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

Tularemia

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INDEX

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William A. O'Brien, M.D.

I. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL

CALENDAR OF EVENTS
January 10 - 15, 1944

Visitors Welcome

Monday, January 10

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff, Main 515, U.H.

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff, Todd Amphitheater, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U. H.

12:30 - 1:30 Pediatrics Seminar; To be announced; W-205 U. H.

12:30 - 1:30 Pathology Seminar; Significance of Phosphatase in Renal Tubules; Harry A. Wilmer, 104 I.A.

8:30 - 9:30 Cancer Biology Seminar; Estrogenic Hormones and Breast Cancer in Mice; Staff; 116 M.H.

Tuesday, January 11

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff, Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff, Main 515, U. H.

12:30 - 1:30 Pathology Conference; Autopsies. Pathology Staff, 102 I.A.

12:30 - 1:30 Physiology-Pharmacology Seminar; A Study of the Mechanism of Acetone Formation with Heavy Carbon Acetic Acid; Harland G. Wood; 214 M. H.

4:00 - 5:00 Pediatrics; Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

5:00 - 6:00 Roentgen Diagnosis Conference; C. L. Ould and H. S. Kaplan. M-515 U.H.

Wednesday, January 12

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Acute Leukemia-Chloroma; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff, Todd Amphitheater, U. H.

12:30 - 1:30 Pharmacology Seminar; To be announced; 105 M.H.

4:30 - 5:30 Physiology Seminar; Conditioned Reflexes; E. Gellhorn; 116 M.H.

Thursday, January 13

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Rounds; R. J. Watson and Staff, East 214 U.H.

12:30 - 1:30 Physiological Chemistry Seminar; Factors affecting the Metabolism of Bones and Teeth; Staff; 116 M.H.

12:30 - 1:30 Poliomyelitis Research Seminar; Coordination in Muscle Training; Ancel Keys; 113 M.S.

Thursday, January 13 (Cont.)

4:30 - 5:30 Bacteriology Seminar; 129 M. H.

4:30 - 5:30 Neurophysiology Seminar; Historical Introduction into the Theory of Neurohumors (Chemical Transmission of Nerve Impulses); E. Gellhorn, 129 M. H.

8:30 - Special Meeting, Room 15 Medical Sciences.

"The Surgeon Generals of the U. S. Army, Navy, and Public Health Service are sending representatives on a country-wide tour for the purpose of informing all physicians about medical aspects of the war and the needs and programs at the present time of their respective services.

This is a wonderful opportunity to get first-hand information about the situation from qualified spokesmen and to find out just what will be expected of Minnesota in the next year of the war.

W. F. Braasch, M.D., Chr. Minnesota.

Friday, January 14

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff, Todd Amphitheater, U.H.

8:30 - 10:00 Grand Rounds; I. McQuarrie and Staff.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U. H.

11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Nutritional Requirements of Surgical Patients; R. L. Varco and F. Kolouch; Powell Hall, Recreation Room.

1:00 - 2:00 Medicine Case Presentation; C. J. Watson and Staff; Main 515, U. H.

1:00 - 2:30 Dermatology and Syphilology; Demonstration; Selected Cases of the Week; West 306 U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff, Todd Amphitheater, U. M.

Saturday, January 8

9:00 - 11:30 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; Main 515, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214, U. H.

11:30 - 12:30 Anatomy Seminar; Review of "Central Autonomic Regulation" by H. R. Miller; A. T. Rasmussen: Pernicious-like Anemia in Infants - Report of one case; Robert Reiff; 226 I. A.

II. TULAREMIA

Robert G. Green
Charles A. Evans

Introduction

Although tularemia is one of the more recently discovered diseases, it has doubtless long been a common infection in the animals of the Northern Hemisphere. It is a disease so variable in some of its manifestations that it may easily be confused with other better-known diseases. Probably the first allusion to this disease was made by Pearse[1] in 1911. It was McCoy,[2] however, in 1911, who first recognized the disease as an entity and described it as a "plague-like disease of rodents." This work was followed in 1912 by cultivation of the causative organism by McCoy and Chapin,[3] who called the organism "Bacterium tularense."

The infection of human beings with this organism was established in 1914 by Wherry,[4,5] who also showed that the infection was a common one in rabbits and that the human disease was obtained by contact with rabbits. In 1919 Francis[6] demonstrated that "deer-fly fever" in Utah was caused by Bacterium tularense, and he suggested the term "tularemia" as a name for the infection. The agglutination test for the diagnosis of human tularemia was introduced by Francis,[7] and from the time of its introduction, the number of human cases correctly diagnosed progressively increased. In 1924 Parker, Spencer, and Francis[8] demonstrated the disease in the western wood tick. Tularemia was shown to be a disease of birds in 1929 by Green and Wade.[9] Green[10] also isolated the organism from the eastern wood tick in 1931. In 1932 Foshay[11] demonstrated the state of hypersensitivity to the organism which occurs in the disease and he also introduced an antiserum which has had limited use.

The Human Infection

Tularemia in human beings is a highly variable infection but is typically characterized by a generalized infection of three weeks' duration, by a localized ulcer, and by a regional lymphadenitis of about three months' duration. As tularemia is widely distributed among wild animals and birds, the specific sources of tularemia in human beings are numerous, but the general sources are as follows:

1. Animals: rabbits, game birds, fur animals, other animals.
2. Wood ticks: Dermacentor (variabilis, andersoni, occidentalis).
3. Deer fly: Chrysops discalis.

Portal of entry

Pasteurella tularensis is easily capable of invading the unbroken skin. However, most infections result from the organism's penetrating the skin through a cut or abrasion. The unbroken mucous membranes are also a favorable tissue for entrance of the infection. The various sites and modes of entry may be listed as follows:

1. Skin abrasion: dressing game, handling wood ticks or other infected material, insect bites.
2. Intact skin: crushed deer fly, picking off ticks, rabbit blood.
3. Conjunctiva: contamination of fingers from infected animals or infected ticks and transfer to eye.
4. Alimentary tract: infected game, contaminated food, contaminated water.

Incubation period

The incubation period is relatively short, being generally about $3\frac{1}{2}$ days. The period may be as short as one day or as long as 7 days or more.

Onset

The onset of tularemia is typically sudden. An expression of well-being may be followed in a few hours by definite and marked symptoms. The disease is ushered in by chills, fever, sweating, and severe aching.

Remission

A common peculiarity of the tularemic infection is a remission, which not infrequently occurs about 24 hours after

the initial symptoms. The remission lasts from 12 to 36 hours, and during this period the patient may get out of bed and attempt to resume normal activity.

Stage of increasing severity

There is an increasing severity of symptoms for a period of 7 to 14 days. During this time the fever is maintained and chills and night sweats become severe, as do generalized aches and pains. Nervous symptoms appear which vary from extreme restlessness and muttering to complete delirium.

Decline of symptoms

A rather sudden decline of symptoms occurs, generally at the end of the second or the beginning of the third week. The change may be so marked as to represent a crisis. The decline of general symptoms continues during the third week so that by the end of that week, convalescence from the systemic infection is established. The patient may have undergone a very marked loss of weight. Convalescence is slow and is further retarded by the regional lymphadenitis proximal to the source of infection.

Ulcer

The development of an ulcer when the portal of entry is through the skin depends upon injury to the skin, as well as upon presence of the organism. Entrance of the organism through the unbroken skin is accomplished without a local lesion, as was demonstrated by Ohara[12] in a human case, and as is commonly seen in the experimental inoculation of guinea pigs. In its earliest development, the local lesion appears as a small papule in the infected abrasion or at the point of a tick- or fly-bite; the papule may be evident at the time the first symptoms of the disease occur or may appear a few days thereafter. Ulceration of the swelling begins during the second week and progresses until a well-defined ulcer is present at the end of the third week. The ulcer persists as a clean punched-out lesion similar to a chancre and sometimes referred to as such. Organisms can be demonstrated on the indurated wall. Healing of the ulcer occurs about the ninth week.

Regional lymphadenitis

The first depot of lymph nodes proximal to the ulcer or point of entry is typically involved with a regional infection. Lymphadenopathy is rarely bilateral. The first enlargement of lymph nodes is evident during the second week. If more than one node is involved, the enlargements usually appear successively. The first lymph node reaches maximum enlargement about the sixth week, softens and ruptures about the eighth week, and heals about the twelfth week. Successive lymph-node enlargements increase the length of the disease beyond three months. Lymphadenopathy may recede without necrosis and rupture, so that the typical course of the regional infection is shortened. Involvement of the skin or subcutaneous nodules between the ulcer and the proximal lymph nodes is occasionally observed. The lesion may have the appearance of sporotrichosis.

Clinical types

Typical tularemia, described above, involves a local ulcer, regional lymphadenitis, and a generalized infection; it has been termed by Francis the "ulcer-glandular type." Since the ulceroglandular type of tularemia represents more than 85 per cent of the cases, it is to be considered the typical form of the disease.

Atypical types

Oculoglandular. In this clinical form of the disease, the ulcer is replaced by a severe conjunctivitis similar to Parinaud's conjunctivitis. This type of the infection, the first reported in human beings, was described by Vail,[13] who worked with Wherry. The regional lymphadenopathy and a generalized infection present in this type of tularemia make it similar to the ulceroglandular form of the disease except for the primary lesion.

Glandular type. In this type of the disease, there is no local ulcer, probably because of lack of sufficient injury at

the time of infection. The organism progresses from the point of entry to the regional lymph nodes, which enlarge in typical manner.

Typhoid type. Only the generalized infection is evident in this form of the disease. Both the local lesion and the regional lymphadenopathy are absent. This type of the disease has occurred almost uniformly among laboratory workers. Recent studies by Green[14] on changes in the virulence of Pasteurella tularensis upon guinea-pig passages indicate that this type of the infection may be caused by strains of the organism that have special affinities due to a particular animal-origin.

Pneumonic type. A small number of cases of tularemia appear as a primary pneumonia without any evidence of a skin lesion or lymph-node enlargement. Such cases may be discovered by the recognition of the pathology of tularemia in mice injected routinely with sputum. On the other hand, many cases of thpical or atypical tularemia show involvement of the lungs, which may be demonstrated in some cases only by x-ray. Pulmonary lesions may occur as late as during the third week without producing symptoms or interfering with convalescence. As a complication in other forms of tularemia pulmonary involvement may be represented by a bronchitis, bronchopneumonia, lobar pneumonia, or pleuritis, with or without effusion.

Rare clinical types

Meningitis and the excessive development of skin lesions have been described. Primary involvement of the tonsils with bilateral lymphadenitis evidently has occurred. The ulcer may appear entirely by itself. Similarly, an enlarged lymph node may appear alone, without either the ulcer or a general infection.

Complications and mortality

A delayed pneumonia, one of the most common complications of tularemia, occurs in nearly half the cases and results in death within the first month. A succession of suppurating lymph nodes may extend the course of the disease to as long as two years. Pleural effusion, peritonitis, and extensive skin ulcerations have been described. Francis[15] has reported a mortality of 5.3 per cent in a group of 10,118 collected cases.

Etiology

Pasteurella tularensis is unlike other members of the Pasteurella group in its morphology and growth characters. It is classified as a Pasteurella principally because the disease it produces is similar to a Pasteurella infection. Pasteurella tularensis is a small, pleomorphic, gram-negative rod, about 0.2 microns in diameter, and 0.3 to 0.7 microns in length. It often occurs as a spherical coccus. It is nonmotile and produces capsules in tissues.

Pasteurella tularensis grows only on egg-yolk medium or media containing the amino-acid, cystine. Cystine is added to give a 0.1 per cent concentration. The best medium for cultivation is veal-infusion cystine-glucose-blood agar. After initial growth on this medium or on egg-yolk medium, growth can be obtained on plain agar containing cystine. Growth is enhanced by the addition of 0.5 per cent glucose. Minute, transparent, drop-like colonies are formed. Little or no growth is obtained in 24 hours; growth is visible in 48 hours, and a luxuriant, spreading growth on slants appears on the third day. The first point in laboratory identification is growth on blood agar containing cystine, and no growth on blood agar without cystine. Final identification is established by agglutination with a specific serum.

Pathogenicity for laboratory animals

All rodents are highly susceptible to laboratory infections of tularemia. Guinea pigs, mice, and rabbits are usually used. Subcutaneous inoculation results in enlarged regional lymph nodes embedded in gelatinous exudate, and in multiple abscesses of the liver and spleen. Death occurs in 2 to 14 days: the infection is shortest in mice and longest in rabbits. Intraperitoneal injection of large doses produces short infection with little

pathology. Inoculation of the skin by scarification results in extended infections with a maximum display of abscesses in the spleen and liver.

Pathology in Laboratory Animals

In the typically virulent disease which occurs in rodents, tularemia is similar to plague. In highly susceptible animals or in animals with an excessive dosage of the organism, death occurs in 24 to 48 hours. There are no marked pathological findings at necropsy. In rodents of ordinary resistance inoculated by skin scarification, the disease runs an acute course of 5 to 10 days, and at necropsy the liver and spleen are studded with fine abscesses. In rodents inoculated with strains of low virulence, such as those obtained from birds, the disease may run a course of 30 days or more. At necropsy the abscesses seen are fewer but much larger than in the acute form of the disease. Microscopically, abscesses are somewhat similar in appearance to tubercles because of the presence of epithelioid cells which resemble giant cells.

Pathology in Man

Man is relatively resistant to tularemia. The human pathology observed corresponds to that produced by the more chronic infections in animals. Abscess-formation apparently occurs only in the more severe types of the disease, which usually terminate fatally. Mocroscopically, the lesions are similar to those observed in animals; they are somewhat tubercle-like, with epithelioid cells.

Immunologic Reactions in Tularemia

Agglutinins

In tularemia, antibodies make their appearance during the second week or, less often, during the third week of illness. In the fourth to seventh week the agglutination titer is at maximum, which, in some cases, is above 10,000. From the published reports, it appears that in this disease the agglutination test is of highest reliability. According to Foshay[16], "the reliability of the macroscopic serum agglutination test in tularemia approximates perfection. Although many thousands of cases have been studied in this and other countries, there is no report of a single failure of a patient to develop serum agglutinins unless death occurred during the first two weeks of the disease. Moreover, once agglutinins have been acquired as a result of infection, they have not yet been found to disappear completely thereafter, even if tested for as long as 33 years after recovery." Agglutinins never appear during the first week and occasionally do not appear until the third or, rarely the fourth week.

Cross-agglutination with the organisms of the genus Brucella is observed in about 25 per cent of cases. The titer of agglutinins for the homologous organisms is usually higher than that for the heterologous species.

In spite of the remarkably constant occurrence of agglutinins, this serologic test leaves something to be desired as a specific diagnostic test, for it is negative during the first week of the disease. An earlier and equally specific test, which becomes positive in the first day or two of the disease, has been devised on the basis of an acquired skin-sensitivity demonstrated by Foshay.[16]

Bacterial-antigen intradermal test

A profound hypersensivity to Pasteurella tularensis developing early in the course of tularemia has been demonstrated by Foshay. Injection of a small amount of a bacterial suspension into the skin of a person who has or has had tularemia, results in the development of a local inflammatory reaction that closely resembles the tuberculin reaction. In a positive test, the maximum effect is seen in about 48 hours, at which time the site of inoculation exhibits changes essentially like those of a positive Mantoux test.

Dilute suspensions of heat-killed or formaldehyde-killed bacteria are unsuitable for the test, as they frequently induce necrotic local lesions, fever, and

severe reactions in distant parts of the body involved in the tularemic process. Rapid accumulation of pleural fluid or enlargement of pneumonic areas in the lungs has been observed. The danger of causing such undesirable local and general reactions has been reduced to a minimum by oxidizing the bacterial suspension with nitrous acid or hydrogen peroxide. A properly prepared suspension of bacteria retains its potency for a year. The specificity of the skin test appears to be equal to that of the agglutination test, as Foshay states that falsely positive tests have not been seen "even in brucellosis patients whose serums cross-agglutinated B. tularense."

This skin test is of greatest usefulness as an aid to early diagnosis, since it may be positive even on persons tested on the first day of the disease. Of 108 patients tested by Foshay during the first six days of illness, 100 were positive. Subsequent tests gave positive skin reactions in seven of the remaining eight patients before the agglutination test became positive. The reliability of this test is further shown by the fact that of an additional 483 patients who were tested on or after the eighth day of illness, all but three were positive.

Antiserum intradermal test

A second type of diagnostic skin test that has been used by Foshay in tularemia is based on the intradermal injection of a small amount of specific antiserum. A positive reaction is signified by the prompt formation of a central wheal surrounded by a zone of erythema. Goat serum is preferred to horse serum because with it fewer nonspecific reactions, as a result of protein sensitivity, are obtained. Foshay emphasizes that ordinary commercial antiserum sold for therapeutic use is not satisfactory. In the skin test, a serum of high potency that has been subjected to little or no filtration through silicious filters should be used. According to Foshay, reactivity to this parallels that to the bacterial skin test. Of the 108 previously mentioned patients tested during the first week of illness, the same eight who failed to react to intradermal injection of a bacterial suspension also failed to react to the simultaneous injection of antiserum into the skin. The advantage of the serum skin test is that it can be read in 15 minutes, whereas reading of the bacterial test must wait 48 hours.

Friedewald and Hunt[17] have found the skin test in which serum is employed less satisfactory because of the large proportion of people who react to a control injection of normal horse or goat serum. They agree on the high degree of specificity of the test and state that in persons who gave no reaction to the control serum and reacted to the test serum, "a diagnosis of tularemia could be made and was always substantiated later by the agglutination test and the antigen skin test." Because of nonspecific reactions, the test was of value in only about one-third of the patients.

It is well known that skin-testing with the brucellosis antigen may stimulate the production of antibodies and in this way reduce the significance of later agglutination tests. According to Firedewald and Hunt, this is not the case in tularemia. Twelve persons given the antigen skin test were found two weeks later to be negative to the agglutination test or, in a few cases, to have a positive titer of 1:20 or 1:40. (They consider a titer a 1:80 necessary for diagnosis unless an earlier negative test is on record.)

Diagnosis

Clinical diagnosis

The ulcer, the regional lymph-node enlargement, and the acute fever, together with a history of contact with wildlife, make a characteristic picture. The course of tularemia and the physical findings are so characteristic in 85 per cent or more of cases that a clinical diagnosis of the disease may usually be arrived at by the fourteenth day. The local lesion may not be evident at the time of the acute onset but usually appears within a few days. As a rule, enlarging lymph nodes are not painful and show little tenderness; so they must

be discovered by physical examination. An early clinical diagnosis depends primarily on an accurate history and a careful physical examination. The disease is apt to be confused with enteric fevers, rickettsial infection, undulant fever, septic infections, tuberculosis with pleural effusion, atypical pneumonia, sporotrichosis, and fevers of unknown cause. The protean manifestations of tularemia frequently stimulate a complicated but erroneous diagnosis, such as "rheumatic fever complicated with erythema nodosum." While a clinical diagnosis can easily be arrived at in a majority of cases, an absolute diagnosis can be established only by laboratory procedures. Among the atypical cases which make up 15 per cent, a clinical diagnosis may be made for such forms as the oculoglandular and the glandular types. In some cases, however, there is little clinical evidence to suggest tularemia specifically, so that tularemia must be considered a possible cause in all infectious fevers of undetermined origin. On the other hand, it is recognized that fevers do occur, following insect bites and accompanied by local ulcer and enlarged lymph nodes, that are not due to Pasteurella tularensis but have an unknown causation.

Laboratory diagnosis

Laboratory diagnosis of tularemia may be accomplished by standard methods in common use, by isolation and identification of the organism, or by the demonstration of agglutinins in the blood. The skin tests introduced by Foshay, although not in common use, offer the only means of diagnosis during the first four days of the disease and the only means of quick diagnosis before the appearance of agglutinins in the blood.

Laboratory diagnosis during the first ten days of the disease.

1. Blood culture

   A sample of citrated blood is spread over the surface of several blood-glucose-cystine agar plates. In 48 hours, colonies should be evident that can be identified by typical morphology, inability of the organism to grow without cystine, and agglutination by a known active serum. As the organism does not occur consistently in the blood, little reliance can be placed upon the use of blood cultures.

2. Animal inoculation

   a. Blood sample

      White or guinea pigs are injected with citrated blood: The dosage for mice is 1 cc. and for guinea pigs, 5 to 10 cc. If organisms are present, death usually occurs within 5 days, and the typical spotted liver and spleen are found at necropsy. Small pieces of liver and spleen, and heart's blood, should be used to inoculate blood-glucose-cystine agar. A positive diagnosis is established by isolating the organism from colonies and identifying the organism.

   b. Ulcer-scrapings

      Ulcer-scrapings may be obtained from the infected wound or developing ulcer by careful, light scraping of the wound with a sterile scalpel. For the demonstration of typical pathology and for the isolation of the organism mice or guinea pigs may be inoculated with the scrapings suspended in salt solution.

   c. Sputum

      In cases of pneumonia caused by Pasteurella tularensis, sputum may be used for animal inoculation.

Laboratory diagnosis after the first ten days of the infection

1. Agglutination test

   The agglutination test usually becomes positive between the tenth and sixteenth days. A negative agglutination test before the tenty day, followed by a positive test in low dilution, such as 1:20 or 1:40, after the tenth day, gives the earliest possible diagnosis by agglu-

tination. After the fourteenth day the agglutination test is usually of high enough titer to establish a positive diagnosis without a previous negative test. A single test is diagnostic if positive in a dilution of 1:80, or above.

2. Isolation of Pasteurella tularensis from ulcer

The probability of isolating the causative organism from the ulcer is high until healing commences, about the fifth or sixth week. Heavily contaminated material from an ulcer can be scarified into the abdominal skin of a guinea pig.

3. Isolation of the organism from lymph nodes.

Late in the course of the infection, the organism may be isolated from the wall of the suppurating or incised lymph nodes, providing material is curetted from the wall of the lesion. Pus obtained by drainage from a suppurating lymph node is usually sterile.

Treatment

Serum therapy

The most extensive studies of specific serum therapy for tularemia are those of Foshay.[16] Serums from horses and goats hyperimmunized by a prolonged course of injections of bacterial suspensions, made up of a pool of eight to twelve strains of Pasteurella tularensis, have been used.

From detailed observations on 600 treated patients, Foshay concluded that serum treatment results in prompt relief of symptoms, a reduction in incidence of complications, a shortening of the period of disability, and some reduction in the mortality rate. The average period of disability in the 600 treated patients was 2.22 months; in 518 control patients that did not receive immune serum, it was about a month longer, 3.36 months. The incidence of suppurative adenitis was reduced from 56 per cent in the control group to 42 per cent in the treated group. The fatality rate was 6 per cent in the controls, whereas in the treated group it was 3.8 per cent. All measurable results were best if serum was given during the first 12 days of illness, and Foshay does not recommend the routine use of serum after the first two weeks of illness if the course of the disease is favorable.

The amount of serum required to produce a favorable result was greater in patients with tularemic pneumonia than in those without pulmonary involvement. Because of the unfavorable effect of tularemia on the heart in patients with previous rheumatic or coronary heart disease, these conditions were considered indications for doubling the usual dosage of serum. A sustained high fever associated with delirium or other psychic changes is interpreted as evidence of septicemia and carries with it a very poor prognosis. Such symptoms are "an extremely uegent indication for immediate serum administration" in maximum amounts.

A high incidence of serum sickness was observed, presumably because the whole serum was employed. It is Foshay's opinion that valuable antibodies are lost by concentration procedures commonly employed with other antiserums. Such procedures eliminate the serum albumens and other inactive materials and are generally recognized to reduce the incidence of unfavorable reactions. Serum sickness was observed in more than half of the patients treated and in 16 per cent it was severe. The incidence of severe reactions was only half as great in patients receiving goat serum as in those given horse serum. The two types of serum were equally effective therapeutically.

Experimental studies of antitularemic serum have been reported by Francis and Felton.[18] Using antiserum prepared in rabbits, sheep, and horses, and one specimen of human convalescent serum, they were unable to protect mice against from 1 to 10 lethal doses of Pasteurella tularensis. Elsewhere Francis[19] has indicated that in view of the low mortality associated with tularemia, the high incidence of severe serum reactions encountered by Foshay, and the inability of experimental tests to yield evidence of protective qualities of antitularemic

serum, the general use of antiserum in this disease is not to be recommended.

General treatment

While serum therapy does seem of value in the treatment of tularemia if used early in the course of the disease, the general treatment is symptomatic. Most important is rest in bed and careful nursing. Lymph nodes should be incised when fluctuation develops.

Sources of Infection

Some thirty or more sources of human infection have been incriminated in tularemia. Rabbits are more important than all others, as several species (cottontails, showshoes, and jack rabbits) can infect human beings. Hunters, marketmen, and housewives are infected while dressing rabbits shot in the wild. Domestic rabbits, although susceptible to the disease experimentally, do not serve as a source of human infection. In most instances, infection is introduced through abrasions in the skin, either previously present or acquired from a splinter of bone or a slip of the knife during the dressing of the rabbit. In some cases, the organism penetrates the intact skin. However, it is probably true that in a good many cases infected rabbits are dressed by persons who escape infection. One such case came to our attention when a forester performed a necropsy on a freshly killed rabbit with his bare hands, and brought the liver of the rabbit and engorged ticks from it to us. Pasteurella tularensis was isolated from the ticks; the liver, which had been fixed, exhibited typical gross and microscopic lesions of tularemia. The forester remained well. Agglutination tests showed no antibodies against Pasteurella tularensis in his serum, good evidence that he had had no previous immunizing infection.

In a series of 600 human cases of tularemia studied by Foshay, the source of infection in 519 was rabbits. According to Francis, these animals are the cause of more than 90 per cent of human cases in the United States.

Ticks of the genus Dermacentor are a second source of infection that is particularly important in Minnesota. Whereas only 6 of Foshay's 600 cases could be traced to the bite of a tick, this was listed as the most probable source of infection in 119 of a total of 396 Minnesota cases, according to data of the Division of Preventable Diseases of the Minnesota Department of Health. The rabbit tick (Haemaphysalis leporis-palustris), perhaps the most important vector of the disease in nature, is of negligible importance as a cause of human disease since it does not bite man.

Deer flies have been known as a source of tularemia since Francis[6] (1919) first proved the identity of "deer-fly fever" in Utah with the "plague-like disease of rodents" that McCoy[2] had described in California. In the series of 396 Minnesota cases, "horse fly or deer fly" was given as the most probable source of infection in only five cases. In Foshay's series, only one case was ascribed to this cause. In 1935 (Hillman and Morgan[20]) an epidemic of 30 cases of tularemia developed in a C.C.C. camp of 170 young men in Utah. Evidence pointed strongly to deer flies as the source of infection. These insects, then are an uncommon cause of human tularemia but may, under special circumstances, become an important source of the disease.

Cats are naturally resistant to tularemia but serve as a source of human infection by mechanical transmission of the causative organism from the carcass of an infected animal to man. In 23 of the Minnesota cases, infection was acquired from cats. Other mammals that have been considered as the source of human tularemic infections include dog, badger, mink, squirrel, mouse, weasel, sheep, beaver, deer, opossum, tree squirrel, red fox, ground squirrel, coyote, skunk, muskrat, ground hog, and raccoon. Game birds may also cause the disease in man. Cases have been traced to ruffed grouse, quail, pheasant, sage hen, and a hawk.

In eastern Europe, the principal reservoir of the disease is the water rat (Arvicola amphibius). More than 1,000

cases occurred in Russia in 1928 among persons who skinned these animals for their pelts.[21]

General Distribution of Tularemia

Geographical distribution

Tularemia appears to be distributed in a great variety of animals, birds, arthropods, and insects throughout the entire Northern Hemisphere. The disease at the present time is unknown in the Southern Hemisphere, although rabbits and Haemaphysalis ticks similar to those of the Northern Hemisphere are found there. Wherever it is known, tularemia is transmissible to man. In the Northern Hemisphere the infection appears to be absent at the arctic timberline and farther north. Green was unable to find the disease in snowshoe rabbits on the west coast of Hudson Bay. Not a single tick nor other external parasite was found on any of the specimens of showshoe hare or ptarmigan collected in the locality of Churchill, although the season was right for the greatest abundance of ticks. Tularemia in snowshoe hares and grouse, and in the ticks they carried, was easily demonstrated 250 miles south of Churchill. From the region just below the northern timberline, tularemia extends southward to the Gulf of Mexico.

Seasonal distribution

In the northern region of its distribution, tularemia seems to be limited to midsummer, since transmitting agents appear only during a short summer season. In the latitude of Minnesota, the disease is definitely more common among wild animals in the spring and fall than during midsummer. In any area that has cold winters, the disease is almost entirely absent from animals during the winter months because of the hibernation of ticks. An occasional chronic infection of a pulmonary type may be found in snowshoe rabbits during midwinter in such a cold region as central Minnesota. However, the disease is generally quiescent during the cold months and does not spread. In the southern states, the disease is known, from human infections, to be active in the wild in autumn and in the early winter months. The senior author found ticks present on rabbits and quail collected in the Gulf states during February, and tularemia was isolated from a number of specimens. It seems probable that in the southern states tularemia has a fall-winter-spring distribution rathern than a spring-summer-fall distribution, as in the northern states. Since the distribution of tularemia seems closely related to the effect of seasonal weather changes upon ticks, its distribution in mountainous regions must be closely related to altitude, which governs seasonal changes.

Local distribution

Tularemia, in any given area in which the disease is found, is apt to be a much more common infection of wildlife forms than is indicated by the occurrence of human infections. The variety of small animals and birds susceptible to tularemia, the abundance of ticks, and the persistence of the infection in ticks for many months make almost certain the contir ual endemic existence of tularemia in any area, either farm land or woodland. On farm lands, mice, ground squirrels, gophers, woodchucks, and game birds form an extensive animal reservoir; and Haemaphysalis ticks, wood ticks, and deer flies also harbor and transmit the infection. Dogs, wild carnivores, and grazing animals, although of low susceptibility tc tularemia, are an important factor in amintenance of the disease, as they feed adult stages of the wood tick. The immature stages of the wood tick are important in the transmission of tularemia among mice and other small rodents. Almost any highly cultivated farm may carry a wild-animal population sufficient to perpetuate endemic tularemia, even though presence of the animals may not be evident to the casual observer.

Animal-Susceptibility

Animals and birds of different species show various degrees of susceptibility to tularemia. Violent infections seem to be usual in the cottontail rabbit and the muskrat. On the other hand, many species, such as the fox and the ring-necked pheasant, are so resistant to the disease that they probably exhibit in nature only the subclinical infections seen in these

species when given the disease experimentally. The human infection, it seems, may be obtained as readily from animals with tularemia of the subclinical type as from animals with highly virulent infections. Thus, cases of tularemia have been obtained from the ring-necked pheasant and the fox, species in which only the subclinical experimental infection is known. Contraction of the human disease apparently depends only upon contact with an infected animal, but the severity of the infection in man depends upon the individual's susceptibility and also, as will be discussed later, upon the virulence of the particular strain of tularemia for human beings. The principal significance of high susceptibility in animals is that it facilitates the spread of violent epizootics among certain species. Moreover, animals in which a profusion of the organism occurs in the blood stream pass the infection to ticks to a greater degree.

It is now recognized that all of the rodents have a relatively high susceptibility to tularemia, but considerable differences do occur among species within the same general group. Thus the disease is extremely virulent and highly fatal in cottontail rabbits, while in snowshoe hares it is so mild that infected hares commonly recover. In general, the ungulates appear to be resistant to the disease, although human infections have been obtained from pits. From information thus far available regarding dogs, foxes, raccoons, and cats, the carnivores, also, seem to be rather highly resistant to tularemia, but sometimes suffer from mild or subclinical infections. As human cases of tularemia have been contracted from opossums, it is most probable that this highly primitive marsupial is susceptible to the infection. Tularemia is likewise a disease of birds. It seems to be confined almost entirely to certain game species, but this assumption may be due to failure to look for the disease in other species. Tularemia has been identified in the quail, the ruffed grouse, the sharp-tailed grouse, the pinnated grouse, and the sage hen, as well as in the imported ring-necked pheasant. In our studies the disease has also been identified in a nestling owl. The common occurrence of Haemaphysalis ticks on both rabbits and game birds makes the latter of considerable significance as part of the animal reservoir of tularemia and as a source of human infection.

Epizootics and Epidemics

Epizootics of tularemia among wild animals appear to be a common and somewhat regular occurrence. When certain conditions of contact with human beings come into play during an extensive epizootic, an increased occurrence of this disease among human beings may take place that could be described as an epidemic. Such seems to have been the case in Russia, where mass infection of the human population was reported in 1928[21], and in the State of Illinois in 1938 and 1939. In both cases an epizootic had first spread in an abundant animal population. In one Russian outbreak, floods dislodged water poles, and thus brought about contact with human beings, who collected the animals for fur. In Illinois an epidemic of tularemia seems to have developed when the hunting season was opened early during a mild fall. As a result, hunters bagged an unusually large number of cottontails infected with tularemia, and more than a thousand people contracted the disease. The occurrence of epizootics of tularemia among animals is basic to the hazard of human infection. Among wild animals and birds there is a continuous movement of the disease. Within a single species, upward surges of the disease come with the development of large populations. The infection moves from one animal population to another. This movement is directed by the multiple-host-relationship of ticks and other parasites. When snowshoe hares die off, their dependent tick population migrates to grouse, mice, or other animals. The ticks carry with them the tularemic infection, which becomes further disseminated among available hosts as the new host species reach periods of abundance. While the details of these interspecies relationships are as yet only incompletely understood, the Lake Alexander studies have defined certain of the relationships and the general pattern in which they operate with respect to hares, rabbits, and grouse.

Tularemia as a Water-borne Disease

Evidence that tularemia may occur as a water-borne disease has come during recent years from several different sources. In 1936, Karpoff and Antonoff[22], reported the bacteriologic and epidemiologic evidence for the spread of tularemia thrugh water to a grup of field workers in the U.S.S.R. A careful study was made of 43 of those infected. An undetermined number of others contracted the disease in the same epidemic. In the Middle East, human disease was traced to water from a stream "probably infected by excreta of rodents on the bank or by a dead animal in the water."[23]

Interest in the spread of tularemia through water in this country has been heightened in recent years by epizootiologic studies of the disease in Montana, carried on chiefly by the U. S. Public Health Service. Tularemia has been found to occur as an infection of beaver inhabiting numerous streams in various parts of Montana. Jellison and his associates[24] reported the deaths of beavers from eight different localities in that state. In one instance more than 150 beavers were found dead along one river. Eleven of these animals from seven of the eight localities were studied bacteriologically, and all but one yielded cultures of Pasteurella tularensis.

The source of infection of beaver is uncertain. Biting arthropods are apparently not the vector, as the epizootics studied occurred principally during the winter (November through February), when ticks, biting flies, and mosquitoes are at a minimum. No blood-sucking arthropods were found on the beavers.

Water from four of the streams was tested and in all four the organism was demonstrated readily. In some cases as little as 1 ml. of water proved infective for guinea pigs. This indicates a tremendously high degree of infectivity of the water. Repeated tests of water from one stream showed Pasteurella tularensis to be present over a period of 31 days.

In seeking a correlation of the occurrence of tularemia in beaver with its occurrence in land animals, the writers tested six field mice found dead near the streams studied. All six were positive for Pasteurella tularensis. It is suggested that water may become contaminated from infected land animals, or that when beaver go on land in search of food they may become infected in some way from land animals.

The extensive occurrence of Pasteurella tularensis in streams of water in Montana suggests that human infections caused by contaminated water will probably be observed in this country, as they have been in Russia and the Middle East.

The Wild Animal and Arthropod Reservoirs of Tularemia

Tularemia is a widespread disease of wild animals and birds. Among the species considerably affected by this disease, its spread is accomplished chiefly through transfer of the infection by ticks and biting flies. The rabbit tick, Haemaphysalis leporis-palustris, seems by far the most important vector in the spread and maintenance of tularemia. The Haemaphysalis ticks have a world-wide distribution, and are found on both animals and birds of great variety. Their preferred host is evidently the rabbit, especially the snowshoe hare, since they attain their greatest abundance on this animal. The host of second preference appears to be various species of grouse. However, it is obvious that the preference of these ticks are dictated to a great extent by the availability and habits of the animal host. Other Haemaphysalis ticks, such as the grouse tick, Haemaphysalis cinnabarina, are less active in the maintenance of the disease in North America. Although a great variety of ticks that infest animals and birds are known to be associated with the transmission of tularemia, in most cases it is not known how extensive a role each individual species plays. In the case of some species of anthropods, systematic studies of their relatipnship to the spread of tularemia have been pursued under natural conditions. The following description includes

most species that have been series that have been seriously incriminated in the spread of tularemia.

Transmitting agents

Tularemia is transmitted among animals and man by a variety of ticks and fleas, and by the deer fly. It is probable that the disease is at least occasionally transmitted in nature by other agents not now recognized. The body louse has been shown to be capable of transmitting the experimental disease, but there is no evidence that it ever does so naturally. The mosquitoes have been suspected to be vectors of tularemia, but it has not been proved that they are. The stable fly (Stomoxys calcitrans) would seem to be a possible carrier but has not been incriminated. Those forms for which transmission has been proved and accepted include species described below.

Arthropods. Haemaphysalis and Dermacentor ticks are true biological hosts of Pasteurella tularensis. This organism invades the tissues of the tick, in which it grows as an intracellular parasite. The organism grows in profusion in the epithelial cells lining the gut and is eliminated in the feces. The relationship between the organism and the tick appears to be one of commensalism, in that growth of the bacteria does not seem to harm the tick to the extent of causing inconvenience or fatality. The relationship of Pasteurella tularensis to the tick is such that primary adaptation of this organism may be considered parasitism of the tick, with infection in animals simply a means of transfer from tick to tick.

1. Hereditary transmission in ticks

Ticks have four stages in their life chcle: egg, larva, nymph, and adult. It has been shown by Parker that tularemia may be strnsmitted from one stage to another in this life cycle. Female ticks may lay eggs which, on hatching, yield larvae that carry tho infection. These larvae, after feeding and moulting, produce numphal stages in which a certain percentage of individuals are infected. While this so-called hereditary transmission" has been demonstrated in the case of both Haemaphysalis and Dermacentor ticks and is of great importance in maintaining the disease in nature, it is not an extensive or long-continued process. Infected female ticks may lay eggs that are not infected. Moreover, if the infection is transmitted, it does not persist longer than four stages, or through a complete life cycle. Of utmost importance, however, is the fact that infected larvae give rise to infected nymphs, and that infected nymphs give rise to infected adults.

2. The Haemaphysalis ticks

Haemaphysalis ticks are apparently the most common ticks distributed throughout North America. They are found in greatest abundance on rabbits and grouse in the northern wilderness areas. In Minnesota[25] during late summer their numbers may reach as many as 15,000 on a single snowshoe hare or ruffed grouse. They infest a variety of animals and birds. Since they have been seen on migrating birds, they are apparently transported throughout the length of North America and possibly to and from South America. While they are probably the most important ticks in transmitting disease among animals, the Haemaphysalis do not feed on larger animals, such as deer or dogs, and they do not bite man. In the region of Minnesota these ticks appea in April and increase in numbers throughout the summer and early fall, Peak infestation occurs during the latter half of August, or the first half of September, depending upon the Interval before the onset of cold weather. In climates comparable to that of Minnesota, the ticks are reduced to small numbers on animals early in October. Most rabbits and grouse are free of ticks by the first of November.

a. Relation to animal population

The Haemaphysalis ticks have been shown to be extremely sensi-

tive to changes in the size of their host population. With the increase in numbers of rabbits in the Lake Alexander area, the tick population mounted rapidly.

b. Infection in Haemaphysalis ticks

A study of the Haemaphysalis tick in central Minnesota over a period of ten years has shown a percentage of infection varying from 0 to 0.24. The highest percentage of infection has been found during the spring months when the ticks emerge from hibernation and during rarly fal when the ticks go into hibernation. As these ticks are the most numerous of any species and are usually present in large numbers, they are the best index of the occurrence of tularemia in any area.

c. Tick movements

The rabbit tick, Haemaphysalis leporis-palustris, is present in such large numbers on rabbits and grouse in Minnesota that it far exceeds any other variety of tick. As rabbits and grouse live in the same territory and utilize the same dusting places, it becomes obvious that there is a constant interchange of ticks between rabbits and grouse. The difference found in the virulence for guinea pigs of Pasteurella tularensis obtained from ticks indicates that ticks that obtain their infection from grouse are apt to be found in small numbers on rabbits, and ticks that obtain their infection from rabbits are apt to be found in small numbers on grouse. From the close association of rabbits, meadow mice, and other small rodents, it would seem that there is a constant interchange of Haemaphysalis ticks among many species of rodents that are highly susceptible to tularemia.

d. Importance of Haemaphysalis ticks

The Haemaphysalis ticks are undoubtedly the most common transmitting agent of tularemia among wild animals. They habitually harbor the causative organism during hibernation in the winter months; and because they attach themselves to many species of small birds, they are probably responsible for the continuous transfer of tularemia from one area to another throughout North America.

3. The Dermacentor ticks

The Dermacentor ticks, like the Haemaphysalis, are four-stage ticks. The role of Dermacentor ticks in the spread of tularemia is in most respects similar to that of Haemaphysalis. The principal diferences are that the adult stage of the Dermacentor tick feeds only on large animals, although it may be found occasionally on grouse. The adult stage is seldom seen on rabbits or small rodents, while the larval and nymphal stages appear to feed entirely on mice, gophers, and other species of the smallest rodents. The adult stage attaches itself to man and is a common means of transmitting tularemia to human beings.

a. Distribution of Dermacentor

Species of Dermacentor are distributed generally over the North American continent. They are absent in some localities and exceedingly abundant in other There are three species, distributed as follows:

(1) Dermacentor variabilis, the wood tick or common dog tick is widespread east of the Rocky Mountains. It is found in both northern and southern regions.

(2) Dermacentor andersoni, often called the spotted-fever tick, is distributed in the mountainous area of the western section of the United Stated. This tick is the

common source of human infections of spotted fever, but appears to be equally as much infected with tularemia as is Dermacentor variabilis.

(3) Dermacentor occidentalis, found in the region of California, has likewise been shown to carry and transmit tularemia.

b. Seasonal occurrence of Dermacentor

The Dermacentor ticks are highly seasonal. The adults appear early in the spring as the snow melts, and reach their highest abundance in late spring. Their numbers begin to decrease with the onset of hot weather, and they have all gone into aestivation-hibernation by midsummer. An occasional tick is found attached to a large animal in late summer or even early fall.

c. Tularemia in Dermacentor

Like the Haemaphysalis ticks, the Dermacentor ticks are true biological hosts of Pasteurella tularensis and transmit the organism from one stage of their life cycle to the next. The infection of tularemia in adult Dermacentor variabilis was obtained by the larval or nymphal stage feeding on an infected animal during a previous year. The strain of tularemia carried by adult wood ticks is, therefore, most likely to have come from some small rodent, generally a species of mouse, and more particularly, the meadow mouse. In Minnesota studies of the wood tick over a period of ten years has yielded a percentage of infection varying from 0 to 0.57. The latter figure represents one infected tick in 175.

d. Transmission of tularemia to man by wood ticks

A wood tick sinks its head into the skin, and upon filling itself with blood, forces out its intestinal contents, which are deposited upon the skin. The organism may penetrate the unbroken skin or may contaminate the wound left upon removal of the tick. The fingers used in handling the tick also become contaminated and the organisms may be transferred from them to the mouth or to the eye.

Insects. Two species of blood-sucking insects have been definitely shown to transmit tularemia: the deer fly and the common rabbit flea.

1. The deer fly (Chrysops discalis)

One of the original descriptions of the tularemia was given in 1911 in Utah by Pearse, who called the disease "deer-fly fever." After having shown that "deer-fly fever" was caused by Pasteurella tularensis, Francis experimentally demonstrated the transmission of the organism by the deer fly. Whether or not the deer fly is a true biological host or a mechanical carrier has not been determined and it is not known to what extent the deer fly is responsible for transmission and maintenance of tularemia among animals. The great importance of this vector is its ability to transmit the disease to man; it is one of the principal means of human contact with tularemia in some geographical areas in the western section of the United States.

2. The rabbit flea (Siphonaptera)

The flea seen on cottontail rabbits in Minnesota has been found occasionally to harbor Pasteurella tularensis. From this it is inferred that the flea is a means of transmitting the disease among wild animals, although it is evident that it is not nearly so significant a vector as the rabbit tick. Fleas are found more commonly on cottontail rabbits than on snowshoe hares. They appear to thrive on cottontail rabbits, since this animal spends a good share of its time in shallow burrows underground, and the fleas may therefore

maintain their activity on the cottontail in cold climates throughout the winter. The cases of tularemia that occur during winter months in such climates as that of southern Minnesota and Wisconsin would seem to be due to infection from the rabbit flea. Cottontail rabbits in the winter may at times carry from 50 to 100 fleas.

Transmission of tularemia to ticks, deer flies, and fleas

The extent to which transmitting agents may become infected with tularemia while feeding on an infected animal or bird seems to depend upon the virulence of the infection in the animal. In the cottontail rabbit, which usually suffers a violently fatal infection of tularemia, the organisms are found abundantly in the blood. Consequently, most of the ticks feeding on an infected cottontail become infected with the organism. Because of the mild nature of the infection in snowshoehares, the organisms are not abundant in the blood of this animal, and most of the ticks found on a snowshoe hare that has tularemia are not infected with the disease.

Tularemia in mammals

Tularemia has thus far been associated with all groups of mammals except the Edentata and Insectivora. Since the infection is found in hirds, as well, it is probable that all groups of mammals are subject to either a mild invasion or a severe infection by Pasteurella tularensis. The recent discovery that this organism may vary greatly in its virulence for any animal species and that subclinical infections may be demonstrated in snowshoe hares and even in guinea pigs, completely changes previous ideas of susceptibility. Special strains of Pasteurella tularensis may be highly virulent for certain species of animals that we now consider rather resistant.

Marsupilia. The opossum (Didelphis virginiana) has been found to be a source of human infections, although the susceptibility of this animal has not yet been studied.

Rodents. The rodents as a group have been found so highly susceptible to tularemia that this disease is often considered primarily a disease of rodents. However, within this group there is a great difference in susceptiblilties.

1. Cottontail rabbit

Of all species of rodents, the cottontail rabbit appears to be the most susceptible. This is of special importance, since man's contact with the cottontail is greater than with any other rodent. It has been estimated that 70 per cent of the shotgun shells manufactured are fired at cottontail rabbits. This animal is subject to both ticks and fleas. It suffers from a violent and fatal infection of tularemia. In the Lake Alexander studies, no evidence was ever found of a cottontail surviving an infection of tularemia, and rarely was a cottontail picked up that had died of any other disease. An infected cottontail produces a very high percentage of infection in the ticks feeding upon it, and in the Minnesota area this rabbit appears to be principally responsible for the infection of Haemaphysalis ticks.

2. Snowshoe hare

The snowshoe rabbit found in central and northern Minnesota seems to be relatively resistant to tularemia. Pasteurella tularensis is often isolated from the ticks on showshoe hares when the organism cannot be obtained from the animal itself. Tularemia is as apt to be obtained from a snowshoe shot while apparently well as it is from one found dead. The percentage of infection in ticks found on snowshoe hares infected with the disease is not high, as it is in the cottontail rabbit. A considerable percentage of snowshoe hares shot at random have a positive agglutination titer against Pasteurella tularensis. All of these facts indicate that the snowshoe hare is not highly susceptible to tularemia.

3. Jack rabbit

Jack rabbits have been intestigated by Francis anf found to be commonly infected with tularemia. The jack rabbit is closely related to the snowshoe hare and dies off periodically, as does the snowshoe. However, the periodic die-off of the latter has been shown not to be due to tularemia. It may well be that the periodic decimation of the jack rabbit, like that of the snowshoe, is due to some cause other than tularemia.

4. Meadow mouse

An epizootic of tularemia among meadow mice has been described. It is not known to what extent tularemia is responsible for the periodic die-off of wild-mouse populations, which occurs at about four-year intervals, but this disease has been suggested as a logical explanation of the phenomenon.

5. Muskrat

Muskrats, which are closely related to the meadow mouse, suffer from violent experimental infections upon inoculation. Numerous cases of human infection have followed the handling of muskrats, although the trapping of this animal usually is not done at times when tularemia is highly active in other animal species.

6. Beaver

Beavers are highly susceptible to the experimental infection, and the death of beavers from tularemia in the wild has been described as the cause of stream-contamination.

7. Ground squirrel

Tularemia was originally found as a disease of ground squirrels, which are apparently highly susceptible and suffer from epizootics of the disease.

8. Squirrel

Cases of human tularemia have been reported from contact with tree squirrels. Tree squirrels, however, are rather free from external parasites and it would seem doubtful that tularemia is a common infection in them.

9. Woodchuck

As cases of human tularemia have also been described from contact with woodchucks, it is indicated that these animals are susceptible to the infection.

Ungulates. The ungulates appear to be highly resistant to tularemia, although young lambs with heavy tick infestations have contracted fatal infections. Human infections have been obtained from the bite of pigs, but it is not known whether the pigs were infected or whether they mechanically transferred the infection after eating a rabbit carcass.

Carnivores. The carnivores as a group are relatively resistant. They appear to allow, not uncommonly, a symptomless invasion but only in a few unusual cases does a violent case of tularemia develop. Upon inoculation, young foxes usually show no symptoms. Inoculation of cats may produce a symptomless invasion or a mild infection. Raccoons, dogs, and coyotes seem to have a similar resistance to the disease.

Fluctuations in the Incidence of Tularemia

Since tularemia is found in species of animals which make up resident wildlife populations, the prevalence of the disease is related to the abundance of these animals. Throughout the entire Northern Hemisphere there is a continuous ebb-and-flow of the animal and bird life which constitute its permanent residents. The periodic fluctuations in numbers were first described by Seton[26] in 1911, and have since been studied by numerous investigators. As certain species attain great abundance, the the crash, or die-off, period occurs, which reduces that species to scarcity or even extreme rarity. After a period

of low population, the species increases until it is again one of abundance. There are, in general, two such periods of fluctuation. One cycle of about ten years affects rabbits, grouse, Canada lynx, the fox, and some of the other fur-bearers. The other, a cycle of about four years, affects smaller rodents, such as mice, ground squirrels, and lemmings, together with arctic fox, which, like the rodents, has a high rate of reproduction. The years of greatest scarcity of all wildlife occur at such times as there is coincidence between the law of the ten-year cycle and the law of the four-year cycle. The fluctuations of animal populations are accompanied by fluctuations in populations of ticks and other parasites. The relationship between populations of animals and parasites is shown in the accompanying chart, which records the rise-and-fall of the snowshoe hare population in central Minnesota thru the years 1932 to 1940. The tremendous rise-and-fall of the number of ticks feeding on hares is recorded in such a way as to depict its dependence upon the hare population. Systemiatic studies on the occurrence of tularemia during this period demonstrated that this disease was common both in the ticks and in the animals when the populations were high, but that the percentage of infection declined rapidly with the decline in the animal population. Movements of ticks from species declining in population to species whose numbers are increasing are forced migrations, which serve to spread this disease through many varieties of animals and birds. The basic laws of the occurrence of tularemia in animal reservoirs of the disease are concerned with the fluctuations of animal populations and the migrations of transmitting agents.

Occurrence of Tularemia in Minnesota

The first cases of tularemia known to occur in Minnesota were reported in 1926, when 3 were recognized. For a number of years subsequently, the rise in number of cases was probably due to recognition of more cases by physicians. The following table lists the annual numbers of cases of tularemia in Minnesota as reported to the Minnesota Department of Health. The large number of cases from 1933 to 1935 corresponded with the general die-off period of snowshoe rabbits, cottontail rabbits, and ruffed grouse in the State. No significant rise in the number of cases in Minnesota occurred during 1938 and 1939, when a sharp increase in the number of cases of tularemia was noted in the more southern of the central states, such as Illinois and Missouri.

Occurrence of Tularemia in Minnesota, 1926-1943

1926	3	1932	41	1938	20
1927	9	1933	46	1939	23
1928	5	1934	62	1940	13
1929	2	1935	47	1941	20
1930	10	1936	31	1942	21
1931	19	1937	28	1943	13

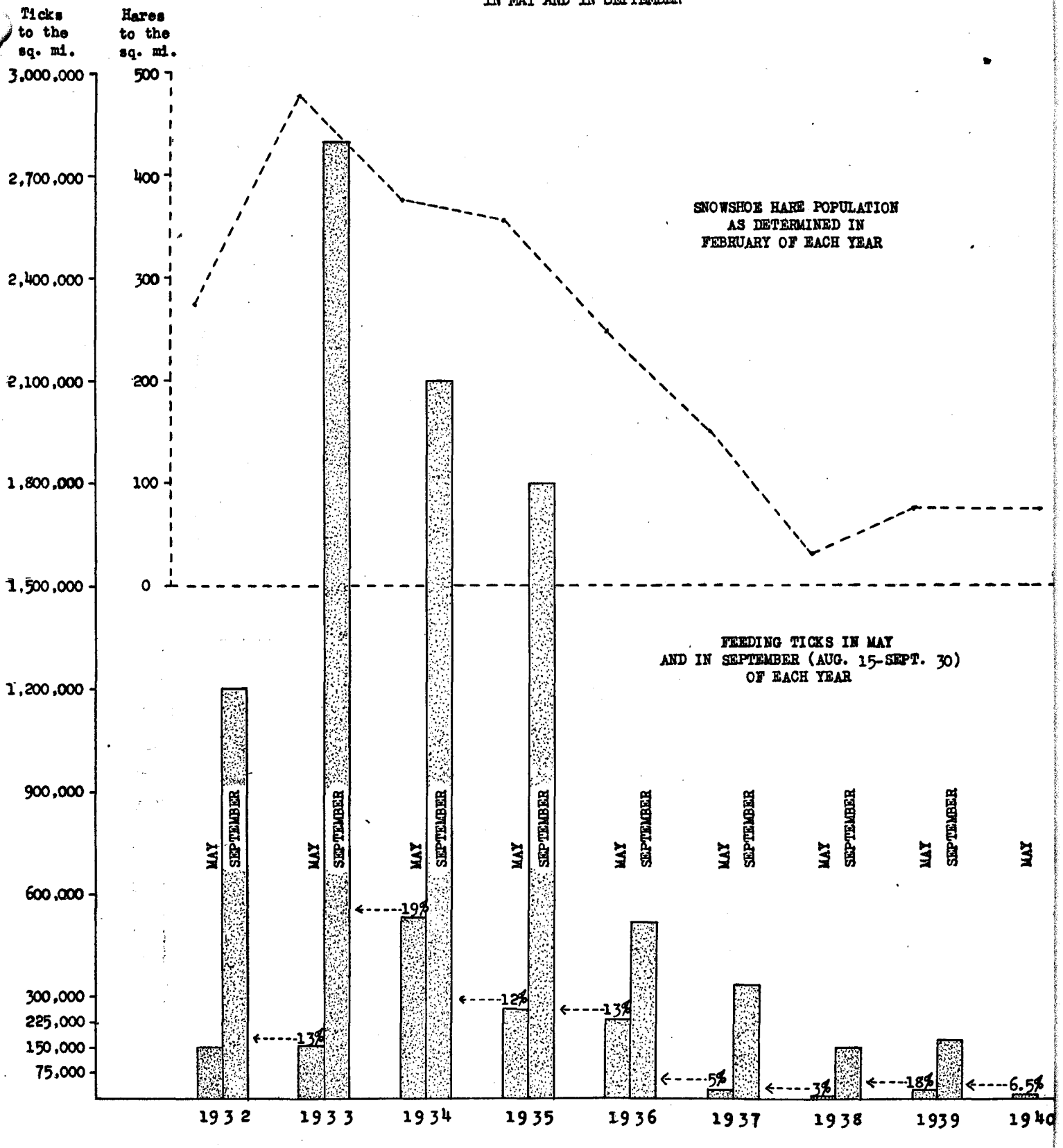
Specific Prevention of Tularemia

An experimental vaccine has been developed by Foshay[27] that consists of a suspension of bacterial cells detoxified by treatment with nitrous acid. Three doses of the killed organisms are injected at weekly intervals. Use of this vaccine among laboratory workers seems to have eliminated laboratory infections. Previous to its use, cases of tularemia occurred periodically in laboratories where experimental work was regularly conducted on this disease.

General Prevention of Tularemia

Since about 90 per cent of human cases of tularemia originate from contact with rabbits, the control of tularemia in general lies in the prevention of contact with infected cottontail rabbits. In northern states, such as Minnesota, Michigan, and Wisconsin, the incidence of tularemia is low compared with the incidence in more southern states, such as Indiana, Iowa, Ohio, Missouri, and Illinois. During the latest epizootic of tularemia among cottontail rabbits in the north-central states, which occurred during 1938-39, the average annual number of human cases in Minnesota was only 21; the average for each year was 11 in Michigan and 36 in

RABBIT POPULATION AS RELATED TO FEEDING-TICK POPULATIONS
IN MAY AND IN SEPTEMBER



Note: The percentage at the head of each column for May is the estimated proportion of rabbit ticks that survived throu the winter.

Wisconsin. The more southern states suffered a much greater annual average incidence for the two years: Indiana, 167, and Illinois, 477. The lower incidence of tularemia in the northern tier of states may be due in part to less occurrence of tularemia among wild animals in general and cottontail rabbits, in particular. However, the difference is more likely due to several factors. Cottontails are more numerous and are hunted to a greater extent in certain states. The milder climates of southern states are probably responsible for the presence of a significant number of ticks after they have disappeared from rabbits in northern regions. Fleas are apparently present in large numbers on cottontail rabbits throughout the winter.

In climates such as that of Minnesota, prevention of tularemia is undoubtedly accomplished to a considerable extent by delaying hunting seasons until after cold weather sets in. To what extent tularemia can be prevented by this means in more southern states is not yet clear. Intensive studies on the seasonal occurrence of ticks and fleas, and other transmitting agents in different regions are necessary, if the dates of hunting seasons are to be adjusted, as has been done in the State of Minnesota, to aid the prevention of tularemia.

Cleanliness in the handling of wild game is always to be advised; and specific advice should be given to wash the hands in several changes of soap and water after cleaning any wild game. No one should clean game when wounds or brasions are present on the hands.

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III. GOSSIP

Dr. Clarence Dennis desires to thank all for assistance, financial and otherwise, in sending our Christmas remembrance to our hospitals overseas. More than $300.00 were collected and divided equally between U. S. General #26 in North Africa or elsewhere, and U. S. Station Hospital #31, in the Southwest Pacific. This station hospital is our junior representative as far as size is concerned, but not as far as spirit is concerned. The box contained tin foodstuffs - olives, fish and other delicacies; lipstick and powder, Christmas party materials, 36 pounds of candy, handkerchiefs for everyone, copies of current magazines, 12 cartons of cigarettes, soap for all, candy suckers, 52 pounds of fruit cake, a football, baseballs and other game materials. Dr. Dennis wishes to especially thank Miss Gilman, Miss Corliss, Mrs. Nelson, Miss Tomkins, Mrs. Finken and Miss Weeds, who spent many extra hours helping pack the materials for shipment. He also wishes to thank in the name of the units, everyone of our employees and staff who contributed. This is the second year we have tried to say Merry Christmas to those who are away, and we now know that some of the materials have arrived for the boxes were opened and acknowledgment received. Last year a good deal of the material failed to arrive in good shape. Word has been received from one of the units that things are looking up and that they are enjoying their new surroundings. When Captain Albert Snell, USNR, was here, he told of seeing some of the men from station hospital #31, and brought greetings from them...Christmas for our patients was an enjoyable event. The Traffic Club of Minneapolis turned out 75 strong to trim the trees, which had been put in place by the housekeeping department. They brought 2 or more gifts for the more than 45 children who were in the hospitals during the holidays. In addition, they brought 250 baskets of fruit for the other patients, and supplied candy for the nurses. They came on Christmas Day to sing Christmas Carols and again lived up to their reputation of being one of the most generous organizations in remembering hospital patients. For many of our children it was the first time they really received Christmas presents. In each instance it was a choice of the patient. At Minneapolis General Hospital the Minneapolis Kiwanis Club remembered the 52 children there with toys galore. The old people enjoyed Santa Claus almost more than the young people, for Santa Claus at the Minneapolis General Hospital speaks in several tongues. The nurses and staff supplied the trees and trimmings and sang the carols. Every patient received a handkerchief. At Ancker Hospital, St. Paul Rotary Club remembered the children with toys. The Sunshine Society brought cakes and jam and fruit for the elderly people. The Catholic Daughters supplied cakes, candies and other good things to eat and in addition brought stamped Christmas greetings, all ready for the patients to send. All the private hospitals had celebrations and it would appear that Christmas was quite an event this year...I had the opportunity to go on the radio on Christmas morning, as it was our regular Saturday date, and tell the public about some of the more pleasant sides of hospital life. The holidays were most enjoyable, except for those who wished to indulge in snow sports. There was plenty of ice for skating and the weather was ideal. At Rochester, Minnesota, clinic members and their families skated down the river and had outdoor picnics. The New Years holiday was also characterized by mild weather - in fact, sports writers called attention to the unusual fact that we could have had bowl games under more ideal circumstances than in some of the places where they were scheduled...We apologize for the irregular appearance of the Calendar of Events during the past few weeks. From now on we assure you that it will appear at the regular time. Holidays and vague responses from departments were responsible for its irregular publication. Our staff meeting program has been arranged for the balance of the year and we eagerly anticipate the appearance of many departmental representatives who have much to give.....