A resume of undulant fever

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A RESUME

-OF-

UNDULANT FEVER

-BY-

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COLLEGE OF MEDICINE
Recognition of the disease, undulant fever, presents a gross problem to the average general practitioner. Literature is overloaded with articles dealing with the symptomatology and diagnosis of the disease so that it is constantly kept in the eye of the medical profession, consequently recognition of the disease when seen should not be mistaken. Unfortunately, however, such is not the case for there are areas in this country where no diagnoses of undulant fever have been reported, and in sections adjoining these the incidence of the disease has reached appalling heights. The most plausible explanation for this existing condition is that once a case is recognized, other similar maladies are suspicioned and by laboratory aid the diagnosis is made. Therefore, when symptoms are presented which are not typical of any disease entity, the possibility of undulant fever should be kept in mind.

The purpose of this paper is, therefore, that it may serve as a general reminder of the frequency of the disease and also as a review of the current literature on the subject. Six case reports are also included which emphasize some of the more common symptoms and various methods of treatment of the disease.

HISTORY

A few words relating a bit of the history of undulant fever should be of considerable interest. Hippocrates himself records observations that lead us to believe the disease existed in his day. He described cases of protracted fever lasting many months, some exhibiting recurrent rhythmical pyrexial waves. Then in 1859, Marston, working on the island of Malta gave a full and minute
description of the disease. Later, in 1879, Veale working on soldiers
and sailors invalided from Malta to England, confirmed the reports of
Marston.

The greatest work done on the disease, and the discovery of the
causative organism was brought to light by David Bruce in 1887. Were
it not for a fistic combat between Bruce and one of his superior offi-
cers in the English army he might not have had the good fortune of
making his discovery. Bruce was court-martialled and sent to the is-
land of Malta. While there he became very much interested in the
disease so prevalent on the island at the time, and from the spleens
of six men dying of the fever he cultured the organism and called it
micrococcus melitensis (29). He further proved that the disease was
acquired by contact with goats and by drinking the milk of infected
goats.

Somewhat later, about 1904 the work of Bruce was confirmed when
a ship load of goats was transported from Malta to America (34). All
of the crew aboard the steamer "Joshua Nicholson" developed the dis-
ease with the exception of the cook, who had wisely boiled all of the
goats' milk before he drank it. Upon landing the goats in America
cases of Malta fever immediately sprang up. Whether or not this was
the first incidence of the disease in the United States is doubtful
for case reports of similar conditions were recorded during the Civil
War.

In connection with the discovery made by Bruce, a similar organ-
ism was found to be the cause of infectious abortion in cattle, the
organism was isolated by Bang of Denmark in 1897. He called the bac-
terium, bacillus abortus. Not until 1918 was the close relationship
between the two organisms discovered when Alice Evans found that they were morphologically and culturally identical and could be distinguished from each other only by absorption agglutination reactions (28). In 1914, Gram in America discovered a similar organism in swine. In 1920, Meyer and Shaw proposed the term Brucella for the group of organisms which cause undulant fever. Thus the terminology which is accepted today classifies the organisms as the Brucella melitensis group, the bovine strain is the Brucella melitensis, variety abortus; the caprine strain is the Brucella melitensis, variety melitensis; and the porcine strain is called the Brucella melitensis, variety suis. In 1924, Keefer established the fact that humans are infected by the abortus variety.

As the disease is of universal occurrence so we find nearly as many names for the disease as there are countries in which it is found. Some of the more common names applied are Malta fever, Mediterranean fever, Gibraltar or rock fever, Neopolitan or Cyprus fever, Mediterranean phthisis, Country fever of Constantinople, New fever of Crete, adeno-typhoid, intermittent typhoid, and gastric or bilious remittent fever. From these names we can infer not only the locational distribution of the disease but also its multiplicity of characteristics. In 1897, M. L. Hughes of British Army Medical Staff proposed the name "Undulant Fever" and the suggestion was adopted by the International Congress of Medicine held in London in 1913.

ETIOLOGY

Knowing that there are several strains of organisms included in the Brucella group, which are pathogenic to man? Hasseltine (10) answers the question by stating that all types infect the human.
It seems to be a general consensus of opinion that all strains had as their origin one common type, but upon passage through various hosts have adopted individual peculiarities. Thus, Huddleston states that Malta fever is a disease caused by Brucella melitensis which has passed through goats; Brucella abortus infection is caused by the same organism which has passed through cattle or perhaps swine. Theobald Smith (23) goes a step further when he states that the bovine organism is relatively harmless for man and that most human cases are due to porcine infection. Also, Blumer (54) adds that all infections reported in which it was possible to get a culture, proved to be caused by the porcine variety. But this doesn't rule out cows' milk as a source of infection because cows like men can be infected by the porcine organism. It is noteworthy that the largest number of reported cases have come from the state of Iowa which is notoriously a hog raising state. It is Hasseltine's (10) opinion that the porcine variety is able to infect nearly all species of domestic animals. He also contends that symptoms of an abortus infection are milder than those of a porcine or melitensis infection.

The Brucella group of organisms present identical morphological characteristics. The bacteria are pleomorphic, non-motile, short, slender rods measuring about .5 micron in width and two microns in length. The bacteria may have rounded ends, be oval in shape, or even coccoid. Evans states the opinion that in fresh material isolated from infected organs the bacteria are in the coccus form but under artificial cultivation a bacillary form is obtained (28). The bacteria are not encapsulated and no spores are formed, they stain by the ordinary dyes but do not take a Gram stain.
A culture of one of the Brucella group is often difficult to obtain on artificial media but having once started its growth it is relatively easy to obtain growths when transferred to other media. On agar plates, at 37°C, after two days growth small dew drop colonies are formed. After ten to twelve days a colony usually measures about six m. m. By use of an agar shake the greatest growth appears on the surface. While in broth a slight clouding is seen on the first day and after several days a sediment begins to precipitate. Using litmus milk a slight alkaline reaction is obtained after several days. The Brucella organisms produce no fermentation of sugars.

Huddleston (25) found that a better and quicker growth of Brucella abortus could be obtained in a medium of 10% carbon dioxide tension. This could be obtained by sealing off the culture tubes, by introducing carbon dioxide, or by contaminating the culture with bacillus subtilis which uses up the oxygen and furnishes carbon dioxide. He states that in addition to increased carbon dioxide tension the medium must contain some sulphur containing amino acids. He uses infusion agar beef liver medium with a hydrogen ion concentration of 6.6. This he mixes with a saturated aqueous solution of gentian violet in sufficient quantity to dilute dye solution one to ten thousand. This he claims inhibits growth of Gram positive organisms only and also gives a characteristic color to the colonies.

Culturally there is nothing characteristic of the various varieties of the Brucella group to distinguish one from the other. Evans (28) made a thorough study of the problem and found one variation between the melitensis group and the abortus group when grown on agar and potatoes. A colony of melitensis after a growth of one week was found
to be browner in color than a colony of abortus under similar conditions. She, however, did not consider this a constant or a positive means of differentiation. Huddleston, on the other hand, differentiates the two strains by use of a gentian violet medium. He states that Brucella abortus is inhibited by a dilution of the dye of one to fifty thousand while the melitensis strain is not inhibited. Others (43) have not found Huddleston’s method successful in their hands. As one analyzes the literature one becomes impressed with the essential unity of the two organisms.

Evans in her report states that the only test which has been found to distinguish the melitensis strain from the abortus strain is the agglutination of Brucella melitensis suspensions in higher dilutions of melitensis serum than will agglutinate suspensions of Brucella abortus. By agglutinin absorption the melitensis variety can be separated from the abortus variety, but bovine cannot be distinguished from porcine.

Serologically the organisms have been classified into seven groups. Wainwright (34) in his review of the subject states that Evans working with forty-nine strains of organisms from human, bovine, caprine, porcine, and eqine sources was able to separate them by agglutinin absorption tests into serological groups. Group I was designated as variety Abortus contains chiefly bovine and porcine strains and two human strains. Groups II and III are closely related, the former contains one bovine strain and the later two human strains. Group IV designates variety Melitensis A containing eleven strains of human, bovine, eqine, and caprine origin. Groups V, VI, and VII designate variety Melitensis B and are predominantly coccoid.

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Having considered the causative organisms in some detail, their portal of entrance into the human body bears discussion. Infection is possible through the digestive, genital, or respiratory systems or through abrasions of the skin and conjunctiva. The mode and location of entrance depends not only on the strain of the organism but also on the occupation of the individual.

The melitensis variety invades man chiefly through the gastrointestinal tract. In 1904 there were four hundred and thirty cases of undulant fever in the British navy while in 1907 following discontinuance of the use of goats' milk by the sailors the number of infections was only twelve. From the work done in Malta it was estimated that 70% of the infections were due to ingestion of milk and the remaining 30% were probably infected through the skin. Infection through the skin may result from handling infected goats or from contaminated soil or dust.

Statistics as to mode of infection by the porcine and bovine varieties are less convincing. Hardy (24) in experiments using four series of guinea pigs found that rubbing either bovine or porcine organisms into the abraded skin of the pigs 100% became infected with each variety. But by applying organisms to shaved skin 95% were infected with porcine, while only 82% were infected with bovine variety. When the hair was only clipped off 81% were infected with porcine and 73% using bovine. The incidence of infection was reversed when the organisms were ingested by the animals, 17% infected by porcine and 33% by bovine organisms. He also states that the proportion infected varies with the size of the dose used.

Jordan (2) believes that infection with Brucella melitensis and
disease due to contact are in direct proportion to exposure. In a series of one hundred seventy-six persons agglutination tests were run and of the reactors 80% gave no history of contact with live stock, therefore, the agglutinins must have come from infection from raw dairy products. He also ran agglutination tests on a group of one hundred and twenty veterinarians, 40% showed a partial or complete agglutination in dilutions of one to five to one to twenty, 5% agglutinated in dilution of one to forty. Of the group 21% stated that after delivering fetal membranes from infected cows they had observed an urticarial rash on their arms. He concluded, however, that veterinarians are remarkably free from symptoms of the disease. Another (16) records results on a series of forty-nine veterinarians of Michigan, 57% agglutinated.

Evans (21) speaks of one occasion where sixteen people fell ill at about the same time, ten days after a cow had aborted. Another group of five men all fell ill about the same time after assisting in caring for a cow that had aborted. Bierring (18) thinks that contact is the most common cause of the disease because it is relatively infrequent in children who are the greatest users of milk.

On the other hand the possibility of infection by ingestion of infected milk is very great when we consider that in different sections of this country from 10% to more than 90% of a herd of cattle are infected (39). Wallace (61) in a report speaks of one herd of fifty-eight cattle in which thirty-nine were infected. Bottled milk of these cows gave an agglutination reaction in a dilution of one to fifty. Fully 90% of the herds in Connecticut are infected and likewise 85% of herds in Pennsylvania. Also in proof that many infections
arise from drinking infected milk, it is found that the number of infections decrease as the pasteurization of dairy products increase. In Iowa, for example, the frequency of the disease in urban communities where nearly all of the milk is pasteurized is about four infections per hundred thousand people, but in towns of less than five thousand the incidence goes up to 8.3, and in rural districts up as high as 11.4. Thus in communities of less than five thousand people where pasteurization is quite infrequent the incidence of the disease goes up. Another writer (4) states that 70% of the infections occur in rural districts and small towns.

Yet since there are so many infected cows how is the incidence of infection kept as low as it is? Huddleston (37) says it is rare to find Brucella abortus present in milk from udders of all of the infected cows of a herd. When the organism is found the number is rarely greater than five hundred per c. c. Smith (23) also attempts to answer the question by saying that the bovine type is so slightly invasive for man that it fails to produce appreciable disturbances, but that as a by effect it may immunize towards the more virulent types of swine and caprine origin.

The age incidence of the disease presents some very interesting problems. The great preponderance of cases reported have been in individuals in the second, third, or fourth decade of life. The greatest number being between the age of twenty and thirty-nine, 70% are said to occur within those limits. Of a series of thirty-five cases in Ohio, ten were in people between age of thirty and thirty-nine, seven in third decade, seven in fifth decade and seven in sixth decade (40).
It seems strange that infection of a child should be such a rarity when they of all persons are subjected to the organism the greatest number of times, they whose basic food is milk. Hardy (63) in summarizing all cases of undulant fever reported in United States up to June, 1929, found very few instances in children under ten years of age. Under one year only one case was reported, three cases occurring between age of one and two years, four between two and four years, four between four and six years, two between six and eight years, and one between the eighth and tenth year.

Probably the youngest case reported was that one by Hill and Monger (45) of a girl seven months of age. It is of interest to note that the mother gave a history of having a number of previous abortions. Her Wasserman reaction was negative. The child portrayed the classical symptoms and its blood serum agglutinated the organisms at a dilution of one to six hundred and forty. Kohlbrny (4) reported a case in a child of fifteen months who had clinical and laboratory evidence of the disease. Work done by Guest, (39) in testing the serum of two hundred and fifty children found only one which gave a positive agglutination. In 1913, Larson and Sedgewick studied the complement fixation reaction of the blood of four hundred and twenty-five children and found 17% positive for Brucella abortus. Broadbent (59) reports a case of a three year old boy who presented symptoms of tuberculous meningitis which was later diagnosed undulant fever.

From the few cases reported in children one wonders why the incidence is so low. To explain this one might make an analogy between children and calves. All calves, regardless of reaction of dams are born non reactors. When they are permitted to suck positive dams
within twenty-four hours of life they become reactors in a remarkably short period of time, but again become negative almost invari-
ably before the end of the sixth month of age. It is only after sexual maturity that definite infection is established.

Sex has little or no influence on the possibility of infection, males being infected somewhat oftener than females. The slightly greater incidence of the disease in males is explained by the fact that they are exposed to the organisms much more. To that extent also is the disease of occupational importance; veterinarians, meat packers, butchers, farmers and laboratory workers being especially prone to contract the disease. Most cases of the fever develop during the summer, the majority in July. There seems to be an increase in incidence from January to September but the number decreases from September to December.

In a study of the epidemiology of the disease one is confronted with several problems; first, what should be the basis of a positive diagnosis; secondly, what is the incidence of positive agglutination in relation to the incidence of the disease; and thirdly, what is the possibility of disagreement between different laboratories, should they be asked to test the same sera.

To answer the first question, the basis of a positive diagnosis should be clinical findings of the disease, an agglutination titre of one to eighty or higher dilutions, or a positive blood culture. Often a diagnosis of undulant fever is made by only the finding of agglutinins in the blood serum, to make such a diagnosis is incorrect as is shown by various workers. Jordan (2) in testing the sera of a group of packing house workers found thirty which showed a diagnostic
agglutination but only fourteen of that number gave a history suggestive of the disease. Hardy (24) also running a series of packing house workers found that only one third of those showing agglutination gave a history or suggestible history of the disease. Out of a series of one thousand patients and staff physicians at a sanitarium, King and Caldwell (33) found that nine per cent showed agglutination in dilutions of one to fifteen or less, which in itself is not diagnostic. In examination of one hundred thousand eight hundred and seventy-nine specimens at central laboratory in Albany, New York seven hundred and five gave reactions with Brucella abortus antigen in a one to eighty or higher dilution (46). Of one thousand four hundred sera tested by Litterer (51) sixteen cases were diagnosed but forty gave a high agglutination but no suggestible history. Martin and Meyers (52) tested one hundred control cases who presented no symptoms but a positive agglutination was obtained in three per cent. Kling (57) reports a higher percentage of agglutinations without symptoms, one hundred forty-five were positive out of three hundred samples tested. McKay and McNabb (58) in testing eight hundred fifty-six sera found seventeen or 1.9% positive, but in only two of that number was a positive blood culture found. Magath (62) estimates that four per cent of persons in rural districts have positive agglutination for this organism. Thus, we find that the relationship of incidence of actual disease to incidence of positively reacting sera is relatively small.

And in answer to the last question, the possibility of error on the part of the laboratory in making a positive diagnosis is questionable, but we must admit that it is very possible and in some instances probable. In comparing agglutination reaction of one hundred
sera of persons free from symptoms at the South Carolina Public Health Laboratory and the same one hundred sera at the United States Hygienic Laboratory only in one specimen of blood was there the slightest agreement in findings. The former reported thirty-six positives while the latter reported only five positives (9). Therefore, the reliability of the agglutination test as a criterion for clinical diagnosis of the disease is doubtful.

In view of the fact that so many times the agglutination titre is not high enough to make a diagnosis of the disease, that is, it is less that one to eighty dilution, the significance of the positive reaction is questionable. The reaction may mean that the person has had the disease in the past and that antibodies remain in the circulation. Carpenter (42) followed three patients for over two years and they still showed comparatively high titres. Or the low titre may indicate that the individual is a carrier of the disease and has a focus of the infection somewhere in his body. It has also been suggested that low titres are significant of the fact that there has been absorption of agglutinins from ingested milk. It must be remembered, however, that absorbed agglutinins are excreted rapidly. Lastly, it is possible in some very severe cases of the disease to have a maximum titre of one to fifteen to one to thirty.

Wherever there are any domestic animals it is possible to find undulant fever among the human family. Though it has been relatively recent that the first cases were reported in the United States there are at present no states in the union that have not reported cases. In a survey made by Wallace (61) the rapid increase in the number of
cases in the United States is noted:

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922</td>
<td>1.</td>
</tr>
<tr>
<td>1923</td>
<td>0.</td>
</tr>
<tr>
<td>1924</td>
<td>2.</td>
</tr>
<tr>
<td>1925</td>
<td>8.</td>
</tr>
<tr>
<td>1926</td>
<td>42.</td>
</tr>
<tr>
<td>1927</td>
<td>206.</td>
</tr>
<tr>
<td>1928</td>
<td>649.</td>
</tr>
<tr>
<td>1929</td>
<td>1,301.</td>
</tr>
<tr>
<td>First half of 1930</td>
<td>559 (10).</td>
</tr>
</tbody>
</table>

Kavanaugh (50) surveyed the states during years of 1927 and 1928, he reported:

<table>
<thead>
<tr>
<th>State</th>
<th>Number of Cases in 1927</th>
<th>In 1928</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>5</td>
<td>1.</td>
</tr>
<tr>
<td>California</td>
<td>14</td>
<td>2.</td>
</tr>
<tr>
<td>Washington, D.C.</td>
<td>2</td>
<td>0.</td>
</tr>
<tr>
<td>Georgia</td>
<td>0</td>
<td>2.</td>
</tr>
<tr>
<td>Illinois</td>
<td>5</td>
<td>0.</td>
</tr>
<tr>
<td>Indiana</td>
<td>1</td>
<td>0.</td>
</tr>
<tr>
<td>Iowa</td>
<td>14</td>
<td>4.</td>
</tr>
<tr>
<td>Kansas</td>
<td>3</td>
<td>5.</td>
</tr>
<tr>
<td>Maine</td>
<td>0</td>
<td>1.</td>
</tr>
<tr>
<td>Maryland</td>
<td>2</td>
<td>2.</td>
</tr>
<tr>
<td>Michigan</td>
<td>26</td>
<td>0.</td>
</tr>
<tr>
<td>Minnesota</td>
<td>8</td>
<td>6.</td>
</tr>
<tr>
<td>New Jersey</td>
<td>2</td>
<td>0.</td>
</tr>
<tr>
<td>State</td>
<td>1928</td>
<td>1929</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>New Mexico</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>New York</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Ohio</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>South Carolina</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>South Dakota</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Tennessee</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Virginia</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

States not mentioned made no report of a case.

Then in 1929 the prevalence had increased to such an extent that over twenty cases were reported in each of the states of Arizona, California, Georgia, Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, New York, Ohio, Pennsylvania, and Texas (54). In the state of Nebraska eight cases were reported in 1929, and eight in 1930, but only three in 1931 (64). The first epidemic in the United States (38) was in the summer of 1922 at Phoenix, Arizona, where thirty-seven cases were diagnosed.

In a study of the foreign incidence of the disease, we find it very wide spread. The first case was reported in 1928 in Canada (58). Lisbonne (56) in a survey of France states that during years of 1920 to 1925 there were sixteen hundred definitely proved cases of Malta fever in Midi, he estimates that there must have been about five thousand cases in that period in the regions where the disease had become endemic. Cruickshank and Barbour (60) state that there have been less than thirty cases in England since 1925. In Denmark at one period five hundred cases were reported within thirteen months.
The first diagnosis of the disease in Africa was made in 1921, by March, 1925 there were thirty-five cases reported, (21). Kling (57) writes that during the period of time from December 29, 1927 to August 4, 1928 there were seventy-three cases reported in Sweden.

**PATHOLOGY**

Our knowledge of the pathology of the disease in man is quite incomplete, the reason being that the mortality of the disease is so low, consequently postmortem examinations are rare. No doubt the description given by Bruce (31) is most complete, he describes a swelling and proliferation of Peyer's patches and of the mucosa and sub-mucosa of the small intestine. The mesenteric lymph nodes are slightly enlarged due to cellular hyperplasia. The average weight of the spleen is eighteen ounces, the Malpighian bodies are enlarged, the endothelial plates of marginal sinuses are proliferated and swollen, there is an enormous amount of congestion present. The liver is congested, there is cloudy swelling of the parenchyma and small round cell infiltration into interlobular fissures. The kidneys are congested and are in a condition similar to the picture found in glomerular nephritis.

Lake and Ayers (5) mention the occurrence of a basal congestion and bronchitis of both lungs, orchitis, and often a throat discharge. The tonsils are often infected and at times harbor the organisms for a considerable time, (30). Scott and Saphir (32) collected from the literature five cases of endocarditis associated with undulant fever. Ovarian cysts containing the Brucella organisms are found at times. Hughes describes as most characteristic a broken down appearance of the spleen in acute cases in which the
organ has appearance of a large clot of blood. Gaarde and others have commented on the frequency of nephritis in patients with undulant fever.

A study of the pathology that occurs in animals effected by the disease might prove of value as a comparison to the findings in man. In the cow there is present in the pregnant uterus an acute, sub-acute, or chronic inflammation involving the chorio, placenta and endometrium. With the infection of the chorion and cotyledons there is a gradual blocking of vascular villi. Thus the fetus suffers from an impaired circulation and as a result abortion occurs. The fetus shows extensive sub-cutaneous edema with serous effusions into the body cavities. The ducts of the udder are infected via the blood stream, there the organisms multiply and are discharged in the milk. No mastitis occurs.

Bovine infection can occur anytime during pregnancy but the usual time is in the fourth or fifth month. Susceptible animals may abort once, a few twice, and a small number a third time. This disease acts in the cow similarly to syphilis in a woman, in that, as the infection grows older the probability of abortion decreases and the incidence of a live offspring increases. The calf if born alive is weak and its resistance is low so that a fatal pneumonia frequently follows. After abortion the infecting agent is present in the uterine discharges for several weeks. The infection may last throughout the life of the animal.

Much in contrast to the typical pathological findings in the cow nothing is characteristic of an infection in goats or hogs. Probably the most constant finding in an infected goat is the abundance of organisms in the milk and urine.
Smith (23) carried out extensive experiments using the guinea pig as a host for the bovine organism. Redness occurred at the local site of injection of the bacteria, the regional lymph nodes enlarged, but none suppurred. At post mortem the spleens were found to be markedly congested and one and one-half to three times their normal size, some with and others showing no minute gray foci. Infiltration followed by suppuration occurred in the epididymus of one or both testicles. Swelling of the carpal joints were rare. The bacteria slowly multiplied up to the fourth week and then began to decline. No invasion or multiplication was seen within epithelial cells. Lesions wherever found showed a diffuse multiplication of local reticulo-endothelial cells, or infiltration of mobile cells, or both. In the lymph nodes there is replacement of normal lymphocytes by a larger monocytic type of cell. This process also goes on in the spleen and interstitial tissue of the epididymus. In the liver minute depressions are found which indicate a prompt arrest of a process due to emboli from an enlarged spleen. The enlarged spleen is due often to circulatory interference through formation of epitheliod foci.

When the porcine organism was injected, the strain was more virulent than the bovine type and the organs showed greater involvement with the formation of larger foci. Especially in the liver and lymph nodes were the foci larger.

SYMPTOMATOLOGY

There is probably no other infectious disease that presents such a wide variety of symptoms as undulant fever, it has been
called the "Mimic" disease for it may imitate nearly any other illness. This explains the relative infrequency of its diagnosis.

Four main types of the disease are described:

The intermittent type which has an insidious onset and a mild course. The temperature rarely goes over 100° or 101° F. The symptoms are vague, usually with headache, insomnia, anorexia, epigastric tenderness, muscle and joint pains, and sweats.

The undulant type which is more common, and is most typical of what the name undulant fever implies. It is characterized by exacerbations of temperature at regular intervals, but it may be distinctly intermittent with remissions and relapses. There is also headache, anorexia, insomnia, pain in the back, and limbs, epigastric tenderness, and obstinate constipation. In this type sweats occur with greatest frequency.

The malignant type is characterized by a sudden onset, a stormy course and is rapidly fatal. Fortunately this type of the disease is uncommon for it accounts for most of the mortality. The temperature often goes up to 106° F. with development of a typhoid state, followed by coma, heart failure and death.

The fourth or ambulatory type of the disease often goes unrecognized for there are few if any symptoms, frequently the fever is so slight as to be unaccompanied by any discomfort. Not only have the organisms been recovered from the urine of these patients but the disease has also been artificially produced in monkeys and goats. These individuals may possibly serve as carriers of the disease.

So much for a general consideration of the symptoms; the
incubation period may vary from two days to three weeks. Reports of accidental infections in laboratory workers have stated the onset of symptoms occurred within six to twelve days. Eyre states that agglutinins frequently appear in the blood of a Malta fever patient by the fifth day and sometimes earlier.

The onset of the symptoms may be very sudden with chills, rigor, sweats, fever undulating in character, joint and muscle pains, and loss of weight. More commonly, however, the onset is insidious, the individual feels tired during the afternoon, has sweats, and runs a fever at those times. The most striking thing is the lack of discomfort which some patients exhibit. They appear to be able to attend to their ordinary work during the earlier weeks of the disease when they are carrying a fever which would ordinarily interfere with such duties. The patient usually feels quite fresh in the morning but very fatigued in the later part of the afternoon and finally they become so tired that they can hardly get around. Then a headache develops which is followed by backache, loss of appetite, and after a few days, possibly a few weeks, muscle weakness and joint pains are characteristic.

As the disease progresses all symptoms are increased in intensity and many other symptoms are manifest. The fever, as has been mentioned, is often of the undulatory type and usually runs a chronic course. In a typical temperature curve, the fever rises in step-like gradations for a period of seven to fourteen days. Each day the temperature reaches a higher point and exhibiting a morning remission to, or near, normal. The fever having reached a daily peak of $103^\circ$ to $104^\circ$ F., with a morning remission of $2^\circ$ or $3^\circ$ begins to exhibit the undulatory phenomenon. The daily peak and low point in
remission each day occur at a higher point than the preceding day, until the crest of a 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 reviewed over a period of weeks exhibits a series of undulations, each requiring the same number of days for completion. The period of an undulation may vary from four to eight days. The length of the entire series may vary from four weeks to several months. At present the tendency is from the undulating type of curve to a constant septic fever with moderate daily remissions. The entire period of fever lasting from two weeks to ten months.

Chills are as variable as the fever and are equally as constant. They may vary from a mild chilliness to a violent rigor and are usually followed by a rise in temperature.

Sweats are very characteristic of the disease, they are often drenching and usually come on in the morning hours of the night. A characteristic offensive odor is at times perceptible.

Headaches are common, usually occipital pain which extends down the neck and over the shoulders. There is a tendency to periodicity, varying with the fever; it occurs at about the same time every day.

Backache occurs usually in the lumbar region, sometimes in the upper dorsal region.

Arthralgia appears early but is usually lessened with the appearance of acute septic symptoms. Occurrence is usually over the smaller joints, possibly it may be due to periarticular neuritis.

Development of arthritis may be early or late or it may be a dominant symptom throughout the course of the illness. There may
be a definite periodicity of reoccurrence. The joints become swollen and tender, there is seldom any redness. Suppuration is rare but it is often possible to recover organisms by aspiration. Usually the hips, knees, shoulders, ankles, wrists, and fingers are affected.

Likewise neuritis may occur at any stage of the disease, and at times may be the only symptom. Most often the pain is about the joints and in the back. There may be cutaneous hyperesthesia. Often "eye ache" is complained of in the absence of visual disorders.

Nervous manifestations are asthenia, depression, irritability, anxiety neuroses, exaggerated reflexes, tremor, and insomnia. Psychic and functional nervous disorders are a most common sequelae.

Gastro-intestinal symptoms present are anorexia, epigastric distress, constipation, sometimes diarrhea, nausea, and vomiting. Cholecystitis is simulated and may be suspected.

Orchitis, oophoritis, and epididymitis may occur. If present they occur during the febrile stage and are accompanied by tenderness and swelling.

Huddleston (16) describes a cutaneous erruption that often occurs on the arms of a veterinarian following insertion into the infected vagina of a cow. Out a series of fifty veterinarians 20% gave a positive history of such an erruption. It usually occurs on the lateral surface of the forearm in about twenty minutes after contact. Two types are recognized:

Light red irregular blotches occur on the skin, or the entire surface of the forearm may become red. Observed closely they are minute macules; from a distance it has appearance of an erythema. It is intensely itching and burning. The lesion disappears in four
to eight hours.

The second variety is characterized by the appearance of small discrete red papules more widely separated. Itching and burning is severe. This eruption may persist for three or four days, their color changing to a dark brown.

This condition is called "erythema brucellum" and is considered more or less of an allergic reaction.

Other less common symptoms are jaundice and tenderness over liver area, epistaxis, tinnitus, cough with scanty expectoration, sore and bleeding gums, and palpitation. Belyea (22) describes a case in a woman in which the menstrual flow was of a black mucinous character. The cervix was soft and blue as seen in pregnancy.

By and Orsdall (8) in a study of a number of cases determined the relative frequency of the symptoms, fever was present in 99%, weakness in 96%, chills in 88%, sweats in 87%, general aching in 85%, backache in 80%, joint pains in 61%, rigors in 57%, dizziness in 56%, abdominal pain in 54%, nausea in 44%, vomiting in 33%, cardiovascular disturbance in 16% and joint swelling in 6%. Hardy's figures show practically the same order of frequency.

Laboratory findings of a patient with the disease are quite characteristic. In a high percentage of cases the urine shows a slight amount of albumin, no doubt a febrile reaction. The blood picture shows constant changes of a secondary anemia, the hemoglobin may drop as low as 50 or 60%, the red cell count to as low as three million six hundred thousand. A leukopenia is usual with a progressive relative lymphocytosis. The polymorph count may go to 40% or even to 30%. Awe and Palmer (36) in a report of five cases stated
that each showed a leukopenia and a relative mononucleosia.

DIAGNOSIS

Diagnosis of undulant fever, though suggested by the symptoms and history, rests entirely upon the laboratory. Finding the organisms in the blood, urine, stool or a positive agglutination of the blood serum against the Brucella antigen in a dilution of one to eighty forms a positive diagnosis of the disease.

The British Commission found the organism in blood cultures in over one half of a series of one hundred and fifty cases. They found that positive cultures were more readily obtained by removing the blood in the evening. It must also be remembered that the organisms require special atmospheric conditions and that they are quite slow in growth. It is suggested, therefore, that the culture should not be discarded for at least twenty days.

Urine cultures are less likely to be found positive, although the British Commission found the urine to be positive in 50% of their cases. Recovery of the organism from the urine is more likely as the wave of fever is subsiding, and excretion tends to cease during the onset of a relapse.

Ordinarily it is difficult to obtain the organisms from feces, this no doubt is because on the culture media the intestinal flora outgrows the Brucella organisms, and because the Brucella organisms are so finely divided. Amoss and Poston (12) suggest, therefore, that by making a suspension of the feces in saline solution and adding immune serum an agglutination of the Brucella organisms is brought about. Then by centrifuging and culturing on eosin-methylene blue plates the colonies are more easily identified.
Amoss and Poston in another publication (14), describe one case in which they were able to obtain a culture of Brucella organisms from the gall bladder by duodenal drainage and again from the organ following cholecystectomy.

As suggested diagnosis of undulant fever is made usually by the agglutination reaction of the blood serum. The serum may agglutinate the antigen in dilutions ranging from one to five to one to twenty thousand; a dilution of one to eighty is accepted as sufficient evidence of the disease. Huddleston describes two methods to determine the agglutination titre of the blood serum. In the slide method, the organisms are grown on liver agar and suspended in 12% solution of sodium chloride with .5% phenol. The suspension is boiled for five minutes. One drop of the suspension is then added to a variable quantity of undiluted serum placed on a slide. Agglutination of the organisms can be detected macroscopically. The second, or tube method of agglutination is carried out as follows: The serum in diluted with physiological saline making .5 c.c. in each tube. The dilutions should range from one to five to one to two thousand five hundred and sixty. An equal amount of antigen is added to each tube thereby doubling the dilution. The tubes are incubated for two hours at 37°C, and then placed in the ice box over night. Agglutination can be determined macroscopically as in the typical Widal reaction. The antigen is formed by growing the organisms in veal peptone broth at a hydrogen ion concentration of 6.8 to 7.2. The antigen is brought to a turbidity of one thousand (silica standard of American Public Health Association).
Carpenter and Boak (42) give the warning that in a number of sera a phenomenon occurs in which no agglutination takes place in the lower dilutions but only after dilutions have passed a certain amount. This is known as the pre-zone of agglutination and is defined as the lowest dilution of serum which will not agglutinate the antigen, while perfect agglutination is observed in the serum diluted one to four hundred or above this point. Therefore, in carrying out the tests it is always necessary to make a number of dilutions above the pre-zone limit.

The complement fixation test for diagnosis has no advantages over the agglutination test, and is more complicated, and occasionally the serum is anti-complementary. The technique is the same as with the Wasserman reaction except that an abortus antigen is used. King believes that with many sera the complement fixation test becomes positive before the agglutination reaction.

Animal inoculation for diagnosis is too slow and impractical. Either the guinea pig or mouse may be used. Autopsy is performed in four or five weeks.

By means of the intra-dermal test a diagnosis of undulant fever may be made. For this purpose a bullion culture filtrate is used, .05 c.c. is injected intra-cutaneously on the lateral surface of the forearm. A positive reaction demonstrates an erythema about the point of injection within five minutes. Within one or two hours the area has increased to a diameter of three to six inches. At two hours an elevation arises at the site of the puncture and increases to about four inches in four hours. The local reaction may persist for forty hours. There are also often contilutional reactions of
general malaise, severe chill, fever, sweat, and joint and muscle pains. Skin tests are uniformly positive in infected individuals, but occasionally a strong positive reaction is obtained in healthy persons and about twenty-five per cent of the apparently well individuals show a weakly positive reaction.

Strouse and Howell (43) are of the opinion that the opsonic index of the blood serum is specific for the melitensis group and that it shows more strain specificity than agglutinin determinations. They also studied the phagocytic activity of patients leukocytes. In those who had a positive agglutination reaction the phagocytic index was always found to be considerably increased.

PROGNOSIS

Mortality of undulant fever is exceptionally low ranging from two per cent to eight per cent; during epidemics of the disease the mortality may reach fourteen per cent. The fever causes severe economical losses however, because of the duration of the disease, symptoms may persist for three weeks to one year or more.

PROPHYLAXIS

Prevention of the disease is important but difficult, and at the present time inadequate. To pasteurize all dairy products would surely lower the incidence of the disease. Careful handling and disposing of infected animal excreta is important. Vaccination of cows with attenuated strains of Brucella abortus before they become infected is an adequate method of prophylaxis. Surely, it should be-hove the medical practitioners to report all cases of the disease, and to then take acts to determine the source of the disease, and then attempt to remove the source of the infection.
TREATMENT

There is no specific treatment for undulant fever, consequently, methods of treating the disease are nearly as numerous as there are patients. General symptomatic and supportive treatment should be carried out in order that the patient does not lose a great amount of weight or suffer severe weakness. The patient should be kept in bed and should be fed a good, abundant, wholesome diet made up mainly of carbohydrates. Sedatives should be used when necessary.

Mercurochrome intravenously has been used quite commonly with variable results. Gage and Gregory (19) report successful treatment by using .22 gms. of two hundred and twenty soluble mercurochrome. Carpenter and Merrian (20) have also observed cures using twenty-three c.c. of one per cent mercurochrome. Others (1) failed to recognize any good effects from its administration.

Thionine is thought by some (15) to have a specific reaction on the bovine organisms in high dilution. They gave the drug in tablet form, giving twenty-five to two hundred mgm. in twenty-four hours. Retention enemas of three hundred c.c. of a solution diluted from one to twenty-five thousand to one to one hundred thousand were given daily. This treatment was given over a seven day period at intervals of about two weeks. Methyl violet may be given in the same fashion when the organism is of the porcine variety.

Hoffman (17) reports good results by using acriflavine base intravenously. He used increasing doses beginning with .2 gm. and gradually increasing up to .4 gm. intravenously. The drug was given at two day intervals.

Treatment using an autogenous vaccine has probably given good
results more constantly than any other method. Schilling, et al., (11) give a very good description of its preparation. They inject one c.c. of the antigen intramuscularly.

A stock vaccine has been prepared and Angle (53) in a report of ten cases has had very good results. Five pathogenic strains of the bovine organism and one of the porcine variety are included in the vaccine. He gives .25 c.c. as an initial dose and increases this .25 c.c. with each succeeding dose until one c.c. is given. These are administered on consecutive days unless some symptoms seem to contraindicate. Reactions usually occur after the second or third dose, it is advisable to continue the treatment until a severe reaction is obtained.

Quite in opposition to the use of the vaccine, the Council of Pharmacy and Chemistry (44), came to the conclusion that the reports of success with the vaccine were not convincing.

CASE REPORTS

The following are reports of six cases of undulant fever that have occurred in or about Omaha, Nebraska within the last three years. It is interesting to note the various diagnoses made on these patients upon their entrance into the hospital. In one case a diagnosis of sub-phrenic abscess was made, in another, neurasthenia, and in another, sinusitis. The final diagnosis was made by the laboratory by use of agglutination reaction and blood cultures.

O.S.-patient number 36262, a white, male, age twenty-seven who had previously been employed as a farm hand, entered the University Hospital on September 15, 1931 complaining of weakness, fatigue, anorexia, constipation, headache and severe night sweats.
This patient is of particular interest for it brings to light a very striking symptom of the disease. On entrance he was put on the psychiatric ward because of the prevalence of neurasthenic symptoms. He was of the introvertive type of personality, over apprehensive concerning his somatic symptoms, was especially concerned about his genitalia, going so far on one occasion as to ask that an X-ray film be taken of his penis and scrotum to determine the pathology present. He was very much discouraged and depressed, stating that everything seemed against him. He had a masturbation complex about which he worried a great deal.

Upon questioning the patient further it was found that he had begun work on a farm in April, 1930. Soon after beginning work he developed a series of boils on his neck and hands which remained for about three months and then disappeared. Then in February, 1931 he got to be very weak and began to sweat excessively, particularly at night, he soon developed shortness of breath, palpitation, and precordial pain. He stated that he was more tired in the morning than when he went to bed the night before. About the first of August 1931 all symptoms were increased in severity, and his greatest complaints were profuse night sweats, severe headache, weakness, and anorexia.

When diagnosis of undulant fever was made on November 1, 1931 he was transferred to the medical ward, and an attempt was made to determine the source of his infection. He stated that infectious abortion was present among the cattle on the farm at which he worked, and that three or four cattle had aborted while he had worked there. There is no history of any contact with goats.

The patient had measles in 1920, an appendectomy in 1926 and a
tonsillectomy in 1929.

On physical examination his hearing was found normal. Eyes reacted to light and accommodation, no nystagmus. Teeth were fair, a moderately severe pyorrhea. Tonsils were out. Chest gave no evidence of rales or consolidation. Heart was of normal size, no murmurs, blood pressure was 123/80. The liver was not enlarged. The spleen was palpable. There were no testicles in the scrotum or in the inguinal canals.

While in the hospital his temperature curve was of the typical undulating type. For the first four days in the hospital it was over 99.5°F, for the following four days it was subnormal, and then again rose above 100°. It remained high for twelve days then became subnormal for about four days then rose again for three days, after which it became normal and remained so until his dismissal. The maximum temperature was 102.5°F, pulse 100 and respiration 27.

The urine analysis showed a trace of albumin on several occasions. The blood count was as follows: hemoglobin 95%, red count 6,032,000, white blood cells 4600, polymorphonuclears 50%, lymphocytes 36%, monocytes 10%, eosinophiles 3%, basophiles 1%. The leukopenia is characteristic of the disease. Gastric analysis was normal with a free acid of 20° and a total acid of 80°. The Wasserman test was negative. The Widal was negative for bacillus typhosis and paratyphosis A and B. Rapid agglutination (Huddleston) for bacillus melitensis and abortus was positive in a dilution of one to five hundred. On September 30 blood culture was negative after five days; on November 9 the blood culture after ten days showed presence of small Gram negative bacilli which were agglutinated by
bacillus melitensis serum in a dilution of one to one thousand.

In addition to general supportive treatment an autogenous vaccine was prepared of the organisms. Following the first subcutaneous of 1/5 c.c. the temperature dropped down to normal and remained there until dismissal of the patient. A second injection of 2/5 c.c. followed the first in eleven days, a third of 2/5 c.c. in five days and a fourth injection after five days.

The patient was discharged from the hospital in a very much improved condition fifty-one days after admittance.

F. M. number 32081 male, American, white, age thirty-one, was admitted at the University Hospital on June 11, 1930. His chief complaints were frontal headache and severe lower abdominal pain on left side which radiated to the penis.

The complaints not being typical of any clinical entity but suggesting renal colic a tentative diagnosis, made on the findings, was recorded as calculi with pyelonephritis. Further development of the history was as follows: two years ago the patient had a severe colicy pain in left lower abdomen--this pain later radiated down toward the penis and scrotum. The patient stated that the pain lasted for about ten days following which time he passed some gravel from the wreathra.

One month previous to entrance he had another attack of pain of the same character but less intense. The pain came on in the morning, lasted two hours and disappeared. A sense of burning on urination followed the attack. There was no history of having passed blood but the urine had a smoky appearance.

The entrance complaint of headache was elaborated upon, it had
started three days previous and had kept the patient awake during the night.

He had smallpox and measles during childhood but no illness since that time. There was no history of any injuries or operations.

His family history was essentially negative, he having one brother and one sister both living and in good health. His father and mother were in good health. There was no history of tuberculosis, epilepsy, carcinoma, or insanity in the family.

Upon physical examination his eyes reacted to light and accommodation, no nystagmus or discharge. The nasal septum was deviated to the right but not sufficient to cause obstruction. His teeth were in good condition and his tonsils were small. There were no lymph nodes palpable in the neck. Expansion and shape of chest was normal, no rales or murmurs were heard. The lungs were resonant throughout. The heart was not enlarged, blood pressure was 128/83. On abdominal palpation tenderness was noticed just above the umbilicus, there were no masses felt. All reflexes were in tact.

During his stay of twenty-three days in the hospital his temperature gave a characteristic intermittent appearance. The late afternoon and evening temperature would go as high as 104°F, and dropping each morning to normal or subnormal.

Reports from the laboratory showed the urine to have only a trace of albumin present. Blood counts found the hemoglobin at 85% and 4,620,000 r.h.c. White cells numbered 6,800 with a differential of 48% polymorphonuclears, 36% lymphocytes, 16% monocytes. The Wasserman reaction was negative.

Agglutination reactions of a mixed antigen of bacillus melitensis,
abortus and melitensis was positive at a dilution of one to one hundred by the rapid method. Using the slow method or tube agglutination a positive reaction was obtained in a dilution of one to eighty. The complement fixation test was strongly positive.

Blood culture was negative after two days.

The Widal reaction was negative for bacillus typhosis and bacillus paratyphosis A and B.

In addition to general supportive treatment acriflavine was injected intravenously. Two days following the first injection of .1 gm. acriflavine the temperature came down to normal and remained there. Three days following the first administration .2 gms. was injected.

H. O., patient number 30388 a Mexican, male, age thirty-seven entered the University Hospital November 30, 1929 complaining of chills, drenching sweats and malaise.

His first symptoms developed on November 13, 1929 when he became more or less dizzy, was nauseated, and vomited several times. The symptoms were relieved by medication but he was confined to bed for a week. On November 11 he had a severe chill at four P. M. which lasted for about forty-five minutes and was followed by a drenching sweat. A second and similar chill occurred at midnight. These chills reappeared daily until November 25 when the afternoon attack disappeared but the midnight attack persisted. The sweats which followed each chill were unusually profuse. For two months previous to admission the patient had a general feeling of malaise and weakness. Since the onset of chills his general condition and attitude had been one of euphoria. He had been employed in a local packing plant, working
in the various departments. The patient had been a resident of Nebraska for seven years during which time he had not left the state.

Upon reviewing his past history, he had influenza in 1918. There was no history of measles, mumps, whooping cough, scarlet fever, or diphtheria. He had experienced no injuries or operations.

A complete history by systems was as follows:

Eyes - no strabismus, diplopia, or blurring.

Ears - no impairment of hearing, tinnitus or discharge.

Nose and throat - no epistaxis, discharge or obstruction.

He had been subjected to frequent attacks of rhinitis.

Heart - no dyspnoea, edema but occasional palpitation.

Respiratory system - no cough, hemoptysis or pleurisy.

Gastro-intestinal tract - no nausea, vomiting, pain, distress, constipation, diarrhea or hemorrhoids.

Genito-urinary - no hematuria, nocturia or incontinence. In 1919 he had a purulent wreathral discharge which was accompanied by burning on urination. This lasted one week. He denied any venereal infection.

Neuro-muscular - no shooting, muscular or joint pains.

Habits and weight - Patient mildly indulged in alcohol and tobacco. There was no recent loss of weight.

From his family history we found that his father was not living, the cause of death unknown. His mother was seventy-seven living and well. He had four brothers, two living and two dead, four sisters living and well. His wife was living and they had six children all living. There was no family history of tuberculosis, cancer, diabetes or insanity.
Physical examination showed a very well nourished and well developed Mexican lying quietly in bed in no apparent distress.

Head - of normal shape, hair was of medium texture.

Eyes - pupils reacted to light and accommodation. A small scar on sclera of left eye. No strabismus, nystagmus or ptosis.

Ears - drums negative, range of audition good.

Nose - moderate obstruction on right side.

Mouth - teeth good, tonsils small.

Neck - no masses palpable.

Thorax - asthenic type, expansion equal.

Lungs - resonant thru-out, no rales.

Heart - apex beat not palpable, no thrills or murmurs, rate one hundred, blood pressure 110/80.

Abdomen - feeling of resistance over splenic area but spleen itself not palpable, no shifting dulness or herniae.

Extremities - no deformities, scar on both thighs. Right forearm tattooed. Reflexes intact.

Laboratory reports showed the urine to be negative. Blood had a hemoglobin of 85% with 4,380,000 r.b.c. A leukopenia was present of 5,800 with a differential of 68% polymorphonuclears, 28% lymphocytes and 4% monocytes.

The Widal reaction for bacillus typhosis, bacillus paratyphosis A and B were negative. Blood culture was negative after four days.

The agglutination reaction using for an antigen bacillus melitensis abortus and melitensis was positive in a dilution of one to three hundred and twenty.

During the patients course in the hospital the temperature curve
was of an intermittent type. The greatest height reached was 104°F in the afternoon or evening. Each morning the temperature again became normal or subnormal. He was discharged from the hospital February 5, 1930, the temperature having become normal.

P. H., University Hospital number 29420, a male, age fifty, entered the hospital August 17, 1929 complaining of chills, fever, sweating, constant headache, constipation, and occasional nocturia and frequency.

His complaints began about eight weeks before entrance with a steady headache, three weeks later chills and fever began. He quit work three weeks before he came to the hospital. His bowel and urinary disturbances had also come on within the previous three weeks.

Previous childhood diseases could not be recalled by the patient. He had "blood poisoning" in a finger a year previous, and a herniorrhaphy eight years previous.

He had suffered no disturbances with his eyes or ears; nose and throat history was negative. There was no cardiac history of significance. His respiratory tract was essentially negative, no asthma, pleurisy, or night sweats. He had suffered no constipation previously, no hemorrhoids, vomiting or digestive disturbances. Genito-urinary system history was suggestive in that he had frequency and nocturia beginning six weeks before admittance. There was no history of any muscular or joint pains; no dizziness.

His habits had been fair, he smoked a little, drank no alcohol.

His previous weight was one hundred forty-two pounds, at time of admittance was one hundred twenty-six pounds.

The family history was not significant. Father died at eighty,
cause unknown. Mother died at fifty-four, cause unknown. There was no history of tuberculosis or insanity in the family.

Physical examination of eyes was negative, the pupils were equal and regular, and reacted to light and accommodation. Hearing was impaired on the left side. The nose showed a moderate obstruction on the left. The anterior tonsillar pillars were injected and there were small grayish deposits on the surfaces of the tonsils. Submaxillary lymph nodes were palpable. Examination of the thorax showed the expansion to be fair but equal on the two sides. The chest was resonant throughout and no rales were heard. The apex of the heart was in the fifth interspace, one-half inch lateral to mid-clavicular line. No murmurs were heard. The blood pressure was 104/68. No tenderness, masses, or rigidity was noticed on abdominal examination. By rectal examination the prostate was normal in size. There was no edema of the extremities.

Laboratory examination: Urinalysis was negative. Blood culture was negative after two weeks. Agglutination tests made on the blood serum were positive to Brucella melitensis in dilutions of one to six hundred and forty.

The patient was in the hospital for fifty-three days, during that time he had recurrences of fever every other day for twenty-two days. The maximum temperature was 103.6°F.

A high caloric diet was fed the patient and cathartics were administered to relieve the constipation. Quinine was given as an antipyretic.

Through the kind cooperation of Dr. Lynn T. Hall I obtained the history of Mr. A. B., an American, white, married, male, age forty.
His complaints were general malaise, chills, fever, profuse night sweats, nervousness, insomnia and sweating, itching feet.

Previous to the onset of his illness he had been drinking a considerable amount of milk in an effort to increase his weight. Then about two weeks before hospital entrance he became ill with what he thought was influenza. His strength began to fail and later arthritic pains developed. He became extremely nervous and could not sleep at night. Several days later he began to have chills which were followed by fever and sweats.

His previous history of illnesses was essentially negative. He had the ordinary childhood diseases. There was no history of any accidents or injuries. He was occasionally subjected to attacks of sinusitis.

The family history was of no importance. His mother and father, both seventy years of age were living and well. He had two brothers, both living and well. His wife was forty years of age and in good health. There was no history of tuberculosis or insanity in the family.

On physical examination the patient was a fairly well built man of about stated age. Pupils reacted to light and accommodation, there was no discharge from the eyes. Hearing was good in each ear, no discharge. Nose showed no evidence of obstruction. There was present in the throat a post-nasal discharge; the pharynx was congested and injected. The tonsils had been removed. There were no masses palpable in the neck. The chest was essentially negative, resonance was good, no rales were heard. The apex of the heart was one cm. within the mid-clavicular line in the fifth interspace. No
murmurs were heard. There was no tenderness or rigidity of the abdomen, the spleen was not palpable. Examination of the extremities showed the fingers to have a rapid course tremor.

When the patient was admitted to the hospital he had a temperature of 103°F. and a pulse of ninety. He continued to have chills, fever, and sweats while in the hospital. Diagnosis of undulant fever was made by a positive agglutination to Brucella abortus organism at a dilution of one to three hundred and twenty. A blood culture was made and the abortus organisms were recovered. Blood count showed the presence of a secondary anemia and a leukopenia of five thousand two hundred cells. Urinalysis was negative.

When diagnosis was made, acriflavine was administered intravenously but without any demonstrable change in symptoms. This was followed by an ampoule of metaphen but without success. Having recovered the organisms from the blood an autogenous vaccine was prepared. After the first intramuscular injection of .25 c.c. the symptoms gradually subsided. Injections were repeated every other day in increasing doses until a maximum of .5 c.c. had been given. Recovery was effected following the second injection.

Dr. Carl F. Hille submitted to me a case which he had attended at the Covenant Hospital. The patient was a man, age thirty, married, and a farmer by occupation. One month before entrance into the hospital he noticed that he was not quite up to par and suffered a general malaise, weakness and joint pains. Shortly afterward he had a severe chill which lasted all of one night. The next day he felt better but as soon as he attempted some work he became very weak. At this time he began to have profuse afternoon and evening sweats. His appetite became very poor.
Upon inquiring into his past history, it was found that he had been drinking a considerable amount of milk, and about two months before the onset of his illness he had attended an aborting cow.

Physical examination disclosed nothing of particular interest. His pupils reacted to light and accommodation. Hearing was normal. His teeth were in poor condition. Anterior cervical lymph nodes were enlarged. On examination of the chest, it was found to be resonant throughout; no rales were heard. The apex of the heart was eight cm. to left of mid-sternal line, no murmurs were heard. The abdomen showed no evidence of pathology. The knee jerks were absent.

Reports from the laboratory stated that urinalysis was negative. The blood picture showed 80% hemoglobin, 4,800,000 r.b.c., 7,000 w.b.c., polys 47%, small lymphocytes 30%, large lymphocytes 13%, eosinophiles 10%. Stool examination was negative. Wasserman reaction was negative. A positive blood culture for Brucella abortis organisms was obtained. Agglutination of the Brucella group of organisms occurred at one to one hundred and sixty dilution.

Upon entrance into the hospital his temperature was 100°F, and pulse was ninety. There were daily exacerbations and remissions of the temperature. An autogenous vaccine was prepared and administered; .15 c.c. was injected sub-cutaneously, this was increased to .5 c.c. The temperature line soon became normal and the patient was discharged seventeen days after admittance.

In an analysis of the six cases, sweats and fever were the most common symptoms. Chills, malaise, and fatigue were less frequent, while headache, constipation, dizziness, nausea, vomiting, joint pains, insomnia, nervousness and anorexia occurred only occasionally.
Diagnosis in each case was made by means of symptomatology, agglutination reactions, and blood cultures. Positive agglutination of the Brucella organism occurred in dilutions varying from one to eighty to one to one thousand. Blood cultures from the patients showed the presence of small, Gram negative, bacillary formed organisms in one-half of the series. In each instance the organism was agglutinated by immune serum.

Treatment in each case, though varied, seemed adequate, it must be remembered, however, that the disease in itself is self limited. In the three cases in which a positive blood culture was obtained were treated by autogenous vaccine. Results were good; better than when acriflavine was injected or when symptomatic treatment alone was used. The temperature came down to normal after the first injection of acriflavine.

CONCLUSION

Finally, it should be remembered that the occurrence of undulant fever is not rare. Its spread is mainly through infected milk, though contact with infected animals is also a common source of infection. Symptoms of the disease may mimic nearly any other known disease entity. Diagnosis rests entirely upon the laboratory. At present, autogenous vaccines seem to produce the best results in the treatment of undulant fever.
References:


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