms, notably profuse perspiration, arthralgic pains, enlargement of the spleen, weakness and chills.

DIAGNOSIS

MODES OF INFECTION: While the modes of infection are variable, occurrence of the disease following the ingestion of milk containing Brucella abortus in cases reported by Giordana and Sensenich(1), Carpenter(2), Huddleston(3), Evans(4), Kern(5), and others, leaves no doubt as to the manner of infection in these cases. Direct contact with infected live stock no doubt is common and, in a few instances, this has been shown by veterinarians becoming infected while attending cows infected with the germ(1). Huddleston reports cases occurring from accidental laboratory inoculation(6). Infection also occurs from contact with infected hogs.
INCUBATION PERIOD: Data on this is very incomplete and inadequate. In accidental laboratory infections and in veterinarians attending aborting cows, it has varied from seven to twenty days. It has been shown that in monkeys, from the time of ingestion or inoculation, the period may vary from ten to forty-two days before agglutinins appear in the blood.

MODE OF ONSET: The initial symptoms are as widely variant as is the clinical course. An insidious onset with fatigue, anorexia, low fever, headache, with muscular weakness or joint discomfort is the most common. Chills are usually not the initial symptoms and develop after elevation of temperature is noted. The presence of pharyngitis, slight cough, or bronchitis frequently lead to a mistaken diagnosis. Rarely is the onset more abrupt, and the evidences of sepsis are the first and temporarily overwhelming symptoms.

Arthritis with moderate elevation of temperature may be the first and only manifestation of the disease, or the nervous system may be attacked and the invasion may be characterized by meningeal symptoms.

CLINICAL FEATURES: The disease may be acute or chronic, the course in each instance differing not only in duration of illness but in other respects, and varying
to such a degree as to be distinctive. A patient may have chills, sweats, headache, and fever of septic type, with no tendency to undulation, recover in two weeks with no subsequent relapse, whereas another patient may have for a period of illness of more than ten months, a continual course of chills, sweats and septic type of fever without undulation or a single remission; still another patient may have an illness of six, ten or twelve months duration characterized throughout by undulating temperature and apyrexial remissions.

The chronic course of the disease has been commonly described in the literature of Undulant Fever, whereas the acute course has been infrequently discussed, or discussed with the assumption that the apparent short course was accounted for because of an insufficient period of observation and that the illness must have included many such attacks with periods of remission. As a result of this, the chronic type has been generally accepted as the most frequent and typical. Giordano and Sensenich(1) find in their series of cases that the acute type is more frequent than the chronic type and suggest that the tendency to acute or chronic illness may be a differential point between Brucella abortus and
Brucella melitensis infection.

Although the disease due to Brucella abortus represents a widely varied symptomatology and although certain symptoms may increase or diminish in intensity or may be supplanted by other symptoms, there is noted in the cause of illness in most cases a dominance of certain symptoms directly referable to the particular body structures that are being attacked by the disease. This makes a simple and practical classification.

1. Septic type--Cases placed in this group are those in which the course of the disease has been similar to other infectious diseases in which bacteremia is an underlying condition.

2. Arthritic type--Into this group are placed those cases in which dominant symptoms have been referable to the joints. They vary from painful, tender joints in which the involvement may be periarticular to the condition in which recurrent hydrops are the characteristic manifestations.

3. Neurologic type--This classification is limited to those cases in which there is indicated an invasion of the nervous system to such an extent that the resultant clinical manifestations are definitely neurologic in character. The minor manifestations of nervousness which
would generally accompany any infectious disease are excluded.

4. Visceral type--The bacteremia in this disease leads to visceral invasion and lungs, heart, liver gall bladder, bowel, spleen, kidneys, uterus and adnexa have been involved. It is stated by some authors that Brucella abortus infections in women could be the cause of abortion. Cornell(8) examined 1015 blood sera from pregnant women, employing the agglutination reaction. None gave definitely positive reactions and only five were weakly positive. The author(9) examined blood sera from ten cases of spontaneous abortion and found one to have an agglutination of 1-640. The organism could not be cultured. Whether this was the cause of the abortion we could not say. The author does not agree with the work of Cornell as his own researches upon examining 12,000 blood sera shows that at least 4% have agglutinins. These findings agree with those of Harrison(11), McAlpine(12), Giordano (13), Litterer(14) and Carpenter(15), who have examined a large number of blood sera.

The symptoms found in undulant fever, their frequency and character regardless of the type of the disease will each be discussed.

FEVER: Of the individual symptoms, fever is the most constantly present and the most variable in character.
A typical temperature chart in undulant fever showing the undulatory phenomena.

Figure 1.

Note the daily peak and low point in remission each day occur at a higher point than the preceding day until the crest of the wave is outlined, whereupon for an equal number of days the temperature in like manner recedes to a lower level each day. Such a temperature chart viewed over a period of weeks exhibits a series of undulations each requiring about the same number of days for completion.
Owing to the bacteremia of this disease, the fever, in most cases, is somewhat similar to that associated with other septic conditions. The undulant type of fever is the most striking but more often a feature of the chronic cases. The temperature, for a period of from seven to fourteen days, rises by step-like gradations, each day reaching a higher point and exhibiting a morning remission to, or near, normal. (Figure 1.) The fever, having reached a daily peak of 103° or 104° F. with a morning remission of two or three degrees, begins to exhibit the undulatory phenomena as follows: The daily peak and low point in remission each day occur at a higher point than the preceding day until the crest of the wave is outlined, whereupon, for an equal number of days the temperature, in like manner, recedes to a lower level each day. Such a temperature chart viewed over a period of weeks exhibits a series of undulations each requiring the same number of days for completion. In one case the undulations may cover eight days while in others they may be completed in seven, six, five or four days. In the melitensis infection each cycle may cover a period of three weeks or more. Hughes (16), who first suggested undulant fever in Brucella melitensis infection as descriptive of this phenomenon, noted the variable length
of the undulations in different cases but pointed out the striking constancy of the undulatory pattern once it was established in a given individual. The period of typical undulation is variable in length. In one case it may exist only four weeks, while in another this type of fever may persist for many months. There is a gradual tendency to lower levels with apyrexial intermissions followed by short periods of relapse with irregular fever and change to the intermittent type. In the cases due to *Brucella abortus* organisms, the typical febrile pattern is not seen so often. Instead there is usually a tendency to constant septic fever with moderate daily remissions, variable in course from a period of two weeks to ten months, without tendency to undulation or apyrexial intervals. This has been pointed out by Hardy(17).

It is also noted that after improvement has begun there is steady and fairly rapid progress to an apparently complete restoration of health without sequelae or recurrence.

**CHILLS:** Chills are equally as constant as is fever. They are present early in the illness and tend to persist, although they occur less frequently later. They vary in intensity from a mild chilliness to violent rigor
and are usually followed by a rise in temperature, but may occur only as a distressing chilliness while the temperature is elevated. Recurrence at the same time daily throughout a long period of time is frequently noted. This condition is commonly prominent during the period before the patient goes to bed and is easily controlled and often entirely prevented when the patient is being treated in bed.

SWEATS: Sweats are associated with the periods of chills and hyperpyrexia. They may be mild or extremely profuse and may occur independently of chills. These sweats may be of noticeably offensive odor.

HEADACHE: Headache, especially in the early stages of the illness, is constant and extremely distressing. It is more frequently occipital and the pain extends downward through the cervical region and then is diffused over the shoulders and upper portion of the back. The severe pain has a tendency to regular periodicity, recurring at the same time each day, usually with increases in temperature. Later in the illness and in the presence of lower temperature, it is lessened or disappears.

BACKACHE: Backache is at first usually related to the occipital headache as before described, and generally diminishes in intensity with it. It may, however, persist independently or even recur after the febrile period. It.
is frequently confined to the lumbar region.

**ARTHRALGIA:** This is fairly constant and the onset is usually early in the illness. It is generally lessened with disappearance of the acute septic symptoms. It may, however, persist throughout the illness. It is variable from mild discomfort to a persistent pain in the smaller joints likened to the pain of a crushing injury. Less frequently there is discomfort about the larger joints. The pain is apparently due to periartricular neuritis.

**ARThRITIS:** Arthritis is a distressing and frequently disabling manifestation of this disease. It may develop early or late in the course, or may exist as the dominant symptom throughout. In some cases it has apparently been the only manifestation of the disease. All the joints may be involved, separately or together, or it may shift rapidly from joint to joint. There may be a definite periodicity of return in which acute attacks may recur at regular intervals for many months. The joints involved may be painful and tender, but even though they are swollen there is seldom any redness. There may be marked hydrops which recurs at definite intervals of days or weeks, and which may develop rapidly and recede promptly as in a case
reported by Baker(18).

**NEURITIS:** Neuritis, like arthritis, may occur at any stage of the illness, and may be of variable duration or the only symptom of the disease. It may be evidenced by pain in any locality and is probably responsible for most of the pain about joints and in the back, as was described. There may be a noticeably cutaneous hyperesthesia, but no areas of anesthesia have been demonstrated. An unusual type of discomfort is that described by many patients as "eye ache." It is not due to photophobia, is not caused or accompanied by visual disorders, and may be present at any time. Persistent or recurring sciatica is frequently due to this infection.

Other nervous manifestations of this disease are present almost without exception. Asthenia is an early and constant symptom and frequently persists for a long time after relief from all other symptoms. Depression, irritability, or anxiety neurosis are frequent variations in the mental condition of the patient. Even in the presence of high fever there usually is not the dullness or apathy, such as commonly characterized the typhoid state. Exaggerated reflexes and evidence of tension are common. Insomnia is frequently a troublesome symptom.
Psychic and functional nervous disorders are the most common sequelae.

**GASTROINTESTINAL SYMPTOMS:** Anorexia is frequently the first symptom noted, but there is usually a return of appetite as the acute febrile stage subsides. Aside from anorexia and constipation, gastrointestinal symptoms are not common. Nausea and vomiting occur rarely. Epigastric distress is an occasional symptom. There is nothing distinctive about the appearance of the tongue.

**ORCHITIS AND OOPHORITIS:** These conditions are frequently present. They usually occur during the febrile periods of the disease. There is tenderness and perhaps some swelling. This symptom may persist after recovery from other acute symptoms.

**SPLENIC SYMPTOMS:** Splenic enlargement is commonly found in Brucella melitensis infections and is a cardinal symptom, but in Brucella abortus and suis infections it is infrequent.

**RENAL SYMPTOMS:** The kidneys may be impaired. A moderate amount of albumin is sometimes found. The organisms can, in some cases, be cultured from the urine.

**RESPIRATORY SYMPTOMS:** Pharyngitis is frequently an initial complaint. Pulmonary symptoms are common. Bronchitis, varying in intensity, may come early in the
disease and persist throughout. Pneumonia and pleurisy with effusion may occur.

**CARDIAC SYMPTOMS:** Heart manifestations due to Brucella organisms are, fortunately, not common. The pulse rate is accelerated but rhythm and valve sounds are not often altered unless this occurs in previous disease. However, one death from endocarditis due to this organism has been reported by Saphir(19).

**AFFECTION OF THE LYMPHATIC GLANDS:** Lymphatic gland involvement is usually not demonstrable in this disease except in the cases of regional glands which have become infected by reason of close proximity to the point of introduction of an overwhelming number of virulent organisms. No doubt, though, lymph glands frequently harbor this organism throughout protracted periods. Carpenter has cultured organisms from tonsils removed at operation.

Undulant fever, as regards diagnosis on the basis of clinical observation alone, requires differentiation from many lesions due to infection. Typhoid fever, malaria, tuberculosis or other respiratory infections, sinusitis, rheumatism, cholecystitis, liver abscess, meningitis or any pyogenic infection must be considered. The reports in the last few years of leishmaniasis in this country
might rarely make it necessary to consider the possibility of this disease.

The history as to probable ingestion of infected milk or contact with infected animals is frequently strongly suggestive. The chills, fever, sweats, muscle or joint discomfort, headache and evidence of involvement of the nervous system without gastrointestinal symptoms, rose spots, hemorrhage or demonstrable focal infection furnish valuable differential evidence, although all these variations may occur. A persistently chronic course uninfluenced by quinine or salicylates add therapeutic evidence if no laboratory facilities are available. Definite diagnosis must be made by the clinical pathologist.

LABORATORY PROCEDURES

BLOOD COUNTS: The leucocyte count early in the disease is usually diminished. Later in the course, the count varies from 6,000 to 10,000. The differential count usually shows an increase in mononuclears. This, however, may be a variable factor. Hardy(20) states that differential counts are very important in that they show a moderate to marked decrease in polymorphonuclears with a corresponding increase in large mononucleate cells of different types. He found that an average differential count showed about thirty-five per cent of polymorphonuclears,
ten per cent small lymphocytes, and fifty-five per cent large mononuclears which he further classified as large lymphocytes, endothelial leukocytes and pathological lymphocytes. He has found as low as sixteen per cent polymorphonuclears with seventy-five per cent large mononuclears.

In view of the above facts, the differential blood count becomes a valuable piece of evidence in establishing a diagnosis of undulant fever. The author has made differential blood counts on nine proven cases of undulant fever and has found a similar differential blood pictures on each, as described by Hardy.

The erythocyte count in most instances shows a decrease, a definite secondary anemia being the rule and the hemoglobin is decreased in proportion.

AGGLUTINATION TESTS: As a routine diagnostic procedure the agglutination tests will be found most useful. The macroscopic, the rapid macroscopic and the microscopic will be discussed. The advantages and disadvantages of each will be pointed out and recommendation made as to which is preferable.

To present reliable evidence to the physician, certain points must be carefully observed by the laboratory worker, when doing agglutination tests. The
organism or organisms used must be of known agglutinability, properly checked by a positive control test. The density of the antigen must be accurately standardized. Technic must be accurate and plenty of time for agglutination allowed because serums vary in the rapidity with which they cause agglutination and failure to consider this may result in negative readings. Only complete or almost complete agglutination should be reported.

The laboratory interpretation must be weighed by the internist in the light of other clinical conditions. It is generally agreed that titers of less than 1:40 are regarded as negative; 1:40 as doubtful; 1:80 as weakly positive; 1:160 and 1:320 as positive; 1:640 and 1:1,280 as strongly positive and above this as very strongly positive. By the clinician it must always be borne in mind that infections with positive serologic tests but without clinical manifestations occur and that these may be associated with other illness. Hardy(20) noted this twice in malignant disease, once in tularemia and once in appendicitis.

TECHNIC OF THE MACROSCOPIC AGGLUTINATION TEST: The antigen is prepared by growing cultures of Brucella melitensis, abortus, and suis, washing the growth off with \(0.85\%\) NaCl solution and standardizing the suspension to a
density of 500(21). Eight dilutions of serum are used ranging from 1-10 to 1-1280 as shown in the table on the following page. One cubic centimeter is carried from one tube to the next and one cubic centimeter is discarded from the last tube. The antigen is then added, the tubes placed in a water bath at 37.5 degrees Centigrade, left four hours, removed to the refrigerator over night and the titer of the agglutination is read the next morning.

**RAPID MACROSCOPIC AGGLUTINATION TEST:** The rapid macroscopic agglutination test of Huddleson(22) is the best method for detecting Brucella antibodies. It has been shown by the author(10) that this method is as accurate as the regular tube method and the complement fixation method. It requires only a few minutes time to make the test.

The principle of the test is that of mixing a concentrated antigen with a small amount of serum. If antibodies are present flocculation occurs. Huddleson, reasoning along the line of well-established principles governing flocculation of bacteria by specific sera, thought that by further increasing the concentration of the antigen without further dilution "zone" reactions would be eliminated. Further, reducing the electrical potential of the
antigen by increasing the concentration of the salt solution would tend to hasten flocculation on the addition of serum containing the reacting substances. So, by varying the concentration of the antigen, as determined by the Gates(23) apparatus or nephelometer and the concentration of the salt solution, an antigen was arrived at which was highly sensitive to flocculation when brought in contact with sera containing specific agglutinins.

The procedure for the preparation of the antigen and performing the test is as follows:

Strains of Brucella are grown on gentian-violet-beef-liver-infusion agar in Blake bottles for 48-72 hours. At this time the luxuriant growth is removed with a solution containing 12% sodium chlorid(C.P.) and 0.5% phenol. A heavy suspension of the organism is desired so care should be taken not to use too much salt solution in removing the growth. The suspended organisms are filtered through absorbent cotton to remove pieces of culture medium removed with the growth. The suspension is now carefully standardized with the Gates nephelometer to a density of four millimeters. This makes a very dense suspension of the organisms. The pH is adjusted to 6.8 in order to obtain the greatest speed of flocculation. The antigen
**SET UP FOR MACROSCOPIC AGGLUTINATION TEST**

<table>
<thead>
<tr>
<th>Dilution</th>
<th>1-10</th>
<th>1-20</th>
<th>1-40</th>
<th>1-80</th>
<th>1-160</th>
<th>1-320</th>
<th>1-640</th>
<th>1-1280</th>
<th>Positive Control</th>
<th>Negative Control</th>
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<tbody>
<tr>
<td>NaCl</td>
<td>1.8c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
<td>1.8c.c.</td>
<td>1.8c.c.</td>
</tr>
<tr>
<td>Serum</td>
<td>0.2c.c.</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.2c.c.</td>
<td>0.2c.c.</td>
</tr>
<tr>
<td>Total</td>
<td>1.0c.c.</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
</tr>
<tr>
<td>Antigen</td>
<td>1.0c.c.</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0c.c.</td>
<td>1.0c.c.</td>
</tr>
<tr>
<td>Final</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
<td>2.0c.c.</td>
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<tr>
<td>Volume</td>
<td></td>
<td></td>
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</table>

![Table and diagram illustration](image-url)
is very stable and may be kept at room temperature for a considerable length of time. In making the test proper it has been found that between 0.03 and 0.05 c.c. of the antigen gives the optimum results for all agglutinating sera.

The sera and antigen are mixed on a glass ruled plate as indicated by the illustration.

![Diagram of plate and glass ruled plate](image)

This plate fits on top of a box as illustrated below.

![Diagram of box](image)

The sera and plate glass should be brought to a temperature of 25 to 35 degrees centigrade and so this is controlled by the switch and light bulbs in the box.

(Picture of apparatus used by the author, on the opposite page.) Cold retards the clumping of the antigen to a considerable degree. The amounts of serum and antigen used are indicated in the above diagram. After the serum and antigen are placed in the squares on the plate, they are mixed by means of a toothpick. Flocculation begins immediately after mixing and is complete in less
than five minutes. The reading of the results is facilitated by a reflected light against a black background, which is arranged for by the bulbs in the box being placed under the top strip and the background painted white. The remainder of the inside of the box is black.

Below is a photograph showing the results of a positive and a negative test.
Rapid Macroscopic Agglutination Apparatus

Ruled glass plate on which to make serum dilutions. This plate is placed over the above box.

The technic for performing the test has been described elsewhere:

Diagram of the Rapid Macroscopic Agglutination Reaction

Positive reaction.

![Diagram of positive reaction]

Negative reaction.

Reading from left to right the serum dilutions are:
1:25, 1:50, 1:100, 1:200, 1:500. To get these dilutions serum of the amounts of .08, .04, .02, and .004 is placed on the squares from left to right, using a Kahn pipette. One drop of the antigen is then added to each square and thoroughly mixed with the serum. The glass plate is placed on the box and the lights turned on. If the serum is positive, macroscopic flocculation occurs within a few minutes. The antigen is colored with gentian violet, which makes the reading very easy.
THE MICROSCOPIC AGGLUTINATION TEST: In the microscopic either of two methods may be employed, one using fresh serum, the other on dried blood specimens.

On examining the dried blood, it is first dissolved in a small drop of saline. Using a loop, the blood is mixed with the saline until the color of a drop in the loop compares with that of pale vaseline. This will give a final dilution of approximately 1:40. Care is necessary if errors are to be avoided but an experienced worker should have no difficulty in obtaining accurate results. The hanging drop is prepared in the usual manner and incubated for one hour. In this time there seems to be as much clumping as takes place in four hours, and tests are much easier to read after one hour than after four hours. Following a long incubation there is usually a precipitation of moisture around the hanging drop and this makes the reading difficult. Dilutions of the saline suspension of dried blood are made and a loopful is mixed with a loopful of antigen, then incubated one hour and examined for clumping.

In reading, after the controls have been observed, the presence or absence of clumping in the test drops is noted. If this is present, the size of the clump is observed and recorded as small, medium or large. The
presence or absence of free organisms should also be noted. If there is any uncertainty, high power observations should be made. There are many possible errors in the interpretation of a microscopic agglutination test done on a small nonmotile organism. Great caution should, therefore, be used. At the present time, it is considered unwise to make an unqualified positive report. The physicians should be informed of the significant findings and told that there has not been sufficient experience with the test to learn its reliability and request that, in order to confirm the report, wet blood be sent for a macroscopic test. The author, after having performed many microscopic agglutination tests, does not think an opinion should be based on an examination of dried blood.

**THE AGGLUTININ ABSORPTION:** The agglutinin absorption test is used to determine whether a Brucella infection is due to Brucella melitensis, Brucella abortus, or Brucella suis. Antibodies produced in the blood sera by each is specific.

The creation of antibodies is explained on the hypothesis that the bacterium consists of one or more components, each producing its specific agglutinins during the process of immunization. Biologically allied species may possess one or more components in common, hence
the phenomenon of group or coagglutination. It has been demonstrated that by saturating the antiserum with an emulsion of the coagglutinating organism, all these coagglutinins could be removed, leaving the specific agglutinins of the homologous strains intact.

The term specific is relative to the absorbing strain for different bacteria may absorb different amounts and kinds but the residual agglutinins are termed "specific." It may be possible that the definitely specific agglutinins of a bacterium can be measured only by successive saturations of its antiserum with different bacteria, each capable of removing quantitatively and qualitatively its own coagglutinins. But even then there would be a minimum of residual agglutinins beyond which no bacterium except the homologous strain, or one of the same group, could exhaust the antiserum.

TECHNIC: The antiserum is diluted 1:10 with salt solution. An equal quantity of an emulsion of the absorbing antigen is added, making a dilution of 1:20. The tube is left two hours in the incubator and overnight in the ice chest after which it is centrifuged one hour. The clear serum is decanted and a preliminary test made with the absorbing strain, to determine whether all of its
agglutinins are removed. If not, the serum is reabsorbed using packed cells of the antigen in order not to alter the dilution of 1:20. The following day the clear serum is tested for agglutinins. By doing three tests, using antigen of Brucella melitensis, Brucella abortus, and Brucella suis, one can determine the type of infection the patient has inasmuch as the specific strain will remove all of the agglutinins and the other two will not.

**COMPLEMENT FIXATION:** This test may also be used to detect the presence of antibodies of the Brucella group. In performing the complement fixation test, complement, amboceptor, sheep erythrocytes and salt solution are prepared and titrated as for the Wassermann test. The antigen is prepared as for the macroscopic agglutination, previously described, except that the organisms are broken. A good procedure for this is the use of liquid air(10).

While this test is accurate the author(10) has used it on 1200 examinations of sera along with the rapid macroscopic agglutination and the two tests check exactly in their results, therefore, the rapid macroscopic agglutination is much preferred. The latter is simple, quickly performed and accurate.

On the opposite page are photographs of the complement fixation test showing both positive and negative results.
The Complement Fixation Test.

A positive reaction.

A negative reaction.

The technic for performing the complement fixation test for the presence of Brucella antibodies has been described elsewhere:

James W. Martin and John T. Myers, Brucella Antibodies in Human Serum, Jour. of Prev. Med. 5:244-245.
BLOOD CULTURES: Blood cultures play an important part in diagnosing undulant fever. If success is attained in isolating the organism, the diagnosis is proven. The usual methods of handling blood cultures will not reveal Brucella organisms, and only when proper procedures are followed will the results be of value. The reliability of this work will be dependent chiefly on the bacteriologist but two things the clinician must keep clearly in mind. Since the organisms are often present in the blood in very small numbers, an adequate volume must be inoculated, at least 10 c.c. Furthermore, since Brucella organisms multiply slowly, it will be overgrown by an extraneous organism, so particular care must be taken to avoid contamination.

The laboratory worker must supply the proper medium and this is a fresh beef liver infusion with a pH of 6.6(24). Prolonged incubation must be practiced. Subcultures from broth should be made for the first time between the fourth and seventh day, and for the last time before being discarded as negative after more than two weeks' incubation. Differences in carbon dioxide requirements must be remembered and duplicate cultures must be made, one being incubated in air and the other in an atmosphere with an increased carbon dioxide tension. This may be obtained by a method such as described by Fitch(25),
Microphotographs of the organisms of the Brucella group.
Magnification——1800.

Brucella melitensis

Brucella abortus

Brucella suis

Note that these organisms are morphologically identical.
or by the addition of an acid to a carbonate held in a small container in a museum jar. Best results are obtained with from 5% to 10% carbon dioxide by volume. On the opposite page is a photograph of the apparatus used by the author in obtaining an atmosphere with carbon dioxide approximately 10% by volume.

**URINE CULTURES:** In a few cases of undulant fever it is possible to isolate the organisms from the urine. The specimen, obtained by catheter, is run directly into a tube of fresh beef liver infusion broth. It is best to use at least 10 c.c. of urine as the organisms are probably few in number. The tube is then incubated in an increased carbon dioxide tension of 10%.

**STOOL CULTURES:** The method used for isolation of Brucella from feces is described by Arnoss and Poston(26). To a dilute suspension of feces from which the coarser particles have been removed, there is added an amount of positive immune serum adequate to produce agglutination. After two hours' incubation the clumps are thrown down by centrifugation. The sediment is washed in saline solution three or more times and inoculation is then made on solid medium. Here, again, Huddleson's beef liver infusion media (agar) is best.

**GUINEA PIG INOCULATION:** The isolation of Brucella is often possible only through animal inoculation, guinea
Diagram of the apparatus used by the author in obtaining an atmosphere with carbon dioxide approximately 10 per cent by volume.

Liver infusion cultures are placed in the museum jar and the carbon dioxide adjusted to 10\% by volume.
pigs being most satisfactory. Whole blood may be given intraperitoneally, white sediment from urine or feces is best injected subcutaneously in the groin. The organism may be isolated from milk by injecting 2.5 cubic centimeters of the naturally separated cream subcutaneously in each groin. An agglutination test may be performed after four weeks on serum separated from blood removed from the test animal by intracardiac puncture. Positive animals are killed between the sixth and eighth weeks. With aseptic precautions, the spleen, liver, and any enlarged lymph glands are removed. If the cut surface of these organs is smeared on solid media, growth of Brucella usually results. If one animal only has been infected or if from the first of two the organism was not isolated, a portion of macerated spleen is injected into two other pigs. In this way positive results are almost invariably obtained.

DERMAL TEST: This test has not been applied generally in the diagnosing of undulant fever but it has been reported(27) that it yields specific skin reactions in known positive and negative cases. On the other hand, Fleischner and Meyer(28) report that in a series of seventy-five infants fed on a high bacillus abortus containing milk, cutaneous hypersensitiveness was not present. They
take this to mean that infants are not susceptible to Brucella abortus. They find in guinea pigs, infection with Brucella abortus always produces cutaneous hypersensitivity.

**TREATMENT**

The present status of our knowledge of the treatment of undulant fever is notably deficient; consequently any method of attack that seems hopeful is worthy of further study. In general, the curative treatment is symptomatic, comparing with the regimen followed in the treatment of typhoid.

A review of the literature shows that antiserums, parasitotrophic chemicals and vaccines and bacterins, either specific or nonspecific, have been used experimentally with varying degrees of success in the treatment of this disease. The results of the use of antiserums have, in general, been disappointing. Chemotherapy has been restricted largely to the intravenous injection of dyes. Of these, mercuriochrome-220 soluble as used by Gregory and Gage(29), Carpenter and Merriam(30) and Belyea(31), and acriflavine hydrochloride as employed by Izar(32) and others(33),(34),(35), have been attended by more or less beneficial results. These methods of treatment are still
in the experimental stage, and the value of such intravenous injections is probably dependent on nonspecific immunity reactions rather than on antiseptic activity as such. Leavell(36) has reported on the administration of the dyes thionine and methyl violet, both orally and by enemas, for persistent infection in the gastrointestinal tract.

VACCINE THERAPY: Vaccine therapy has been attempted with varying results. Castellani(37) was one of the first to employ vaccines made from the caprine strains or from combinations of Brucella melitensis with the typhoid and para typhoids. Khaled(38) secured marked improvement in three cases treated with a vaccine of Brucella abortus organisms. More recent investigations by Cazalas(39) who used a combination treatment of bouillon culture filtrate and melitococcus vaccine, by Angle(40), who, in a series of ten cases, used a mixed vaccine of pathogenic bovine and swine strains, by Budtz-Olsen(41) who employed nonspecific therapy by using typhoid vaccine in ten cases, and by Leavell(36) who used an autogenous vaccine in two of his cases without permanent improvement, have served to revive the interest in the vaccine method of the treatment of this disease.
A group of French investigators have, in recent years, followed a system of vaccine treatment which, in their hands, gave satisfying results. Courtois-Suffit(42) was able to effect a cure in a case of undulant fever of three months' duration by a single injection of a preparation described as an endoprotein extract of Brucella abortus. Cambessedes(43), using a similar product, obtained an immediate termination of the disease in a case of five months' duration. Liege(44), in another case of five months' duration, used an endoprotein extract of Brucella abortus successfully. Cambessedes and Garnier(45) have summarized the work of these authors and additional cases in which either extracts of Brucella abortus organisms or heavy suspensions of bacterial substance, obtained by grinding great numbers of Brucella abortus organisms in sodium chloride, constituted effective vaccines. Schilling(46) described a method of preparing a highly concentrated relatively soluble, autogenous antigen. He used freezing and thawing to break up the bacteria, thus securing a concentrated extract. This antigen, on intramuscular injection, proved to be absorbed rapidly, and, by a single injection of a large dose, complete and permanent subsidence of the infection was obtained in forty-eight hours.
Such a strikingly prompt response to the administration of the antigen warrants an inquiry into the probable mode of its action in the infected organism. It does not appear likely that the antigen conferred an immunity through the production of antibodies; the sudden character of the cure would not permit this explanation. There did occur, in this case of Schilling's, an increase in the agglutination titer from the original of 1:200 to a maximum titer of 1:500, which evidences a stimulation of the production of agglutinins, yet that increase is too slight to be credited with the establishment of the cure. The relative solubility of the highly concentrated antigen in conjunction with a route of introduction permitting its rapid absorption has very probably an influence on the therapeutic effect. The freezing and thawing method used in preparing the antigen resulted in disrupted bacterial bodies without altering the character of the proteins gave a readily absorbable product. By intramuscular introduction, a route of rapid dispersion of the bacterial proteins through the system was afforded. When Schilling injected the antigen into his patient there resulted an intense inflammatory reaction. This naturally would provoke a general response on the part of the defensive
mechanism and the accelerated activity of the defensive forces probably accounts for the overwhelming of the infection.

One wonders whether his treatment would have been so successful in this case had the agglutination titer been as high as 1:1280 instead of 1:200. With the low titer of his patient's serum, one can see how accelerating the defensive mechanism could result in overcoming the infection.

Vastellani and Taylor(47) were also among the first to employ vaccine in the treatment of undulant fever. They used a vaccine prepared from Brucella melitensis alone and also in combination with typhoid and paratyphoid bacilli. DeFinis(48) reported fifty-five recoveries in fifty-five cases, in many instances after one injection. Schneider(49) reported one hundred and seventy-four cases in which 84% were cured by vaccine. The vaccine was given repeatedly and continued for a month after the fever had subsided.

Most of the reports from the use of vaccine are favorable, but those who have reported the most striking results are the ones who have had a marked reaction following the use of the vaccine preparation. In fact, Cambessedes and Garnier(45) believed that it was
necessary to have a very definite reaction to get results. It seems that the size of the dose of bacterial substance injected bears an important relationship to the final result. Vaccines given in small doses and gradually increased, as has generally been the custom, has, in many instances, given no particularly favorable results but when the vaccine was given in larger doses, as reported by Angle and the French investigators, the results were better.

There is some question whether the results are due to ordinary protein shock or are due to a specific action of the vaccine. While the injection of endoprotein may act in part by ordinary protein shock because of the nucleo-protein which it contains, Liege and Casteran(44) thought that the cure was the result of conflict between the sensitized organism and the inoculated antigen, basing this on the fact that larger doses of vaccine given to normal individuals gave no reaction. They believed that there was an element of specific shock in the reaction rather than ordinary foreign protein shock. Biering(50) saw little hope in the use of vaccine because of the high agglutination titre already present in this condition. Teissier, Reilly, and Rivaller(51) state that the reaction from the vaccine is evidently of a specific nature, but is comparable to ordinary protein shock, the specific
effect from the antigen being shown by the increase in agglutinating power.

Vaccine therapy has not been reported as successful by all authors. Reports by Chiriaco (52), Gate and Billa (53), Fiessinger and Blum (54), Coury (55), and Keefer (56) are far from encouraging. This group of writers report that often no effect whatever on the course of the disease could be noted.

Keefer could not see what vaccine therapy would accomplish in a patient who already had antibodies in high concentration in his blood stream and abundant antigen there to produce them. He gave his patient large doses of vaccine repeatedly over a period of several weeks. No improvement could be noted; the course of the disease did not seem to be altered; the organisms in the peripheral blood did not decrease and the agglutinating power of the blood serum was not raised.

Since improved methods of making concentrated antigens have been devised and large doses given, it is the experience of most writers now that vaccine therapy offers the best results and, in most instances, cures are effected.

DuBois and Solliers (57) even use vaccine to immunize against undulant fever in persons who are constantly exposed.
ANTISERUM: Antiserum has been used by O'Neil(58). He gave goats nitrous acid treated vaccine for a period of eight months. The suspensions represented five billion Brucella abortus bacilli per c.c. and inoculations were given on alternate days, the dose being increased up to 2 c.c. Three patients were treated with goat serum. In all cases the serum treatment brought about a drop in temperature to normal.

Scully(59) treated a case of undulant fever with antimelitensis serum(Mulford) with favorable results. This is a polyvalent serum made from immunizing cattle to Brucella melitensis and abortus. As an initial dose he gave 50 c.c. intravenously, without reaction. There was considerably less temperature for three weeks and less aching and sweating. The temperature gradually elevated again and a second injection was given. This was followed by aching the next day and more severe aching on the eighth day following. A month later another injection was given with a marked shock reaction. There was nausea, a feeling of tightness in the chest and marked flushing of the neck. For a period of three months he gave 10 c.c. to 15 c.c. every two weeks, reactions following each injection. The patient reed to normal and remained there. Thus, in his patient it took repeated small doses to produce a cure.
FOREIGN PROTEIN THERAPY: As has been previously discussed, vaccinotherapy may be due, in part at least, to the foreign protein reaction. Palmer (60) has treated five proven cases of undulant fever with intramuscular injections of sterile milk and cures were effected in three cases. He gave an initial injection of 5 c.c., causing a rise in temperature, usually to 104° or 105°. Five days later another injection of 10 c.c. of milk was given, then in another three days another 10 c.c. of milk was given. The last two injections caused a rise in temperature to 103° and 104° which was accompanied by chills and severe headaches. After this the temperature and other symptoms gradually subsided and in three of his five cases there was no recurrence of symptoms.

ACRIFLAVINE: In using this drug in treating undulant fever, acriflavine hydrochloride tablets, 0.1 or 0.3 gram are usually used. The best method of administration is to pulverize the required number of tablets in a mortar, subsequently dissolving the powder in about 20 c.c. of warm physiological saline solution. This is to be prepared immediately prior to use. An ordinary intravenous saline is then started and when it is assured that this is going smoothly and not infiltrating about the vein to the slightest extent, the 20 c.c. of acriflavine is added to about 200 c.c. of warm normal saline and poured
in. This solution is allowed to enter the vein at the rate of about 5 c.c. per minute, the flow being regulated by an adjustable clamp of the rubber tubing of the apparatus. Quick administration invariably gives rise to burning of the eyes and nose, nausea, cough and vomiting and, if any of these symptoms are noted, the administration must be retarded or stopped temporarily. In some cases chills commence during the administration, especially during the first and in such cases it is wise to stop immediately. Great care must be taken not to allow the solution to escape from the vein, as it will always give rise to a painful inflammatory mass and occasionally a slough. Strong solutions of acriflavine have been found to cause painful obliteration of the veins through which it was administered and even the above dilution will occasionally give rise to a local hardening of the vein.

The dosage varies according to size, age, condition of the patient and the number of previous injections. In an ordinary sized adult, who is not excessively debilitated, it has been found satisfactory to start with 0.1 gram, subsequently giving 0.2 gram and two of 0.3 gram. In those who are very ill it seems better to start with even less than 0.1 gram and in children the ordinary dosage
formula should be used. Usually, after four doses, the maximum effect has been manifested and further dosage is of little or no benefit.

The injection of acriflavine has been used by many and although some feel that the results were not striking, others report a subsiding of symptoms after a course of injections. Thrurber(61) reports seven cases of undulant fever treated by intravenous injections of acriflavine hydrochloride. In five cases, the fever was arrested within one month after starting treatment and in two cases the fever continued, but at a lower level. In seven more of his cases, untreated, the duration of the disease was from nine months to two years. He states that the best results were obtained in patients treated during the earlier weeks of the disease.

Izar(32) in Italy and Dane and Laffaille(33) in France reported excellent results obtained by using acriflavine intravenously. Izar reported that intravenous injection of acriflavine(.01 gram per kilogram of body weight) acted favorably on the course of the fever, two or three injections producing a cure. The French authors reported complete cures after using acriflavine. A single injection of .2 gram caused the fever to subside in twenty-four hours. A relapse eighteen hours later was dispelled in twenty-four hours by another injection. They recommend
the first injection of .2 gram. This is followed two days later by a second injection of .3 gram and three days after the second injection, .4 gram is given. Relapses should be treated in the same manner.

Kopelowitz(35) treated his patient with acriflavine, starting with .2 grams in 200 c.c. of .85% saline (making a 1-1000 solution) intravenously. This was given slowly by the gravity method. The patient vomited while the injection was being given. One hour later the patient had a violent chill, lasting about one hour and the fever going to 105.5°. The next day the temperature was back to normal. Two days later he gave .3 gram and the same dose after two more days. There was no severe reaction after the last two injections. The patient was discharged, recovered and had no recurrences.

Hoffman(34) treated three cases of undulant fever with acriflavine and aborted what apparently would have been prolonged sieges.

In conversing with two Omaha physicians, each of whom had treated a case of undulant fever with acriflavine, it was the opinion of both that it was not good treatment and beside causing their patients much discomfort by its administration, it did not relieve their symptoms.

**MERCUROCHROME:** Intravenous mercurrochrome has not been used so extensively in the treatment of undulant fever
as many other drugs. Todd(62) first used it intravenou-
ly and was quite enthusiastic about his results. In his
first two cases he gave 22 c.c. of l% solution of 220
soluble mercurochrome and admits it was with fear and
trembling. His patients immediately started improving,
got completely well and had no recurrences. One patient
had a sharp reaction but felt well enough to be up the
next day and insisted on going back to work. Todd's(63)
other patient was his own daughter. She was given 10c.c.
of l% mercurochrome intravenously, had a severe reaction
following which her symptoms subsided and she was complete-
ly recovered in one month.

Ross and Martin(64) have used mercurochrome intra-
venously and report favorable results.

Gage and Gregory(29) used mercurochrome 220 on their
case after having used acriflavine intravenously without
any effect on the disease. They gave 0.22 gram of mer-
curochrome-220 soluble intravenously. This was followed
by a severe chill, vomiting, bloody diarrhea and a mark-
ed decrease in urinary excretion. He was given Fisher's
solution intravenously with rapid recovery and was
afebrile three days later and had no recurrence of the
disease.

Belyea and Bellingham(31) gave their patient 30 c.c.
of l% mercurochrome-220 soluble, intravenously. Severe
chills, diarrhea, vomiting and elevation of temperature to 106°F. followed in thirty minutes. By the third day the temperature fell to normal for the first time and remained for twenty days. A second rise then began and the fever stood at 100°F. when a second intravenous injection of mercurochrome was given in the same dosage as at first. The following day, the temperature was again normal and one month later there were no signs of recurrence.

Carpenter's two cases were treated with mercurochrome. One recovered after a single injection of 23 c.c. of 1% mercurochrome. The temperature went up to 104.6°F but gradually receded and the patient remained free of symptoms. His other patient was given 30 c.c. of 1% mercurochrome intravenously and 37 c.c. four days later. Both injections were followed by chills and the temperature increased to 103°F but returned to normal within four or five hours. After the first injection, the patient had none of the symptoms of undulant fever. He was under observation for two months and apparently made a complete recovery.

**THIONIN AND METHYL VIOLET:** This has been used by Leavell in intestinal Brucella infection.

Huddleson described the use of methyl violet and thionin as differential bacteriostatic agents in de-
termining the species of unknown strains of Brucella. He found that in vitro the porcine variety was susceptible to methyl violet in dilutions of 1:100,000 and the bovine type to thionin in dilutions of 1:50,000. The toxicity of these dyes was found by animal experiment to be low when given orally. Intravenously, severe convulsions are produced. Leavell(36) administered the dye to patients in the form of pills coated with phenyl salicylate, from 25 to 200 mg. being given in the course of twenty-four hours. At the same time, a retention enema of 300 c.c. of from 1:25,000 to 1:100,000 of the dye was given daily following a soap suds enema. The dyes were given for approximately a week at a time, and, during periods between courses of dye, cultures were made of the stools daily. Slight constipation was the only symptom that could possibly be attributed to the use of the dyes. He reports disappearance of Brucella from the stools after courses of treatment in three patients and states that the method seems a logical means of combating the infection, especially in those cases which have lapsed into a chronic stage with no foci of Brucella infection demonstrable elsewhere than in the intestinal tract.

Lesions have been noted in the intestine in cases of
undulant fever by Hughes(66), Bruce(67) and Bousfield (68) while Griffin(69) has reported roentgen observations suggestive of intestinal ulceration. Treatment by way of the alimentary tract with dyes which more or less specifically inhibit the growth of Brucella seems rational. Audibert and Rouslacroix(70) administered methylene blue (methylthionin chloride - U.S.P.) in two cases with suggestively favorable results and Rayboud(71) reported a case of laboratory infection in which he felt that the same dye shortened the course of the disease.

Methylene blue possesses little bacteriostatic power for Brucella abortus. It is present in 1:10,000 dilution in eosin-methylene blue plates on which Brucella grows easily, hence there seems to be no particular basis for its use therapeutically when the infection is of the abortus type.

METAPHEN: This drug has been used intravenously by Fortney(72) in the treatment of undulant fever. His patient had an agglutination titer of 1:640. Ten c.c. of metaphen 1:1000 was given intravenously, undiluted, without the slightest sign of either local or general reaction. Five days later, he gave 10 c.c. more and the temperature returned to normal and all symptoms subsided. The clinical duration of the disease was ten days and the temperature became normal six days after
the use of metaphen was instituted, although the agglutination titer did not decrease.

Metaphen has been used in other blood stream infections with gratifying results and deserves to be considered further in the treatment of undulant fever.

**BLOOD TRANSFUSIONS:** Quevli and Nelsen(73) have used whole blood transfusions in a series of cases and are much impressed with the results. Their first patient was given transfusions for other purposes and the transfusions apparently caused her to be free of symptoms of undulant fever. Their first patient was a woman with uterine hemorrhages, bleeding from the gums, macular petechiae, leucopemia, ghastly sweats, marked arthralgia and temperature to 105°F. She was definitely a patient who seemed destined to die under the symptomatic and vaccine treatment plan. She was given whole blood transfusions as the logical supportive measure. After two transfusions, there was a remission of fever, her health returned and the symptoms of the disease disappeared.

With such complete success with a most desperate case, they, at once, decided to use whole blood in treating other patients. They treated ten cases and report cures in nine of these. The one case which had
a recurrence only received 350 c.c. of whole blood whereas the others received 500 c.c. or more each transfusion. Their post transfusion dates range from three to seventeen months, at the time they reported cures.

The results they obtained can only be explained on the basis of a passive immunity obtained from the donor. Theoretically, the ideal donor should be a patient who has recovered from this disease but Quebli and Nelsen state that neither the necessity of the issue nor the opportunity to do this presented itself.
UNDLULANT FEVER CASES OBSERVED BY THE AUTHOR

A series of eleven cases of undulant fever observed is here presented, special reference being given to the type of therapy attempted. Of these cases, eight have been treated with autogenous vaccines; one with a stock vaccine; one with acriflavine and one was given only symptomatic treatment.

In all the cases presented, blood studies were made by the author and the vaccines prepared.

To recover the organisms from the patients, blood and urine cultures were made. I have found Huddleson's liver infusion gentian violet media(24) to be much superior to any other for this purpose. Blood or urine placed in this broth was then incubated at 37.5°C under an increased CO2 tension of 10% by volume. The method described by Fitch(25) was found to be satisfactory. It takes from four to ten days for the organism to grow out and sometimes as long as two weeks. In most cases that I have observed, however, the organism was gotten by the sixth day. Transplants from the broth were then made to liver infusion agar and an abundant growth obtained. This was then washed off and suspended in .85% NaCl. This suspension was standardized to a density of 700(21) and this density was found to contain approximately fifty
billion bacteria per 1 c.c. This suspension was then
inactivated at 65° C. for two hours and recultured for
sterility.

It was thought that in as much as this antigen
was a very concentrated one, there would be therapeutic
benefits by its use, the results being attributed to
both the rapid formation of more antibodies and also
the advantage of foreign protein therapy, this foreign
protein having some degree of specificity.

**CASE I. TREATED WITH AUTOGENOUS VACCINE**

Mrs. Emma Horner, white, housekeeper, forty-six
years old, entered the University Hospital on April 19,
1932, for the first time. About a week previously she
had had a "crampy pain in the stomach" which lasted
for a few days and disappeared. During this time there
was also a high fever. She was constipated and her
condition required frequent cathartics. After a few
days the pain disappeared but the fever persisted. On
the day she came to the Hospital she became jaundiced.
She was in the Hospital one month when an agglutination
test for Brucella antibodies was requested. This was
found to be positive in a dilution of 1-200. A blood
culture was made, the organism isolated and an autogenous
vaccine prepared by the author. On June 7, 1932, an
injection of 0.1 c.c. was given subcutaneously and similar dose every three days for three injections. The temperature fell to normal immediately after the first injection of vaccine and did not rise above normal thereafter. Her temperature chart shows the drop immediately after the first injection. She left the hospital ten days after the first injection of vaccine feeling well and free of symptoms.
The Douglas County Hospital

Name: Mrs. Emma Horner

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- Day 2: 107°, 106°, 105°, 104°, 103°, 102°, 101°, 100°, 98°, 98.6°, 98°, 97°, 96°, 96°

Pulse and Resp.
The Douglas County Hospital

Name: Mrs. Emma Horner

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PULSE
RESP.

96°
The Douglas County Hospital

Name: Mrs. Emma Horner

DATE

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HOUR

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Temperature Range

- 107° to 96°

Pulse

RESP.
### The Douglas County Hospital

**Name:** Mrs. Emma Horner

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|------|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|----|---|---|
| Temp | 107° | 106° | 105° | 104° | 103° | 102° | 101° | 100° | 99° | 98.6° | 98° | 97° | 96° |

**PULSE:**

**RESP.:**
The Douglas County Hospital

Name: Mrs. Emma Horner

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Temperature:
- 107° F
- 106° F
- 105° F
- 104° F
- 103° F
- 102° F
- 101° F
- 100° F
- 98° F
- 98.6° F
- 98° F
- 97° F
- 96° F

Pulse and Resp.

Graph showing temperature fluctuations over the specified dates and times.
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Temperature:

- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 99°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.

No specific values are indicated in the diagram.
The Douglas County Hospital

Name: Mrs. Emma Horner

House Physician

Service of

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Temperature:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse:
- 9

Resp.:
- 12
CASE II. TREATED WITH AUTOGENOUS VACCINE

Otto Sorensen, white laborer, twenty-seven years old, entered the University Hospital for the first time September 15, 1931. He felt well until in April when he noticed feeling weak. He had been working on a farm where there had been three or four abortions among the cattle. On the least exertion he felt very weak, was short of breath and perspired profusely at times. He could not sleep well and was always exceedingly tired when he awoke. In August, he started having night sweats, frequent headaches and it was about this time that anorexia developed. These symptoms gradually progressed until his entrance to the Hospital. His temperature chart shows the undulating character of the curve, characteristic of undulant fever.

A blood culture was made, Brucella abortus isolated and an autogenous vaccine prepared. His chart shows amounts administered and dates. His temperature did not go above normal after the first injection, except during the reaction immediately following the injection of the vaccine.
The Douglas County Hospital

Name: Otto Sorensen

House Physician: Service of

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Temperature:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 99°
- 98°
- 97°
- 96°

Pulse and Resp.

Graph showing variations in temperature over the days.
The Douglas County Hospital

Name: Otto Sorensen

House Physician

Service of

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<td>4 8 12 4 8 12</td>
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Temperature:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.
- 60
The Douglas County Hospital

Name: Otto Sorensen

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- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

PULSE

RESP.

a.a.c. of Vaccine given Subcutaneously
The Douglas County Hospital

Name: Otto Sorensen

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Temperature:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse:
- 62
- 60
- 44
- 42
- 40
- 38
- 36
- 34
- 32
- 30
- 28
- 26
- 24

Notes:
- 4 c.c. of Vaccine given Subcutaneously
The Douglas County Hospital

Name: Otto Sorensen

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| Temperature | 107° | 106° | 105° | 104° | 103° | 102° | 101° | 100° | 98° | 98.6° | 98° | 97° | 96° |

| Pulse | Resp. |
The Douglas County Hospital

House Physician: Otto Sorensen

Date: 11-3-31

Day of Illness: 30, 51, 52

Temperature:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.
CASE III. TREATED WITH STOCK VACCINE

Dawson Thompson, white, packing house laborer, twenty-three years old, entered the University Hospital for the first time July 1, 1932, complaining of regular chills and fever, sweating, weakness, and fatigue on slight exertion. He felt perfectly well until three weeks previous to Hospital entrance, when he had a severe chill and fever which lasted for about one hour, coming on about 10:30 P.M. He stated that his teeth chattered and he shook the bed. Since that time he had had an elevated temperature. During the first week he had two attacks of chills, both times occurring at night. One week later he had a severe chill followed by profuse sweating. The following week, he had a chill every night. He went to the University of Nebraska Dispensary and was admitted to the Hospital.

An agglutination test for Brucella antibodies was positive 1-500 and the lymphocytes were 48%. A blood culture was made by the author but success was not obtained in isolating the organism. This was repeated several times but a positive blood culture was never obtained. On July 12, 1932, 50 c.c. of antimeilitensis serum (Mulford's) was given intravenously. The next day 50 c.c. more was given. This treatment had no effect whatever on bettering the patient's general condition.
or in bringing the temperature back to normal. On July 25, 1932, a stock vaccine was prepared by the author and the patient was given 0.2 c.c. subcutaneously on July 27, 1932. He was dismissed to the Dispensary on this date for further vaccinotherapy.

On August 3, 1932, he was given .1 c.c. of the stock vaccine. There was a rather severe reaction and a fever but this disappeared and he remained temperature free after that. He was given nine injections in all. All symptoms disappeared and there has been no recurrence. His temperature chart shows a subsiding of the temperature.
# The Douglas County Hospital

**Name:** Dawson Thompson

**House Physician**

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- **Temperature**
  - 107°
  - 106°
  - 104°
  - 103°
  - 102°
  - 101°
  - 100°
  - 98°
  - 98.6°
  - 98°
  - 97°
  - 96°

- **Pulse**
  - 8

- **Respiration**

- **Notes**
  - 30 cc. of Antimotiens Serum (Muftords)
  - 50 cc. of Antimotiens Serum (Muftords)
  - Intravenous. Intravenous.
The Douglas County Hospital

Name: Dawson Thompson

House Physician: ____________________________

Service of: ____________________________

DATE: 7-15-32

Day of Illness: 15

HOUR: 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12

Temperature: 98° 98.6° 98° 97° 96°

Pulse: ____________________________

Resp: ____________________________
The Douglas County Hospital

Name: Dawson Thompson

House Physician

Service of

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Temperature:

- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.
### Dispensary Record of Temperature

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- **Temperature**
  - 107°
  - 106°
  - 105°
  - 104°
  - 103°
  - 102°
  - 101°
  - 100°
  - 98°
  - 98.6°
  - 98°
  - 97°
  - 96°

- **Pulse**
  - ...

- **Resp.**
  - ...

- **Treatment**
  - 0.10 c.c. Antigenous Vaccine
  - 0.1 c.c. Vaccine
  - 0.1 c.c. Vaccine
  - 0.1 c.c. Vaccine
  - 0.1 c.c. Vaccine
  - 0.1 c.c. Vaccine
The Douglas County Hospital

Name: Dawson Thompson

Sher Service of

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Dispensary Record of Temperature

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<td>J.C.C.</td>
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<td>Vaccine</td>
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<td>98°</td>
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<td>98.6°</td>
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PULSE

RESP.
CASE IV. TREATED WITH AUTOGENOUS VACCINE

Miss F. Hughes, of Plattsmouth, Nebraska, forty-one years old, was teaching in a mountain school in Kentucky. Early in 1928 she developed lassitude, fatigue, tremor of the hands, and a general feeling of malaise. She continued teaching until the close of the spring term and spent the summer seeking relief in various climates. In the fall she was unable to take up her teaching duties. Under treatment in New York in the fall of 1928, a diagnosis of Undulant fever was made. She was given a course of vaccine treatment without results. In the fall of 1929, she came to Nebraska and was given a second course of vaccine therapy (stock vaccine) again with little, if any, results. In the spring of 1930 she placed herself under the care of a physician in Missouri who used first acriflavine intravenous and later an autogenous vaccine. During all this time she suffered from general malaise and a low grade temperature.

She became a patient of Dr. E. L. MacQuiddy in the fall of 1932. An agglutination test was made by the author for Brucella antibodies and was positive 1-1280. A blood culture made at the same time was positive for Brucella melitensis. This was proven by the agglutination absorption test. An autogenous vaccine was made, each c.c.
of the suspension containing approximately twenty-five billion bacteria. A course of injections were given with marked decrease of symptoms and yet she was never completely free from temperature for over a three day period of time. Injections were started at 0.1 c.c. and increased up to .6 and agglutination test made at this time was positive 1-300. No logical explanation is seen for this decrease. She was dismissed and told to return in four months to check the results of treatment. She returned with almost the identical symptoms that she had presented at the first visit. Blood cultures repeated at this time were again positive and agglutination was positive 1-1280. A second vaccine was made and the strength increased to fifty billion bacteria per 1 c.c. The course of treatment given was lengthened and the final dose was 1 c.c. of the vaccine. Following this course, the patient was decidedly improved but, at times, ran a low grade temperature. The agglutination titer had again dropped to 1-320.

About the middle of January, 1934, the patient began to have symptoms, rather mild, referable to the gall bladder. It was the opinion of Dr. MacQuiddy that this might be attributed to an infection of the gall bladder with Brucella melitensis. He also felt that if the gall bladder was infected with this organism that it
might explain the failure to relieve the symptoms to the extent that we felt it should. A duodenal drainage of the gall bladder was done. Without entering the merits or demerits of this procedure, we felt that its use was justified. Asepsis, as far as possible in such a procedure, was attempted. The usual A, B, and C biles were obtained. The bile was allowed to flow into a sterile container which was tall and slender so that the different colored biles could be easily distinguished. A specimen of the dark B bile was then transferred to liver infusion media. After proper incubation, a variety of organisms was found but among these was an organism whose morphology and gram reaction was that of Brucella. A fairly heavy suspension of these organisms was injected into the abdominal cavity of a guinea pig and after eight days blood was drawn from the pig and the serum tested for antibodies of Brucella melitensis by using an antigen prepared from the organism previously isolated from the patient's blood. It was positive 1-2560. Other strains of Brucella (five in number) were used as antigens and were all found to be agglutinated in high dilutions.

From the work done on this case evidence is presented which would lead one to believe that the patient
under consideration is suffering from a Brucella infection of the gall bladder. Further treatment is now being administered to this patient.
CASE V. TREATED WITH AUTOGENOUS VACCINE

Mr. C. W. Peterson, farmer, age thirty-two years, of Warsaw, Nebraska, came to the office of Dr. E. L. MacQuiddy on July 22, 1932. He was suffering from extreme weakness, fatigue on the least exertion, profuse sweating and a high temperature. These symptoms started about June 22, 1932 and had gradually gotten worse. Undulant fever was suspected and an agglutination test of the blood serum was made by the author. It was positive 1-500. A blood culture was made in liver infusion broth and also a catheterized specimen of urine was cultured. In six days' time, a Brucella organism was isolated from the blood. A staphylococci was gotten from the urine and this, together with the Brucella organism, was used in preparing an autogenous vaccine.

He was given a series of injections of the vaccine, starting with .1 c.c. subcutaneously and increasing it up to .6 c.c. These were given twice each week. After the first few injections of the vaccine all symptoms subsided; he felt perfectly well and started gaining weight.

The patient gave a history of having attended an aborting sow previous to the onset of his illness. Agglutinin absorption showed his antibodies to be of the
suis variety. He most probably became inoculated by direct contact with an infected sow.

The patient was dismissed on September 2, 1932 and instructed to return if any symptoms recurred and he promised that he would. We have not heard from him since so believe that he was permanently cured.
CASE VI. TREATED WITH AUTOGENOUS VACCINE

Mr. John Brown, farmer of Oseola, Nebraska, a patient of Dr. Ralph Schroeder, was referred to Dr. E. L. MacQuiddy. An agglutination test was positive for Brucella antibodies and a blood culture was made in liver infusion broth. An organism, proven to be Brucella abortus, was isolated and an autogenous vaccine prepared. He was given a series of injections and all symptoms subsided. His main complaints were weakness and a temperature ranging from 99° to 103°. These had been present for a period of two or three weeks prior to the first visit to Dr. MacQuiddy's office.

In talking to Dr. Schroeder eighteen months after the patient had received the injections of vaccine, there had been no recurrence.
CASE VII. TREATED WITH AUTOGENOUS VACCINE

Mr. Edward Hoeck, a patient of Doctors MacQuiddy and Emmert, of Hooper, Nebraska, farmer, thirty years old, entered the Covenant Hospital on September 1, 1931 complaining of general weakness, profuse sweating, aching bones, fever, chills and backache of one month's duration. During this time he had lost twelve pounds. He stated that on about August 1, 1931 he had a severe chill which lasted all night. He felt better the next morning but he felt weak from that time on. In the afternoons and evenings he would sweat profusely. After any exertion he always had "aching bones." Two weeks before he entered the Hospital anorexia developed. He stated that he drank raw milk nearly every day.

Blood studies were made and the agglutination test for Brucella antibodies was positive 1-320. A blood culture was positive for Brucella abortus and a catheterized urine culture was positive for staphylococcus aureus. These two organisms were made into an autogenous vaccine and subcutaneous injections started at .1 c.c. on September 13, 1931 and a second injection of .15 c.c. was given on September 19, 1931. Nearly immediate relief of symptoms was obtained and, as can be seen by his temperature chart, it returned to normal. He has had no recurrences.
The Douglas County Hospital

Name: Edward Hoeck

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PULSE
RESP.
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- **102°**
- **101°**
- **100°**
- **98°**
- **98.6°**
- **98°**
- **97°**
- **96°**

**PULSE**

**RESP.**

- O.I.C. of autogenous vaccine
The Douglas County Hospital

Name: Edward Hoeck

House Physician | Service of

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- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse:

- 14
- 12
- 11
- 10

Resp.:

- 4
- 4

0.15 c.c. of "Autogenous Vaccine"
CASE VIII. TREATED WITH AUTOGENOUS VACCINE

Mr. H. E. Bock, Omaha, thirty-eight years old, an employee of the Union Pacific Railroad, was a patient of Dr. Lynn T. Hall. About November 1, 1932, he developed general malaise, fever, weakness, chills and profuse sweating. This persisted for three weeks, most of the time of which he was in bed. An agglutination test showed his blood serum to be positive for Brucella antibodies 1-500. Brucella abortus was isolated from the blood and a vaccine prepared. Injections were started at .1 c.c. and increased up to .2 c.c. After the first injection, his temperature returned to normal and did not go above again. In a week's time he was back to work and has had no recurrence of symptoms since.
CASE IX. TREATED WITH AUTOGENOUS VACCINE

Mr. Leonard Miller of Omaha, steam fitter in a packing plant, thirty-nine years old, entered the Douglas County Hospital for the first time on February 19, 1934. He complained of general malaise, loss of weight (thirty pounds), fever, chills and sweats for a period of four weeks. Four weeks previous to entering the Hospital he developed some epigastric distress and noticed a feeling of weakness. He went to bed to rest up and a few hours later he had a severe chill which lasted about forty minutes, followed by profuse sweating. For three weeks he had similar attacks about twice a day. Anorexia developed and he became weaker and weaker. He was slightly constipated and had to take several enemas the week before coming to the Hospital.

An agglutination test was made and found to be positive for Brucella antibodies 1-500. A blood culture was taken and Brucella abortus was readily isolated. This was used to prepare a vaccine so that 1 c.c. contained approximately fifty billion bacteria.

On March 1, 1934, he was given .5 c.c. intramuscularly and experienced no reaction. On March 3rd, he was given 1.0 c.c. and on March 6th, was given 2.0 c.c., each time experiencing no reaction. Since the injections were started he has felt better, has had no chills or sweating, his
appetite has improved and the temperature has gradually decreased. At this date, March 7, 1934, it cannot be determined whether he has been greatly benefited by the vaccine therapy but it is our feeling that he has been.
The Douglas County Hospital

Name: Leonard Miller

House Physician: ____________________

Service of: ________________________

DATE

Day of Illness

HOUR

2-19-37

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Temperature:

- 2-19-37: 102° F
- 2-20-37: 103° F
- 2-21-37: 104° F
- 2-22-37: 105° F
- 2-23-37: 106° F
- 2-24-37: 107° F
- 2-25-37: 108° F

Pulse and RESP.: Not recorded.
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- **Temperature**:
  - 107°
  - 106°
  - 105°
  - 104°
  - 103°
  - 102°
  - 101°
  - 100°
  - 98°
  - 98.6°
  - 97°
  - 96°

- **Pulse and Resp.**

- **Notes**:
  - ½ C.C. Autogenous Vaccine
  - 1.0 C.C. Autogenous Vaccine
The Douglas County Hospital

Name: Leonard Miller

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Temperature:
- 107°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 96°
- 95.6°
- 98°

Pulse:
- 90

Resp.

20 cc. Antigen Vaccine
CASE X. TREATED WITH ACRIFLAVINE

Fred Miller, white, concrete worker, thirty-one years old, entered the University Hospital for the first time June 11, 1930. His complaints, symptoms and findings led to a diagnosis of renal calculi for which he was treated. He also had frontal headaches frequently and an unexplainable deviation in temperature. An agglutination test for Brucella antibodies was performed by the author and found to be positive 1-100. His lymphocyte count was 36%. No attempt was made to isolate the organism from the blood stream as it had been agreed that this patient would be treated with intravenous acriflavine instead of a vaccine.

On June 21, 1930, .1 gram of acriflavine was given intravenously and the patient experienced no reaction. The next day .2 grams was attempted but the patient became dyspnoeic and restless so the injection was stopped. However, the temperature dropped to practically normal and remained so during his stay in the Hospital.
The Douglas County Hospital

Name: Fred Miller

House Physician

Service of

DATE
6-17-30 19 20 21 22 23 24
Day of Illness 7 9 10 11 12 13 14
HOUR 4 5 6 7 8 9 10

Temperature:
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

Pulse

Resp.

Notes:
0.1 gram
Acetaminophen

tried again
but had to
be discontinued
The Douglas County Hospital

Name: Fred Miller

House Physician: Service of:

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Temperature Graph:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.
CASE XI. SYMPTOMATIC TREATMENT

Mr. Paul Herman, white, laborer, fifty years of age, entered the University Hospital for the first time on August 17, 1929. Eight weeks previously he had started having steady headaches and in three weeks there was an onset of chills and fever which persisted and were present upon entrance to the Hospital. During this time he became constipated and nocturia and frequency of urination developed. Physical examination revealed nothing abnormal. The laboratory findings were significant: lymphocytes, 38%, agglutination for Brucella antibodies, 1-640, blood culture for Brucella, positive.

A diagnosis of undulant fever was made and treatment started, mainly that followed in treating typhoid fever. On the ninth hospital day, quinine gr. 5 t.i.d. was started and his temperature did not go above 101.6° after that. He was in the Hospital fifty-three days, gradually improved under symptomatic treatment. His temperature returned to about normal on the thirty-third day and from then until he was dismissed it reached 100° only once. He went home feeling well.

This patient was employed in a South Omaha packing company, working in the hog killing department. He was
interviewed by me two years after being in the Hospital and I also performed another agglutination test. He had no recurrence of symptoms although his agglutination titer two years later was 1-320. His temperature chart shows the characteristic temperature curve of undulant fever.
### The Douglas County Hospital

**Name:** Paul Herman

**House Physician**

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<td>RESP.</td>
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**Temperature Chart:**

- **Chill** indicated at various points on the chart.

**Pulse:**

- Various pulse rates are marked at different hours.

**Respiration:**

- Various respiration rates are marked at different hours.
The Douglas County Hospital

Name: Paul Herman

House Physician:

Service of:

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- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 99°
- 98.6°
- 98°
- 97°
- 96°

Pulse and Resp.

- 8.2
- 10
- Chill

Quinie F.W. Kid.
# The Douglas County Hospital

**Name:** Paul Herman

| Date       | Day of Illness | HOUR
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**PULSE**

**RESP.**
The Douglas County Hospital

Name: Paul Herman

House Physician

Service of

Date

Day of Illness

HOUR

9-7-24

22

4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12

107°

106°

105°

104°

103°

102°

101°

100°

98°

98.6°

98°

97°

96°

PULSE

RESP.
The Douglas County Hospital

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- 97°
- 96°

Pulse and RESP.
The Douglas County Hospital

Name: Paul Herman

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<td>4</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>12</td>
</tr>
</tbody>
</table>

Temperature (°F):
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 99°
- 98°
- 97°
- 96°

Pulse:

Resp:
# The Douglas County Hospital

**Name:** Paul Herman

<table>
<thead>
<tr>
<th>Date</th>
<th>Day of Illness</th>
<th>Hour</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-23-29</td>
<td>43</td>
<td>4</td>
<td>107.0</td>
</tr>
<tr>
<td>6-24</td>
<td>44</td>
<td>8</td>
<td>106.0</td>
</tr>
<tr>
<td>6-25</td>
<td>45</td>
<td>12</td>
<td>105.0</td>
</tr>
<tr>
<td>6-26</td>
<td>46</td>
<td>4</td>
<td>104.0</td>
</tr>
<tr>
<td>6-27</td>
<td>47</td>
<td>8</td>
<td>103.0</td>
</tr>
<tr>
<td>6-28</td>
<td>48</td>
<td>12</td>
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</tr>
<tr>
<td>6-29</td>
<td>49</td>
<td>4</td>
<td>101.0</td>
</tr>
</tbody>
</table>

**Pulse**

- **RESP.**
The Douglas County Hospital

Name: [Name of Patient]  
House Physician: [House Physician Name]  
Service of: [Service]

<table>
<thead>
<tr>
<th>DATE</th>
<th>10-5-29</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<tbody>
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<td>50</td>
<td>51</td>
<td>52</td>
<td>53</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HOUR</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Temperature Chart:
- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 98°
- 96°

Pulse and Resp. Values:
- Pulse
- Resp.

Graph showing temperature changes over time.
SUMMARY AND CONCLUSIONS

1. Diagnosis of undulant fever has been discussed considering symptoms, physical findings, history and laboratory procedures.

2. A review of the literature on treatment has been made with discussion of the use of vaccines, antiserum, foreign protein, acriflavine, mercurochrome, thionin, methyl violet, metaphen, and blood transfusions.

3. A series of eleven cases of undulant fever is presented.

4. Eight cases were decidedly benefited by the use of autogenous vaccine.

5. One case was treated with antimelitensis serum and was not benefited. With stock vaccine therapy, the temperature returned to normal and all other symptoms subsided.

6. One case was benefited by the use of acriflavine intravenously.

7. One patient was given only symptomatic treatment. He was in the Hospital fifty-three days and still had a low grade temperature. This disappeared within a month after leaving the Hospital.
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