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General survey of the human rickettsial diseases

Roger William Boulden
University of Nebraska Medical Center

A GENERAL SURVEY OF THE HUMAN RICKETTSIAL DISEASES

by

Roger W. Boulden

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INTRODUCTION

The human rickettsial diseases constitute a very interesting group of infections. Their history dates back to antiquity, but it has been only in the past three or four decades that these diseases have, through experimental work and research, been recognized as constituting a new group of infections.

Despite the vast amount of investigation that has been done in the past few years, it is surprising to note the lack of general knowledge that exists concerning the rickettsial disease group as a whole. Therefore, it is the purpose of this paper to present a general survey of the more important human rickettsial diseases with the thought in mind of perhaps obtaining a better understanding of these diseases. With the experience of the past war still fresh in our memory, we can readily see where the need for a better understanding and knowledge of the rickettsial diseases exists.

There has been no attempt made to cover the subject of rickettsial diseases completely in the presentation of this paper. Each rickettsial disease in itself constitutes a large enough field on which a paper of this kind may be written. As a consequence, the references

used constitute only a fraction of the research work done on these diseases. The references cited are more or less selected so that the more important research and experimental investigations are included in the discussion of the different diseases. Much of the early and important investigations on some of these rickettsial diseases has been written in foreign languages; this is especially true of tsutsugamushi where almost all of the early work was done by Japanese investigators. Consequently, in making reference to these foreign investigations, it has been necessary to cite the various English articles in which a summary of the work may be found.

In the discussion, only the rickettsial disease which best represents each sub-division of this group of infections is described. Trench fever is also included in the paper as a rickettsial disease, although some investigators are not satisfied that it is a true rickettsial infection.

RICKETTSIAS

In speaking of rickettsial diseases, it first becomes necessary to define what we mean by Rickettsia. This is not an easy matter, for many differences of opinion still exist as to the decisive criteria which determine the inclusion of any micro-organism in this class. However, there are certain basic common characteristics which lead one to believe that there does actually exist a special genus of micro-organisms that, for the present, must be set aside in a class of their own, separating them from the true bacteria on the one hand and from the ultramicroscopic virus agents on the other. Such is their status at the present time.

Rickettsia is the generic name applied to extremely minute gram-negative bodies which are found in certain arthropods. This name was suggested by da Rocha-Lima (92) (174) in 1916 for these bacteria-like organisms which he had found in the bodies of lice. The term Rickettsia prowazeki was given to these organisms in honor of Howard Taylor Ricketts, who died in 1910 of typhus fever in Mexico City while investigating its etiology; the specific designation prowazeki was added to perpetuate the name of another investigator, von Prowazek, who gave his life in the study of the same disease.

As mentioned previously, the exact nature of these bodies are still in question. Some observers suggested that the rickettsias are unusual, bizarre forms of ordinary bacteria. Others think that they are small inanimate bodies which arise as a result of the disintegration of the red blood cells (175). However, the majority of the more important investigators firmly believe that they are living micro-organisms which are capable of multiplication and can be pathogenic for both man and animals. Although not definitely established, this latter view seems to be the most logical theory, and is the one which is supported by the greatest amount of experimental data.

As to morphology and staining, the rickettsial bodies are found to be small cocco-bacillary forms, and may also appear either as cocci or as short bacilli; long filamentous forms have been reported. They occur singly, in pairs, and occasionally in large irregular clumps or masses in which no particular pattern is discernible. Their measurements are usually within 0.3 to 0.5 mu in length and 0.3 mu in width; however, bacillary and filamentous forms may be as long as 2 mu (92). The pathogenic forms of rickettsia proliferate only intracellularly and are usually observed within the cells, particularly those of mesothelial origin

such as those that line serous cavities. Some particular species of rickettsia appear only in the cytoplasm of the cells while others are definitely intranuclear. The organisms are non-encapsulated and nonmotile. All human pathogenic rickettsias are said to be non-filterable except for the rickettsia of "Q" fever (39).

These organisms take a very poor stain with the usual aniline dyes, but are readily stained a reddish-purple with Giemsa. Castaneda (27) devised a buffered methylene-blue stain and safranine counterstain which stains rickettsias a light blue; the coccus and coccobacillary forms give even stain, but bipolar staining of bacillary forms are quite frequent.

The rickettsias closely resemble the filterable viruses in as much as they have not been cultivated in the absence of living cells. Several of the pathogenic rickettsias are grown on both the usual plasma-tissue cultures and in the various modifications of Maitland's tissue Tyrode media; they are also cultured on the chorioallantoic membrane of the chick embryo. Besides these methods of cultivating the rickettsias, there are several more recently improved ways. Cox (35) has produced large numbers of rickettsias by inoculation of the organism directly into the yolk sac. Zinsser

and his co-workers (183) have recently devised the method of using inoculated minced embryonic chick tissue spread over the surface of Tyrode solution-serum agar, which produces large numbers of rickettsias after a few days' time. These latter two cultural methods are especially important since it affords a means of producing large amounts of material for experimentation and preparation of vaccines from the rickettsial organisms.

CLASSIFICATION

Not only is the relationship of rickettsias to bacteria and viruses not clear, but also the relation of the species of Rickettsia to one another is still somewhat obscure. Up to the present time, only the immunological relationship of the pathogenic rickettsias have been worked out to any degree of satisfaction. However, this method is not altogether satisfactory, since two of these diseases, Typhus and Spotted fever, although distinct epidemiologically and immunologically, do not produce clearly differentiated agglutinins; in addition "Q" fever is said not to agglutinate any of the known strains of Proteus X. Nevertheless, it seems best to accept the immunological classification of the rickettsias, for the present at least, until future investigations can provide a better and more sound basis for classification of this disease group.

The diseases of man with which species of Rickettsia are associated may be divided into four sub-divisions: Typhus, Rocky Mountain Spotted Fever, Tsutsugamushi, and "Q" Fever, the latter being a relatively new addition to the rickettsial group of diseases. Trench Fever also has often been classified as a rickettsial disease since it is louse borne, and rickettsias have been

described in lice and their feces which subsequently have infected volunteers. Therefore, it will be included with a brief discussion in this paper.

In addition to the rickettsial diseases already named, human diseases which belong to this same group have been described in many sections of the world. These diseases have often been given local names or names suggestive of some outstanding characteristic. A few of them have already been identified with or had a close relationship shown to one of the four well-defined members of the group.

The Rocky Mountain spotted fever sub-division is not so clearly delineated as yet, but includes, in addition to Rocky Mountain spotted fever, other identical or similar tick-borne diseases. Among these we have the so-called Sao Paulo exanthematic typhus of Brazil, which was found to be an extremely virulent form of spotted fever which is transmitted by the tick, Amblyomma cajenneuse. Both Parker (127) (129) (130) and Dyer (47) have shown that the Sao Paulo organism cross-immunizes completely with western spotted fever, and thus concluded that these two diseases are identical. Rocky Mountain spotted fever has also been identified in Columbia, where it was originally described as Tobia fever.

Fievre boutonneuse or Marseilles fever is another tick-borne disease which was first described by Connor and Bruch (5) (68) in 1910, and which differs clinically from the spotted fever of the Western hemisphere in that it exhibits distinctive lesions at the sites of the tick bites and runs a brief and mild clinical course with low mortality. Its hereditary tick vector is the dog tick, Rhipicephalus sanguineus, and the animal reservoir is the dog. The immunological studies of Badger (5) and those of Hass and Pinkerton (76) have established the generic relationship of fievre boutonneuse with the group of spotted fevers. The Kenya typhus of East Africa is indicated by Balfour, Anderson, and Pijper and Dau (133) to be identical with fievre boutonneuse. Davis and Parker (40), however, have shown fievre boutonneuse to be less closely related to spotted fever than Sao Paulo typhus.

There was a variant of Rocky Mountain spotted fever first described by Reimann (140) in Minnesota which was at first thought to be a transitional type between spotted fever and murine typhus, but was later shown by immunological and pathological study to belong distinctly to the spotted fever group.

The exact position of the South African tick fever in relation to the spotted fever group is not very clear.

Pijper and Dau (132) (133), in reporting this disease, point out its similarity to the tsutsugamushi disease in as much as there is a local lesion at the point of infection with associated regional lymphadenopathy; it is a mild disease with practically no mortality. These workers have designated the tick larva of the Amblyomma hebraeum as the transmitting vector. The immunological reports presented by Pijper and Dau is somewhat confusing in as much as they report cross-immunization with the local epidemic louse typhus and the sporadic murine typhus of South Africa. At present, it is impossible to state definitely whether this infection is more closely related to the spotted fever or to the tsutsugamushi group; this can be clarified only by further study.

In addition to the aforementioned diseases, there are the tick fevers, which are possible varieties of the spotted fever group, reported from the Tanganyika region in Africa, from Ethopia, and from the Belgian Congo. However, these specific infections have not been studied sufficiently to attempt a precise classification at this time.

The Typhus fever sub-division of rickettsial diseases constitutes a group of rather closely related affections which occur in various parts of the world.

In this group, two types are generally recognized: one, the European type; the other, the murine type. The European type is the classic epidemic form of typhus of world wide occurrence. As the disease exists today, however, it is mostly found in endemic form throughout the world. The widespread typhus epidemics as found described in the pages of history of past centuries are noticeably absent today with the advent of modern medical knowledge in control, vaccination, and the treatment of the disease. Endemic areas of European typhus are found in South Eastern Europe, Russia, Poland, Balkans, North Africa, Ireland, Italy, Spain, Turkey, Egypt, and Ethopia, as well as in China, South Africa, South America, India, and the Philippines where it probably exists together with murine typhus. A mild form of louse-borne European typhus was described in the United States (New York City) by Nathan E. Brill (18) in 1898. The investigator recognized its rather close similarity to the classic European typhus, but believed it to be a separate disease; as a result, the name "Brill's disease" originated. This disease was regarded for a long period of years as a separate entity until Zinsser and Castaneda (181) in 1933 showed the disease, on the basis of both experimental and epidemiological evidence, to be louse-borne and identical with European typhus.

Murine typhus is very closely related to European typhus (97) (182). This disease, which prevails in the Southern United States and in Mexico, was long assumed to be a mild form of the louse-borne European typhus. As will be shown later, murine typhus was found to be a definite disease entity and associated with rats; it was through this association with rodents that the disease acquired its descriptive name of murine typhus. A more complete discussion of the association of these two diseases will be found later in the paper. Murine typhus also occurs elsewhere in the world and is known by several different names. The urban typhus of Malaya or "shop typhus", as described by Lewthwaite and co-workers (103) (105), has been shown to be distinct from the tsutsugamushi and the spotted fever groups and was subsequently classed as murine typhus. The mild form of this disease which exists in the Mediterranean region is known as Toulon typhus, and other infections such as Moscow typhus and Manchurian typhus are all murine typhus, identical or nearly so with the type found in the United States and Mexico. These two types of typhus fevers thus constitute this sub-group of rickettsial diseases.

In the Tsutsugamushi sub-division of rickettsial diseases, we find several diseases which are identical

or are closely related to the type disease of this group, Tsutsugamushi disease of Japan. The mite fever or Mijtekoorts of Sumatra is identical both immunologically and clinically with tsutsugamushi disease (102). Through the recent investigations of Lewthwaite and Savoor (100) (101) (102) (104) (106), the rural or scrub typhus of Malaya has proven to be immunologically identical with tsutsugamushi disease although a considerably milder disease; it also lacks the initial eschar and regional lymphadenopathy found in the latter disease. The pseudotyphoid fever of Deli (Sumatra), as described by Schuffner (155), was found to be a variant of this disease. In Australia, in 1910, Smithson (161) described a disease which rather closely resembled tsutsugamushi; this disease became known as Mossman fever, in addition to such other synonomous names as coastal fever and pseudotyphoid. Subsequent investigators (Priestly and Fielding (139) and Cilento (30)) later showed it to be a variety of tsutsugamushi. From these few diseases which we have pointed out as being identical, or relatively so, with tsutsugamushi disease, we can begin to see the rather wide geographical distribution of this disease. In addition, it has been described in most of the South Pacific islands and mainlands including Formosa, Pescadores, Indo-China,

Philippines, Borneo, Celebes, Java, New Guinea, Burma, India, Ceylon, and other smaller isolated islands and island groups. Recently Heaslip (79) reported a series of fifty-four cases from Queensland Australia in which he concluded that tsutsugamushi was present in that region. Due to the rather extensive military operations in this war, many smaller islands in the South Pacific have undoubtedly been found to be harboring the disease (158), but are as yet unreported.

The sub-division of "Q" fever is a much smaller group than the previous ones, and at the present includes only the two types of "Q" fever, the American and Australian varieties. For the most part, these two seem to be identical except for a few minor differences which will be pointed out. A further and more complete discussion of "Q" fever will follow subsequently.

WEIL-FELIX REACTION

A characteristic of this group of diseases, with the exception of "Q" fever, is the production in patients of agglutinins for the X strains of Proteus bacillus; this is known as the Weil-Felix reaction. This reaction has attained extraordinary importance in the diagnosis of typhus fever and considerable significance for the differentiation of the several groups of Rickettsia infection. The three most important varieties of Proteus bacilli in use at the present time are those known as OX 19, OX 2, and OX K. Zinsser (180) gave a short summary of the history of the development of these particular strains as follows:

"In 1915, Weil and Felix cultivated from the urine of a typhus patient in Roumania an organism belonging to the proteus group. This bacillus, X 1, was agglutinated by the serum of the patient and by those of nine other typhus cases in dilutions of 1-2000. In the same epidemic these investigators again cultivated a proteus, X 2, with agglutinating properties similar to the first one. In the following year, they obtained a third strain of proteus, which they called X 19, which had the property of being agglutinated by typhus sera in titers much higher than those observed with X 1 and

X 2. With this organism, they were able actually to make diagnoses of typhus fever at stages of the disease so early that X 1 and X 2 were not yet agglutinated. In subsequent studies of the antigenic structure of the various proteus bacilli, Weil and Felix dissociated their organisms into the "H" and "O" types. Anti-serum produced with the "O" forms agglutinated its homologous "O" form in small, granular clumps but the "H" form in heavy flakes. In reactions with typhus serum, the proteus agglutinations corresponded to the "O" type. Subsequently the same investigators found that the "O" agglutinogens were more type specific than the "H", and by means of the "O" variants, OX 2 and OX 19, could be differentiated. Since that time the OX forms have been generally used for typhus diagnoses."

There is another strain, the OX K or OX Kingsbury, which is an antigenic variant derived from the original X 19 cultures. This strain was supplied in 1921 to the Bland Sutton Institute by the National Type Culture Collection as a typical proteus X 19, and was taken to the Straits Settlements by A. N. Kingsbury in 1923. It was used by Fletcher and Lesslar (63) in 1925 in investigations which led to the discovery of the nature of the endemic tropical fevers of Malaya. Comparison of the K strain with eight cultures of X 19 from various

sources revealed that it differed from these in agglutination and absorption tests and in certain cultural properties. The K strain was the only one which agglutinated with the blood of the tropical cases.

There have been many theories proposed to explain the Weil-Felix reaction, but nothing definite has been proven up to the present time. Several investigators have explained the reaction by assuming that the proteus bacilli represent dissociation forms of rickettsia. Others have proposed that rickettsia forms and proteus bacilli are phases in a cycle which also includes an ultramicroscopic virus. There is no experimental evidence to justify these theories. Castaneda and Zia (26) (29), in 1933, had found that the proteus bacilli and typhus organisms contain a common antigenic factor, probably a carbohydrate; in subsequent work, Castaneda (25) found that a soluble specific factor, precipitable by antisera and by human typhus serum, could be extracted both from the murine rickettsiae and from proteus X 19. He proposed that this soluble specific substance was probably of a polysaccharide nature. Otto (180) explains the Weil-Felix reaction by what he calls "para-agglutination". By this is meant that the organisms develop agglutinability as a consequence of contact with typhus patients; the organisms under the

environmental conditions of the typhus infected body acquire new receptors which Otto calls "para-receptors". These latter two theories have experimental work and observations on which they are based.

Although the Weil-Felix agglutination reaction has proved to be quite reliable as a laboratory aid in the diagnosis of typhus fever and the other rickettsias, it is by no means an absolute criterion (62). One of the main difficulties that has been encountered by most of the workers using the Weil-Felix reaction in their investigations is the difficulty in maintaining their strains at a uniform standard of agglutinability. Another difficulty that may arise and was just recently brought to the attention of the investigators by Felix (64) is the failure to recognize that two different types of agglutination curves may occur for the same disease. This worker showed that in the routine diagnosis of cases of louse-borne typhus by the Weil-Felix reaction two different types of curve of agglutination formation was present. One type is characterized by the early appearance of the agglutinins, high maximum titers, and the persistence of a raised titer for a long time after recovery; in the second type, the agglutinations appear comparatively late in the disease, reach only low titers, and disappear early during

convalescence. It is easy to see where confusion might arise in diagnosis of such cases if the worker had no knowledge of these two types of agglutination curves. As Felix (64) so aptly states. "In order to derive full advantage from the use of the diagnostic test, it is clearly essential to pay due attention to the distinctive features of the two types of reaction curve". Another common and important source of error in the Weil-Felix reaction is the "H" agglutination with Proteus X strains, since this agglutination has no significance in the diagnosis of typhus, as has been pointed out previously, and the occurrence of "H" agglutinins in normal human sera is not uncommon. It must also be remembered that the Weil-Felix reaction is by no means one hundred per cent infallible, because there have been known cases of typhus fever where the OX 19 titer was so low that it was not diagnostic, and, likewise, cases of scrub typhus have been studied where the OX K agglutination did not develop at any time during the course of the disease or convalescence.

Weil, Felix, and others have shown that the serum of patients infected with any member of the typhus group of diseases develops agglutinins for one or more of these strains of OX proteus. The differences in the agglutinating effect of serum on the three strains,

therefore, can be used to classify the diseases of the typhus group into broad serologic types. The titer of agglutinins in the blood of a patient suffering from one of these infections increases as the disease progresses and decreases quickly during convalescence, usually disappearing entirely upon recovery. The Weil-Felix reaction, therefore, is an indication of active infection, and cannot be used to substantiate a diagnosis of past infection with a rickettsial disease.

The Weil-Felix reaction with OX 19 occurs only in epidemic and murine typhus (and associated variants) and not in the spotted fever or tsutsugamushi groups. However, some investigators (137) maintain that Rocky Mountain spotted fever agglutinates OX 19 to an equally high titer, and thus makes it impossible to differentiate one from the other by means of this test alone. In tsutsugamushi and associated variants an OX K agglutination is commonly obtained, and since this strain is not agglutinated in rising titer by any other known disease, its presence is of diagnostic significance (65). None of the Proteus X strains are agglutinated in "Q" fever or Trench fever. Concerning OX 2 agglutination, Plotz and co-workers (137) remarked that "while the presence of a high OX 2 agglutination is suggestive of Rocky Mountain spotted fever, a diagnosis based on this

test alone is not possible; in this disease, the OX 2 titer may occasionally be equal to or higher than the OX 19 titer, but there are other instances where there is no OX 2 agglutination whatsoever".

A. Felix (64), one of the original discoverers of the Weil-Felix reaction, has made a provisional classification of the typhus group of fevers by placing the various types of diseases in groups according to their reactions with the Proteus OX strains; it is as follows:

Type OX 19:
Classical epidemic typhus, Tabardillo (Mexico), Brill's disease (U.S.A.), Endemic typhus of U.S.A., and Australia, Greece, Syria, Manchuria, Malaya (shop typhus), India, Burma, Philippines, Toulon (fievre nautique, Hawaii, etc.

Type OX K:
Tsutsugamushi fever of Japan, Formosa, Malaya, and Dutch East Indies.
Scrub typhus of Malaya, Dutch East Indies, India, French-Indo-China, and Australia.

Type Undetermined:
Spotted fever of Rocky Mountains, Spotted fever of Eastern U.S.A., Sao Paulo typhus, Fievre boutonneuse (Mediterranean), Fievre exanthematique of Marseilles, Febbre errutiva (Italy), Tick bite fever of South Africa, South African typhus, Tick-borne typhus of India, Kenya, etc.

The Weil-Felix test should be regarded as "positive" when a rise in titer has occurred after examining two or more specimens taken during the course of the disease.

It is safer to follow this rule than to accept any single titer as being positive. Felix points out that in using the Weil-Felix reaction test one must be sure that the patient has not been recently inoculated with typhus vaccine and is not a native of an endemic area. Otherwise, "false positive" tests may result.

TYPHUS FEVER*

Typhus fever has been one of the great pestilences of history. It probably has killed more persons during periods of wars and famines than has any other disease. Hirsch (81) wrote of typhus fever as follows:

"The history of typhus is written in those dark pages of the world's story which tell of the grevious visitations of mankind by war, famine, and misery of every kind. In every age, as far back as the historical inquirer can follow the disease at all, typhus is met with in association with the saddest misfortunes of the populace; and it is, therefore, a well grounded surmise that the numerous pestilences of war and famine in ancient times and in the Middle Ages, which are known to us, had included typhus fever as a prominent figure among them."

Thucydides gave a remarkable account of the plague of Athens which lasted from 430 B.C. to 428 B.C. Many historians and epidemiologists believe that the disease

*Because of the close similarity of the epidemic and the endemic (murine) types of typhus fever, these two diseases will be discussed together, their main differences being largely epidemiologic with variations also in the immunologic observations and reactions produced by the infection in laboratory animals. These differences will be discussed later.

responsible for this pestilence was typhus fever. A complete Jowett translation of this plague appears in Crawfurd's "Plague and Pestilence" (36). However, perhaps the earliest known record of typhus fever was found in an Italian manuscript (179), "The Cronica Cavense", in the year 1083. Its account reads as follows:

"In the year 1083, in the monastery of La Cava (near Salerno) in the months of August and September, there spread a severe fever with peticuli-and parotid swellings, in which one sees clearly the difference, which is found from the Pest, a fever of a different kind and-in this case-accompanied by petechial spots."

Another early mention of typhus fever is made in the year 1096 in a chronicle of Bohemia by Hagecius.

However, it is to Girolamo Fracastorius (164) that we are indebted for describing the first epidemic of typhus fever that can be readily recognized as such; his accurate account of the epidemics occurring in Italy from 1505 to 1530 are found in his treatise on communicable disease, "De Contagione", published in 1546.

Soon after this, typhus became quite widespread over Europe, the epidemiologic records of the eighteenth century revealing that there was scarcely a year in that period in which great or small typhus fever epidemics did not occur.

In brief, there are four period especially distinguished by the more general outbreak and prevalence of this disease. The first period began about 1690 and ended about 1720, and particularly involved Austria, Germany, and Hungary. During this same period, Ireland had three severe epidemics, two having spread to England and Scotland. The years 1734-1744 comprise the second period when Central and Eastern Europe were involved. This was mostly a war pestilence in company with dysentery and typhoid fever. In the third period, from 1757-1775, we find typhus springing up either out of the turmoil of the Seven Year's War or the war between England and Spain. At the same time, a severe famine occurred in Europe which produced favorable conditions for the disease to spread. The fourth period was ushered in by the Revolutionary Wars in France, lasting from 1790 to 1815. This was by far the severest epidemic period of typhus in the eighteenth century, and was spread all over Europe; involving even those populations remotely removed from areas of military concentrations. It is interesting to note that of all the great wars of which there is record, the American Civil War and the Franco-Prussian War in 1870 are the only ones in which epidemic typhus fever did not have a prominent place.

For the Western Hemisphere, the earliest information as to the occurrence of typhus comes from Mexico and Peru. According to the perfectly reliable statements of Francesco Bravo, the disease which he speaks of under the name "tabardete", then current in Spain, broke out in Mexico in 1530 on importation from Spain following the Spanish Conquest. Pizarro began the conquest of Peru in 1526, and typhus fever soon appeared in the highlands of South and Central America.

Typhus came to the United States and Canada much later than to Mexico, and in those countries it has never attained the same importance as in the latter or on the continent of Europe. This disease was imported into Canada about 1847 with the first great wave of Irish immigration, although sporadic cases had occurred among the immigrants since 1659. Several times during the eighteenth and nineteenth centuries, typhus fever had appeared in the seaports of the United States. Philadelphia had its last reported epidemic in 1883 and New York in 1893. However, for some unaccountable reason, epidemic typhus has never established an endemic focus in either Canada or the United States.

Epidemic typhus fever is transmitted from person to person by the human body louse, Pediculus vestimenti. Nicolle, Conte, and Conseil (174) in 1909 proved, by

experiment, that chimpanzees could be infected with the disease by the injection of a small amount of blood from a human case in the active stage of the disease. They then infected monkeys and proved that it could be transmitted from monkey to monkey by bites of the infected body louse. This work was confirmed in the United States in 1910 by Ricketts and Wilder (150). From the work of Goldberger and Anderson (164), it seems clear that the head louse, Pediculus capitis, may transmit the disease under experimental conditions. Its importance in the spread of the disease is not established, although it is not regarded as an important vector.

Epidemic typhus fever is caused by the Rickettsia prowazeki. Although there had been some investigation on the etiology of this disease, no outstanding work had been done up to 1910. At this time, Howard Ricketts and his co-worker, Russell Wilder, were studying typhus fever at first hand in Mexico City. In April of that year they reported the discovery of a short, non-motile bacillus in the blood of typhus cases (148). However, these experiments were interrupted by Ricketts' untimely death on May 3, 1910. This did not halt the investigations for the etiologic agent of typhus, but his discovery seemed to stimulate other workers to confirm his findings. Soon Prowazek confirmed Ricketts'

observations, but he, too, died of typhus. Da Rocha-Lima, who likewise contracted typhus but recovered, presented convincing evidence that the organism described by Ricketts was the cause of typhus fever; he isolated the organism from the bodies of lice taken from typhus fever patients. In honor of these two investigators who gave their life in the study of the disease, da Rocha-Lima named the etiologic agent, Rickettsia prowazeki (92) (174).

Most of our present day knowledge concerning murine typhus has been the result of extensive study of American workers in Southern United States and Mexico. In the latter country, the disease is known as "tabardillo" (119).

In 1913, J. E. Paullin (131), of Atlanta, Georgia, gave the first description of murine typhus in the South. Other reports soon followed in the next few years, Charlotte, North Carolina, and Galveston, Texas, reporting cases in 1914 and 1916 respectively. In 1923 Maxcy and Havens reported a number of cases in Alabama in which the immunologic and serologic findings were identical with epidemic typhus. Three years later Maxcy's (111) important epidemiological observations showed no evidence of louse transmission in the disease, and thus suggested that some other insect vector was

the transmitting agent. His work also disclosed that most of the cases occurred among food handlers, and he thus concluded that the reservoir in nature is the common rat (112). The next advance was made when Dyer, Rumreich, and Badger (55) recovered the rickettsia from rat fleas removed from rats which had been trapped at a typhus focus; they were able to establish a strain of the organism and to produce the disease in laboratory animals. Mooser, Castaneda, and Zinsser (121) had isolated a similar rickettsia from the brains of rats trapped in Mexico City. It was certain from these experiments, therefore, that the rat was the important rodent reservoir as was proposed earlier by Maxcy. Dyer (46) has reported woodchucks, house mice, meadow mice, and white footed mice to be susceptible to infection with murine typhus; however, the possible role that these rodents play in the extension of this disease is unknown. Further work by Dyer and co-workers (52) (53) (54) and Mooser and co-workers (120) established the rat flea, Xenopsylla cheopis, as the transmitting agent. Other species of the rat flea (57) (120) as well as the rat louse, Polyplax spinulosus (122), have been found to be capable of transmitting the disease from rat to rat experimentally, and thus are potential vectors in nature. Thus a definite epidemiological cycle of

rat-flea-rat and rat-flea-man was established for murine typhus and tabardillo. Other insects like the bedbug and a number of varieties of ticks, although they could harbor the organism for a short time under experimental conditions, were shown to have no part in transmission.

Since the first reports of murine typhus in Georgia, Alabama, and North Carolina, there has been an extension of the disease through the other southern states (167) (115). It is also becoming a serious problem in several of these states, and is now reported to be spreading into rural areas in recent years (8) (16). Recognition of the disease in other parts of the United States has occurred, cases being reported recently from Iowa (67), Missouri (31), Ohio (165), District of Columbia (166), and California (72). Since murine typhus became well known in the United States, it has been found in many parts of the world, its distribution having been mentioned previously.

The organism responsible for this disease is the same, except for very slight variations, as that of epidemic typhus, namely Rickettsia prowazeki. However, the organism may be found referred to in various articles as Rickettsia prowazeki mooser or Rickettsia mooseri; this name is added in honor of Dr. H. Mooser

who contributed so much toward the study of this disease in Mexico and the United States.

Besides the epidemiological differences which have already been pointed out, epidemic and murine typhus also differ in the resulting reactions which occur when laboratory animals are infected by each type. The murine strains produce in guinea pigs a shorter, more irregular febrile reaction than do the classical epidemic strains. In addition, the murine strains characteristically produce a swelling of the testicles of male guinea pigs, an edema of the subcutaneous tissues of the scrotum, and a marked erythema of the overlying skin (117) (110) (135). This reaction is quite definite and usually appears with the fever and disappears in four or five days. Further differences in other species of animals have been noted by various workers (118). The epidemic strain produces an inapparent infection in rats and cannot be maintained in mouse passages, while the murine strain produces a fever in rats and can be maintained indefinitely through passage from mouse to mouse.

Clinically, murine typhus does not differ appreciably from the epidemic type, although the former runs a somewhat milder course. Because of the similarity only the clinical features of epidemic typhus will be discussed. The most frequently reported period of

incubation is eight to twelve days, but the period varies from five to fifteen days. The onset of the illness may be preceded by one or two days in which the patient may have some malaise, headache, anorexia, and occasionally nausea. In most cases the disease has an abrupt onset with rapidly rising fever, repeated, though mild, chills, and headache. The fever rises steadily during the following days, usually reaching the maximum of 105° F by the end of the first week. Morning remissions of fever occur. The fever generally falls by rapid lysis after about two weeks. Headache is a prominent symptom, being severe and quite difficult to relieve, and often is the chief complaint of the patient. Prostration and cardiac weakness are common findings from the onset, but are generally more pronounced in the second week. Constipation is the general rule. Mental disturbances varying from confusion, restlessness, insomnia, and irritability to delerium generally appear at the end of the first week. Epistaxis is frequent. There may be indications of a slight upper respiratory infection.

The most characteristic feature of this rickettsial disease is the skin eruption which appears from four to six days after the onset of the illness. The rash consists of rose-red macules and papules which disappear

on pressure at first, leaving stellate radiations, but later become petechial and tend to remain despite pressure. The eruption is first noted about the flanks or in the axilla, and then rapidly spreads to involve the back, chest, and upper abdomen. It very rarely extends to the face, but is seen on the hands and feet although not common. The eruption may last from a few days to a few weeks. In severe cases there may be hemorrhagic rashes which are accompanied by hematuria, hematemesis, and melena. These cases have a very poor prognosis.

Another quite prominent feature of this disease is the cardiac weakness which develops during the course of the disease. As mentioned previously, it commences with the onset of symptoms, but becomes more pronounced the second week. Physical examination of the cardio-vascular system reveals weak heart sounds accompanied by a rapid, weak pulse. The blood pressure is found to run quite low. During convalescence, bradycardia is frequent. In severe cases of epidemic typhus with marked cardiac weakness, gangrene of the extremities, especially the toes, may develop.

There are no characteristic blood findings in epidemic or murine typhus. The white cell count varies from one indicating a moderate leucopenia to one of a

mild leucocytosis of 12,000 to 15,000. Albuminuria is usually present during the disease, but disappears during convalescence.

Bronchitis and bronchopneumonia are the outstanding complications encountered in typhus fever. Infections of the parotid and submaxillary glands are not infrequent complications and should be guarded against. Otitis media and mastoiditis occurs, as in other infectious diseases, with some frequency. Thrombosis of large arteries occurs, peripheral as well as abdominal vessels being affected. With recovery, there are no unfavorable after-effects in individuals who have exhibited marked cardiac weakness. Recovery once assured is usually complete and sequelae are absent.

The fatality rate for epidemic typhus varies from twenty to sixty per cent in different areas, most of the fatal cases (eighty per cent) occurring in those persons over fifty years of age. The fatality for murine typhus in the United States is below five per cent, generally running two to three per cent.

The essential pathologic lesion of epidemic typhus is the focal injury of capillaries and arterioles characterized by endothelial swelling, proliferation, and necrosis with thrombosis, and by nodular perivascular exudation of lymphocytes, plasma cells, and monocytes.

Such lesions are most frequently found in the skin, heart, large blood vessels, kidneys, adrenals, testes, and especially the brain. In the latter the formation of small pericapillary nodes of microglia, especially in the cerebral cortex, are very characteristic; these are commonly known as typhus nodules. In murine typhus, however, these histopathologic findings occur in a much milder degree.

Diagnosis of epidemic typhus fever may be very difficult at times. Prior to the appearance of the rash, signs and symptoms of typhus are so similar to many other acute infections that differential diagnosis may be impossible. Malaria and relapsing fever may be excluded by examination of blood smears for the parasites. Pneumonia may cause some difficulty in the early stages until characteristic pneumonia symptoms appear. Typhoid fever is quite different in its mode of onset than epidemic typhus, and usually there is no difficulty in the differential diagnosis when a good history is obtained. In some cases, blood cultures and Widal tests may have to be resorted to. Probably the most important method of diagnosing epidemic typhus from other diseases is the positive Weil-Felix reaction which the disease gives. The typhus rickettsias produce agglutinins against the OX 19 and OX 2 strains of Proteus bacillus, the titer

usually reaching its height during the second week of the disease and convalescence. As mentioned before, the Weil-Felix reaction has no practical value in differentiating either Rocky Mountain spotted fever or murine typhus from epidemic typhus. The Weil-Felix reaction is positive in both diseases. Although there are some differences in the agglutination reactions to the OX 19, OX 2, and OX K strains of the Proteus bacillus, they are not sufficiently constant for the purpose of differential diagnosis. In many instances, it is necessary to resort to animal inoculation and to cross-immunity tests. Recently a specific complement fixation reaction for murine typhus, by use of an antigen prepared from rickettsias grown in the yolk sac of developing chick embryos, has been reported by Bengtson (10). She states that the test is specific when dealing only with Rocky Mountain spotted fever and "Q" fever cases, a certain amount of cross-fixation resulting with sera of epidemic typhus cases. Castaneda (28) had been experimenting with complement fixation some five years earlier and had pointed out at that time the possibility of its use as a specific test for typhus. However, his procedure never became popular.

No specific treatment has proven of value. Many of the more recent chemotherapeutic agents have been

used with little success; in several cases there has been evidence of harm from them. Convalescent human serums and serums from horses inoculated with rickettsia have been tried without convincing results. A hyper-immune rabbit serum has been described and the results, in a small series of cases, indicate it may be of therapeutic value. Treatment should be directed toward supporting the patient and eliminating, as far as possible, the sources of exhaustion until spontaneous recovery can occur. Recently Woodward and Bland (176) stressed the importance of using intravenous fluids and plasma in the treatment of typhus cases as a means of preventing dehydration and aiding the body in the elimination of increased nitrogenous wastes through kidney excretion. The relief of severe headaches may necessitate the use of codeine or morphine at times. The bowels should be kept open with enemas or mild laxatives and retention of urine should be guarded against. Digitalis is contra-indicated in typhus fever unless there are definite signs of cardiac failure. Cardiac depressants are to be avoided. Rest, quiet, and good nursing are all requirements in treatment of typhus fever.

Vaccines of various types have been prepared for immunization against typhus fever. Attenuation of the

living rickettsias by heat or by addition of such substances as bile, as well as partial neutralization by convalescent serum, has been used (66). However, the dangers inherent in the use of a vaccine containing living rickettsias as shown by the fact that attacks of the disease have been produced by inoculation with such vaccines have, for the most part, prohibited their use in vaccine preparations. Several preparations have been made which utilize rickettsias killed usually by solution of formaldehyde or phenol. One of them, that of Weigl (178) (180), apparently gives good immunity, but unfortunately it cannot be produced on any very large scale. Its production consists of infecting lice per rectum with suspensions of living rickettsias and allowing the lice to feed on immune persons; after a few days the louse intestines are dissected out and prepared as a treated suspension, which is used as the vaccine. Between one hundred and two hundred lice are needed to prepare vaccine enough to immunize one person, and a large skilled staff is needed to superintend the inoculation. These factors necessarily make the cost of the vaccine high and impractical for general use.
A second source of rickettsias for the preparation of vaccine of killed organisms is the yolk sac of the developing chick embryo after its inoculation with typhus

rickettsias (35). Vaccines made from killed rickettsias secured from the lungs of intranasally infected mice, rats, or rabbits have also been prepared (66). The vaccines of killed rickettsias at present in use give good results when tested in animals, but no adequate field tests in the presence of epidemic typhus have as yet been made. The present method of vaccination used is a series of three initial inoculations followed by a booster dose every few months when in a typhus fever area.

Epidemic typhus can be controlled by the destruction of lice. In a campaign against this disease, measures should be taken to include all persons in infected districts. This can be done only by house to house inspection, with removal of patients to hospitals and disinfestation of all contacts, their clothing, and houses. Clothing and bedding can be disinfested either by heat or by chemical means, that is, by new louse powders. The control of murine typhus, from the present knowledge, should be based on the control of the rat population--by trapping, poisoning, and rat proofing. Of these measures the last is the only one that may be considered as of some permanent value. Trapping and poisoning must be continuous to be of any practical value, and must necessarily be supplemented by an attack

on the rat's home and feeding places by rat proof construction of buildings and ships.

ROCKY MOUNTAIN SPOTTED FEVER

As the name implies, Rocky Mountain spotted fever was first recognized in the Rocky Mountain section of the United States. The early history of the disease presumably begins with the Indians living in this area. Mitchie and Parsons (116) give an account of an old Indian chief of the Flathead and Nez Perce tribes in Montana who told about the visit of evil spirits in certain areas during the spring of the year which caused much sickness among the tribes; this was, in all probability, Rocky Mountain spotted fever. However, the first published record of the disease was made in 1896, in an annual report to the Surgeon General by W. W. Wood, (162) an army surgeon, who reviewed the clinical data on cases submitted to him by eight Idaho physicians; these men, at this time, regarded spotted fever as a distinct new disease entity of an unknown origin. A year later a complete clinical description of the disease as it occurred in Idaho was given by Maxcy (162). In 1902 McCullough (162) described a more virulent form of the infection in western Montana. In the same year, Wilson and Chowning (172), working under the direction of the Montana State Board of Health, made some important laboratory and field investigations

on this disease. In their research work, they found a piroplasma in the blood of man and rabbits infected with Rocky Mountain spotted fever; it was through these findings that they advanced the theory that the disease was a piroplasmosis, and suggested that it was transmitted by the bite of the infected wood tick.

Up until 1906, there had not been too much experimental work done on Rocky Mountain spotted fever, and very little, if any, definite knowledge concerning the disease had been learned. In April of 1906, Howard Taylor Ricketts arrived in Missoula, Montana, on the invitation of that state to extensively study the disease; the results of his studies have added more valuable information concerning this condition than any other investigator, and have laid the foundation for future and more extensive laboratory studies. During his first year there, Ricketts successfully established a strain of the disease in laboratory animals (144) (146), and transmitted the disease from an infected guinea pig to another uninfected guinea pig by means of ticks (147). In his work on the relationship of the wood tick to Rocky Mountain spotted fever, he was able to demonstrate the presence of infected ticks in nature (141) (145), and showed that the causative agent could be transferred from one generation of ticks to

another by means of an infected female passing the disease to her young through the egg (141). Ricketts also worked out the complete life history of the wood tick during his study of the transmitting agent (142) (145).

In 1909 Ricketts (143) described the micro-organism which he thought was the causative agent of Rocky Mountain spotted fever and which was subsequently to be known as Rickettsia rickettsii. His original description was as follows:

"Since the spring and summer of 1906, bodies referred to as diplococcoid bodies and sometimes short bacillary forms have been found with considerable constancy in the blood of guinea pigs and monkeys which were infected with Rocky Mountain spotted fever. The form most commonly found is that of two somewhat lanceolate chromatin-staining bodies, separated by a slight amount of eosin-staining substance."

Several years later Wolbach (173) described rickettsia-like micro-organisms found in humans, laboratory animals, and ticks suffering from Rocky Mountain spotted fever similar to those originally described by Ricketts; Wolbach named them Dermacentroxenus rickettsii. Subsequent investigators, Nicholson (124), Becker (9), and Hayashi and Takeuchi (78) confirmed Ricketts and Wolbach's findings.

About the time of the discovery of the causative organism (1908), McCalla (162) published the results of an experiment in which a wood tick was removed from a spotted fever patient and was allowed to bite two human volunteers who subsequently became ill with the disease. Thus the disease was successfully reproduced through human transmission, this being the only such experiment on record.

Rocky Mountain spotted fever, when first identified, was thought to be limited to the northwestern mountain sections of the United States, and, for many years, was believed to be confined to those states lying west of the Mississippi river. However, in 1930, the geographical limits of the disease were widely enlarged when Rumreich, Dyer, and Badger (6) (152), incidental to a typhus survey in the eastern states, discovered the eastern type of spotted fever. Subsequent experimental work showed the western and eastern types to cross-immunize completely, but the latter runs a somewhat milder course and has a lower mortality than the western type except for a few exceptional cases (168). Most observers believe these two disease types are entirely identical, the eastern type being only a less virulent variant of the Western Rocky Mountain spotted fever (17). Since the time of definite identification

of the disease in states outside the originally known area, new states or sections of states have been added to the known distribution of the disease each year (37) (94) (95) (160). At present, study of suspected cases has shown that the area of distribution includes fourty-one states. Five of the New England states--Maine, New Hampshire, Vermount, Connecticut, and Rhode Island--have not as yet been reported as having a case of Rocky Mountain spotted fever; in the Midwest only Michigan and Wisconsin are not known to be infected (49). There are two areas in the United States, however, that account for 93% of the total number of reported cases, 65.5% occurring in the Mountain and Pacific states and 27.4% occurring in the South Atlantic group (74).

As we have shown by the early works of Ricketts, the transmitting agent of Rocky Mountain spotted fever was found to be the wood tick, Dermacentor andersoni (or occidentalis, as Ricketts knew it). However, Mayer (113) in 1911 showed through experimental transmission that this disease could also be spread by the dog tick, Dermacentor variabilis, a close relative of the wood tick. Later Dyer and his associates (51) reported the same findings in their investigations of the eastern type of Rocky Mountain spotted fever. Although several species of ticks are known to be capable of transmitting

the disease experimentally, the ticks Dermacentor andersoni and variabilis are the only two species biting man in which the disease has been found naturally present. A third tick, the rabbit tick, Haemaphysalis leporis palustris, has been found to be naturally infected, but this species does not bite man; however, its importance is pointed out because of the part it plays in preserving and spreading the disease in nature.

Clinically Rocky Mountain spotted fever shows considerable variation. Attacks range from mild ambulatory and abortive forms to fulminating infections with early fatal termination (89). The incubation period varies according to the severity of the case, the more severe infections running from two to five days and the milder ones from three to fourteen days. A prodromal period of two or three days is quite common, and is characterized by malaise, chilly sensations, loss of appetite, and irritability. The actual onset of the disease is quite sudden and is marked usually by a chill. The symptoms most often complained of are severe general pains referred to the bones, muscles, back and joints (particularly in the calf muscles, large joints, and lumbar region of the back), marked malaise, and severe frontal and occipital headaches. These may be accompanied by sweating, nosebleed, nausea and vomiting,

injection of the conjunctivae, and photophobia. Following the chill, the temperature rises fairly rapidly and reaches 102° to 104° F by the second day; it continues to rise gradually to a maximum of 104° to 105° F. In very severe cases temperatures of 106° to 107° F have been recorded. Another common characteristic of this disease is the presence of cyanosis, the face assuming a rather typical dusky flush. Quite often the spleen is palpable. Restlessness and insomnia are accompanying distressing features; a severe hyperesthesia may be present.

The typical rash appears usually on the third to fifth day of fever, making its appearance first on the wrists, ankles and back, then on the forehead, arms, legs, chest and abdomen. Occasionally this rash is preceded by a mottled appearance of the skin. The eruption is in the form of rose colored macules one to four or five mm. in diameter usually, but papular forms sometimes occur; these macules soon become deep red or purple and increase in size. Early the spots disappear on digital pressure. Cutaneous and subcutaneous hemorrhages occur frequently in severe cases.

There are no significant pathologic changes in the blood outside of a moderate leucocytosis. The white cell count usually does not exceed 15,000 but

may be 30,000. Occasionally there is a leucopenia. A relative mononucleosis is usual. The erythrocyte count may be below or slightly above normal.

The histopathologic picture of Rocky Mountain spotted fever resembles, in may respects, that of typhus. The early stage of this cutaneous manifestation consists of a proliferation of the endothelial lining of the small vessels followed by thrombosis, either mural or occluding. Later, typical manifestations of phlebitis and gangrene may be present. A considerable degree of perivascular infiltration occurs, but the perivascular nodules so distinctive of typhus do not develop. Minute focal lesions of the central nervous system resembling those seen in typhus, but accompanied by more conspicuous infarction of arterioles, are common in cases which survive more than twelve days. The right side of the heart is commonly dilated, but the myocardium shows no pathologic changes.

The most common complications found in Rocky Mountain spotted fever are lobar, bronchial or hypostatic pneumonia, hiccough, phlebitis, gangrene, hemorrhage from the nose, intestines or kidneys. Iritis, acute nephritis, and hemiplegia occasionally occur.

The clinical diagnosis of Rocky Mountain spotted fever is often difficult; particularly is this true of

the very mild attacks and the rapidly fatal attacks of the fulminating type. History of a tick bite or exposure to such bites in areas where the tick is especially prevalent followed by the appearance of the symptoms mentioned above usually is enough to establish a diagnosis in most cases. However, since Rocky Mountain spotted fever and murine typhus both occur in some twenty-five states, the problem of differential diagnosis often arises. The outstanding clinical difference between these two diseases is in the development and distribution of the rash. At times animal inoculations and cross-immunity tests may be necessary to decide which disease is encountered (134). The Weil-Felix reaction gives no aid in differentiating Rocky Mountain spotted fever from the typhus fevers. As was pointed out before, on large numbers of cases it has been noted that agglutinins for Proteus OX 2 occur more frequently in the spotted fever cases than in the typhus cases, but since they do occur in endemic or murine typhus, the above finding is of no help in the individual case. Recently, however, Plotz and his co-workers (136) have devised a specific complement fixation test in which a specific spotted fever antigen has been prepared from suspensions of rickettsial organisms cultivated on agar tissue cultures. By means of this test

differentiation between Rocky Mountain spotted fever and other rickettsial diseases is possible.

With Rocky Mountain spotted fever as with the other rickettsial diseases, there is no specific treatment of proven value. The newer chemicals--sulfanilamide, sulfathiazole, sulfadiazine, penicillin, and mapharsen--have all been tried. Edmunds (58) claims improvement of a case using penicillin injections, while Baker (7) has used neosalvarsan dissolved in aqueous metaphen solution intravenously with apparently good clinical results. However, these reports have not been confirmed by any further investigations as yet. The experimental use of sulfas in treatment of spotted fever in both guinea pigs and rabbits increases both the severity of the infection and the death rate; in clinical cases, the sulfas have been shown to be ineffective and occasionally makes the patients worse. Another very recent report has been published by Rose, Duane, and Fischel (151) in which they claim para-aminobenzoic acid to be a specific chemotherapeutic agent in the treatment of Rocky Mountain spotted fever. Earlier experimental work by Hamilton, Plotz, and Smadel (73), and Anigstein and Bader (3) has shown definitely that this agent will inhibit the growth of rickettsias in egg cultures and is effective against

spotted fever in guinea pigs infected with the disease. Yeomans and co-workers (177) claim almost identical results on louse-borne typhus in Cairo, Egypt. However, since this is the only clinical report in which this chemical agent has been used, there must be further confirmation before it can be accepted as a specific agent in the treatment of Rocky Mountain spotted fever.

So, for the present, we must consider the best treatment of this disease to be symptomatic and supportive. Good nursing care, avoidance of mental or physical exertion, maintainence of fluid intake--particularly of plasma and whole blood in association with glucose and saline solutions (75)--and relief of headache and other general body pains by acetylsalicylic acid, codeine or morphine. Treatment on a conservative basis has been found to be the most successful. Injection of convalescent serum as well as transfusions from immune donors have both been used in the treatment of this disease but without any definite beneficial results.

Probably the most effective method of prevention is the exercise of personal care. Known infected areas should be avoided especially during the tick season. Those people such as lumbermen, surveyors and the like who must visit such infested areas should frequently examine their clothes and bodies for ticks. Special

care must be observed in removing ticks from the person or pets; the safest method is to use small forceps or a piece of paper held in the fingers while removing the ticks. Of course, the washing of hands is very important especially after handling ticks.

A vaccine for use against spotted fever was developed by Spencer and Parker (163), and is now prepared by the United States Public Health Service at Hamilton, Montana. The vaccine is injected in two doses of 2 cc. each at an interval of five days, either subcutaneously or intramuscularly. This protects the majority of persons against the less virulent strains, but the average person is only partially protected against the highly fatal type of Rocky Mountain spotted fever. The maximum degree of protection is usually only retained for one year at the most. Since vaccines cannot be produced in sufficient quantities for wholesale vaccination, only those persons whose occupations or play expose them to the ticks should be vaccinated. Other methods such as poisoning of rodents, clearing away and burning of brush or infected areas, and dipping of stock have all been done in an attempt to reduce the tick population. However, there is very little evidence that much has been accomplished by these procedures in the way of limiting the disease.

TSUTSUGAMUSHI DISEASE

This disease was apparently well known in ancient times in China. Li Shih-Chen (63) cites the description of Keh-Hung in his Choo-ho-fang (third century A.D.) in which an accurate account of the clinical symptoms of the disease appears, as well as a description of a minute red insect, the sha-shi, to whose bite he attributes the disease. This is assumed to be a reference made to the trombiculid larva, which will be discussed later as the transmitting agent. Another early Chinese reference is a medical book written in the Sei era in the sixth century which mentions tsutsugamushi as a sand louse. This insect was described in detail by Lishiting in "Honso Komoku" written in the sixteenth century. The earliest description of tsutsugamushi found in the Niigata prefecture was written by Hakuju Hashimoto in 1810; nine years later Genkii Ohtomo similarly described it in the Akita prefecture (93). It is interesting to note that, although the disease was, no doubt, in existence in South China in the early centuries, it is not to be found anywhere in China today.

The first scientific reports of tsutsugamushi in modern times were those of Palm (82), a medical missionary, in a letter to the Edinburgh Medical Society, and

of Baelz and Kawakami (63) in 1878. Their reports revealed that the disease had been known for many years to the Japanese physicians on Honshu island of Japan, being restricted almost entirely to the flood plains of the Omono, Shinano, and Mogami rivers. They also reported that the natives of the area thought this disease was caused by the bite of the akamushi (trombiculid larva).

The early investigations on tsutsugamushi disease were concentrated on the study of its etiology. Many theories have been proposed to account for the causative agent of this disease. Baelz at first proposed the mite transmission theory, but later rejected this in favor of a miasmatic theory. In 1893 Kitasato described a small body in the red corpuscles of a patient suffering from this disease which he thought was a plasmodium. Tanaka had hypothesized a protozoan parasite as the causative agent, but later (1904) rejected this theory in favor of a proteus which he had identified at the site of the insect bite. Two years later he discarded this theory also, and stated that the disease was caused by a toxic substance or enzyme elaborated by the salivary glands of the akamushi larval mite. In 1912, on the basis of several years' investigation, Ogata set forth a schizomycetic hypothesis for the etiology of tsutsugamushi. Kitashima and Miyajima have suggested

a yeast-like organism which they found on the body of the akamushi and have named "Chlamydomyces akamushi" as a possible etiological agent of this disease. These and several other theories had been proposed to explain the etiology of tsutsugamushi (93).

Although many of these and other investigators undoubtedly had been working with rickettsias unknowingly, there was not much investigation done on this organism as the etiologic agent until recent years. The organism was probably first observed, however, by Hayashi in 1908, but it was not until 1920 (77) that he described the organism and named it "Theileria tsutsugamushi". In 1928 Ogata (63) found a non-filterable, pleomorphic, gram-negative organism which he named "Rickettsia tsutsugamushi"; he later concluded this to be identical with that described by Hayashi. Although these investigators had contributed much toward establishing the rickettsia as the etiologic agent of this disease, it was probably the experiments of Nagoya and co-workers (63) that conclusively confirmed this etiology. In 1930 they proposed the name "Rickettsia orientalis" for the organism with which they had been working. This causative agent has, in addition to the other names, been called "Rickettsia nipponica" by Sellards (159) and "Rickettsia akamushi" by Kawamura and Imagawa (2). These have all

been relegated to synonymy, the name "Rickettsia tsutsugamushi" being commonly accepted today as the standard terminology.

As we mentioned previously, the early Chinese literature as well as the Japanese folklore had associated tsutsugamushi disease with trombiculid larvae long before the advent of scientific investigations. Baelz and Kawakami in 1879 first proposed the mite theory but soon rejected it. Thirteen years later this theory was revived by Tanaka who attributed the disease to a minute red mite. By 1920 the investigations of Kitashima and Miyajima (93), Hayashi and co-workers (63), Kawamura (93) and others had not only demonstrated the life cycle of Trombiculid akamushi, but also had implicated this species as the vector of tsutsugamushi disease. The experiments of Kawamura (93) in 1918 also established the fact that the etiologic organism is transmitted from one generation of mites to the next via the ova. The larval form of the mite genus Trombicula is, to date, the only mite known to be definitely associated with tsutsugamushi disease. Several species of Trombicula, and even variants of one species, may be vectors in different localities. Walsh and Keukenschrijver (63) have reported Trombicula deliensis to be the vector in the Dutch East Indies, and Heaslip (79)

has implicated the same species as a vector in northern Australia. Gunther (63), on the basis of his epidemiologic observations, has suggested Trombicula hirsti as the vector in New Guinea. Various other species of Trombicula, namely fletcheri and minor, or variants of these species, have been suspected as vectors of the disease among different island groups in the South Pacific during World War II (2).

Very little reliable information on the natural reservoir hosts of the rickettsias has been reported to date. This is a field in which considerable investigation is needed before the problem of reservoir hosts is solved. In Japan, the field vole, Microtus montebelli montebelli, has definitely been established as a reservoir host since it has been possible to demonstrate its natural infection with Rickettsia tsutsugamushi. Various species of wild rats have been suspected as hosts. Hayashi (63), Sambon (153), and Kawamura (93) have all suggested that various birds may have important roles in the epidemiology of this disease. Gunther lists some seventeen hosts of the larval mite, including the bush fowl, parrot, bandicoot, and wild pig. However, definite proof of the cycle necessary for transmission of the disease has not been established in any of these, thus leaving much to be done before the complete

epidemiology of tsutsugamushi disease is known.

Clinically, tsutsugamushi resembles typhus and spotted fever, but is characterized by one or more small ulcers or eschars which arise at the site of the insect bite followed by regional and general lymphadenitis. This disease generally has a prodromal period lasting from one to five days in which the patients usually complain of chilliness, malaise, dizziness, headache, backache, insomnia, anorexia, and orbital, retro-orbital, and supra-orbital pain. Toward the end of this period there may be a low grade fever. The onset of the acute febrile stage is generally gradual and insidious, exhibiting only an accentuation of the prodromal symptoms. The febrile period is characterized by a high remittent fever which lasts on the average of fourteen to eighteen days, subsiding by lysis; it is diurnal in character, rangeing from 101° F in the morning to 104° to 105° F in the afternoon and evening. The pulse rate is proportionately increased and averages about 104 per minute. Between the fourth and eighth days of illness a macular or maculo-papular rash develops, disappearing usually by the tenth or twelfth day. There is no pruritis or other sensory changes accompanying the rash. The distribution of the rash is generally more prominent over the back, chest, and abdomen, while the extremities

are least affected. The rash often assumes a light brown, dry appearance as it gradually disappears (15) (108).

Physical examination of patients ill with tsutsugamushi reveal marked weakness and lassitude associated with a non-concern attitude. Besides the rash and the generalized lymphadenopathy, the spleen may be found to be firm and tender upon palpation. Tympanites may develop during the febrile stage. Ocular findings such as hyperemia of the conjunctivae, subconjunctival hemorrhages, engorgement of retinal veins, edema of the disc and retina, and retinal hemorrhages are occasionally found in tsutsugamushi disease; however, there apparently is no permanent loss of visual acuity after recovery (61) (126). There may be tinnitus, bilateral deafness, and even minor involvement of the cochlear system during the course of the disease, but these clear up completely during the convalescent period also (61). Tracheitis, pharyngitis, and bronchitis associated with fine scattered rales throughout both lungs occasionally are found. The development of muscular twitchings, clonic convulsions, carpopedal spasm, delerium and coma appear in the late stages of the illness and may end in death. The incubation period for this disease varies from five to fourteen days in most cases (157).

The ulcerated lesion, the eschar, is usually on the lower extremities, in the inguinal region, in the axilla, or about the waist, the moist areas seemingly being the choice spots; these ulcers represent the site of attachment of the vector. They usually form during the incubation period and vary in size from one mm. to one cm. in diameter. On examination the eschar consists of a single raised round or oval lesion with a black adherent center surrounded by a cloudy red areola. About eighty per cent of the cases reveal eschars.

Following the acute stage of the disease, a prolonged period of convalescence is advised. The Army and Navy doctors in World War II usually required that four to six months should elapse before the patient returned to full active duty (154) (156).

The blood picture in uncomplicated cases of tsutsugamushi disease reveals a leucocyte count within normal limits or perhaps a leucopenia. The red blood count usually shows a secondary anemia, the count varying between 3,500,000 and 4,000,000 cells. Sedimentation rate ranges from fifteen to fifty mm. per hour by the Wintrobe method. Urine analysis is negative in uncomplicated cases of the disease (108).

Complications of various sorts occur during the course of this disease (107), the cardiovascular system

being the most commonly involved. The complications vary from tachycardia to complete peripheral vascular failure, including congestive heart failure, pericarditis with effusion, development of various heart murmurs, hypotension and pulmonary emboli. It has been a common finding among patients recovering from the disease to find a persistent tachycardia upon slight exertion for several months following recovery. Electrocardiograph tracings have been run on large series of such patients to determine if there might be any permanent damage to the heart and vascular system. Benjamin and co-workers (14), Levine (98), and other workers (1) have shown the electrocardiograph to be essentially normal on such patients, thus revealing no damage to the heart. The tachycardia and other signs of poor response to exercise and changes of posture during convalescence are explained by Levine to be due to the poor peripheral vascular tonus rather than any cardiac involvement.

Bronchopneumonia was found to be the most common pulmonary complication in tsutsugamushi disease, it having occurred in nine per cent of all the patients in one series. Less common are pleural effusion, empyema, and rarely lobar atelectosis. In a very few cases bronchial asthma complicates the picture, the patients

not previously experiencing any asthmatic attacks.

Very rarely, isolated cases of hepatitis, splenic infarcts, thrombophlebitis, and transient peripheral neuritides have complicated the course of this disease. However, the majority of fatalities that result from this infection are due to circulatory failure or pneumonia, the other complications causing a very small portion of the deaths. The mortality rate varies from two to ten per cent, although in certain areas, especially Japan, a fifty per cent death rate has been reported.

The general pathologic picture is a vasculitis and a perivasculitis of the smaller blood vessels, principally of the skin, eyes, lungs, heart, and brain. Surrounding the vessels are accumulations of plasma cells, monocytes, and lymphocytes with damage to the surrounding cells in severe lesions. There may be focal edema and interstitial infiltration of round cells. Thrombus formation is noted in some of the capillaries. The brain shows perivascular infiltration of monocytes and early resultant gliosis, this forming the so-called typhus nodule. This pathology occurs more frequently in the pons and medulla and also the cerebellar portions of the brain. In some cases, the lungs have shown swelling of the alveolar walls and an exudate of mononuclear cells, red cells, and plasma. Petechial

hemorrhages are quite common in the heart, lungs, kidneys, and alimentary tract.

In endemic areas where tsutsugamushi is known to exist, any febrile illness should be carefully studied before this disease is excluded in a differential diagnosis. Because of the frequent co-existence of malaria and tsutsugamushi, frequent blood smears should be examined to exclude malarial parasites. This rickettsial disease is differentiated from typhus and spotted fever mainly by means of the positive agglutination in a moderately high titer with OX K strain of Proteus bacillus in the Weil-Felix reaction. Also the characteristic eschar and regional or general lymphadenitis of tsutsugamushi are diagnostic aids. In atypical cases of this disease which show a low agglutination titer for OX K and absence of the primary lesion, animal inoculation, cross-immunity tests, and other special laboratory studies may be required to establish the diagnosis.

In tsutsugamushi, as in the other rickettsial diseases, there is no specific therapy. In general, the treatment should be symptomatic and supportive, the principles being identical with those employed in other rickettsial diseases. The sulfonamides have no place in the treatment of tsutsugamushi. Strict bed

rest and quiet are essential. A special high protein and high vitamin diet is required, and good adequate nursing care is important. Very often the support and general care that the patient receives in the first two weeks, especially, is a very important factor in the final outcome. Digitalis is absolutely contra-indicated except for cardiac failure, and then the results prove disappointing. Oxygen therapy may afford some relief. Blood plasma and vasomotor stimulants are of special help in cases of peripheral vascular failure without congestive heart failure (44).

Vaccination is of no value in tsutsugamushi in as much as no efficient vaccine has been prepared against this disease. Since there is no cross-immunity between this and other sub-divisions of the rickettsial diseases, it is not expected that vaccines against typhus or spotted fever will be of any value against tsutsugamushi. Very recent investigations by Bell and Plotz (60) have shown in experimental animals that an active immunity can be developed following infection with tsutsugamushi, but, as yet, no progress toward actively, or passively, immunizing humans against this disease has been made.

Prevention of the disease naturally centers about the eradication of the mite and avoidance of its bite by protective clothing and chemical sprays. The Army

and Navy in World War II used these preventative measures quite extensively in an attempt to decrease the number of casualties resulting from tsutsugamushi. The fighting men wore clothing impregnated with dimethyl phthalate and other chemicals (90) (138), and wore tight leggings. D.D.T. powder and other insect repellents were used. Camp sites were carefully selected and, when possible, were cleared by natives. The kunai grass, in which the trombiculid larva mite and animal reservoir host, such as the rat, are found (109), was cut and burned. The hospital areas, the barracks, and paths were usually sanded and soaked with petroleum oil. All of these measures were done in an attempt to eradicate the mite and its habitat (156) (170). Sleeping on the ground was prohibited. Of course, extensive rat poisoning and trapping programs were instituted to control, if not destroy, the natural reservoir hosts of this disease. The fighting men, especially those in patrols and such, were instructed to carefully examine themselves for mites. With the institution of all of these preventive and protective measures, a dramatic decrease in the number of new cases resulted (123).

"Q" FEVER

"Q" fever was first described as a separate and distinct entity in 1937 by Derrick (41) in Australia. This investigator showed that it had certain resemblances to the typhus group, but was distinguished from it particularly by the absence of the characteristic rash and by the consistently negative Weil-Felix reaction with Proteus bacillus. His investigations further showed that most of these cases occurred in meat workers, abattoir workers, and dairymen, and thereby suggested cattle or pigs as a reservoir of infection. Burnet and Freeman (21), working at the same time on this new disease entity, succeeded in isolating the causative organism from laboratory animals infected by inoculation with human sera obtained from patients ill with "Q" fever; the organism was isolated as a rickettsia which was found only in intracytoplasmic accumulations. Like all true rickettsias, it failed to grow on standard bacteriological media, but was cultured on media containing tissue cells (19). Dr. Derrick (42) proposed the name Rickettsia burneti for the new organism in honor of Dr. Burnet who discovered it.

The following year Davis (39) and Cox (33), while working near Nine Mile Creek in Montana, isolated a

filter-passing rickettsia from the Rocky Mountain wood tick, Dermacentor andersoni. This same infectious agent was isolated some twelve years earlier by Noguchi (125) from the wood tick, and it was noted at that time that guinea pigs which recovered from infection by this agent were not immune to subsequent infections with the organism of spotted fever and vice versa. However, no further work was reported up to the time of Davis and Cox's report. The rickettsia isolated in this case was designated Rickettsia diaporica by Cox (34). This disease was first known as Nine Mile fever, but now is generally termed American "Q" fever. Also, in 1938, Parker and Davis (128) succeeded in transmitting the disease experimentally by tick. The first case of human infection in the United States resulting from this disease was reported by Dyer (45). This was apparently a laboratory infection acquired by a member of the staff of the National Institute of Health while he visited a few days at the Public Health laboratory in Hamilton, Montana, as the organism isolated from his blood was found to be the causative agent of American "Q" fever. A few years later an outbreak of pneumonitis occurred among employes of the National Institute of Health in Washington, D.C. (83), and the bacteriologic studies carried out by Dyer (56) revealed

the causative organism to be the rickettsia responsible for "Q" fever. Subsequently, cases other than laboratory infections were soon observed in the United States (80).

With the almost simultaneous discovery of these two similar disease entities in different countries, investigations were begun to determine the relationship, if any, that existed between American and Australian "Q" fever. Several workers had suggested such a relationship earlier, but it was not established definitely until Burnet and Freemen (20), while working in Australia, showed that the two isolated rickettsial organisms were immunologically indistinguishable; they suggested that both types be included in the same species. Subsequent work by Dyer (50) and other workers (12) confirmed these findings. Guinea pig experimentation has shown, however, that the American "Q" fever is a more virulent type of infection than the Australian variety (22). At the same time cross-immunity tests were performed in which the relationship of "Q" fever to other rickettsial diseases was determined; the results of these experiments revealed that there was no evidence of any immunological relationship between this new disease and the other rickettsioses tested (23).

The transmitting agent of "Q" fever has not been definitely proven. Although the causative organism has been isolated from ticks caught in Montana, tick bites have not been proven in human cases. There is also evidence that "Q" fever may be transmitted from man to man without the agency of ticks. Thus, the role of ticks as the transmitting agents for American "Q" fever still remains obscure. As we have mentioned previously, most of the cases in Australia have occurred in people who have contact with cattle or pigs. This suggests a reservoir of infection in these animals with a blood-sucking parasite as a vector. A tick, Haemophysalis humerosa, has been suspected but never proven as the transmitter of the disease. Various animals of the bush areas in Australia have been investigated as reservoirs of infection in nature. Bandicoots (59) were shown by Derrick and co-workers (43) to be involved in the natural cycle of "Q" fever; sera taken from these animals produced infections in laboratory animals. However, as in America, the true transmitting agent or agents have not been determined.

Clinically, "Q" fever is characterized by a sudden acute onset. The outstanding symptom is a generalized headache; it is severe and persistent, and is, in most cases, the chief complaint. The patients also run a

mild fever (100° to 101° F) which may last from a few days to three or four weeks. The pulse rate is comparatively slow, in most cases not exceeding ninety per minute. Chilly sensations and chills, malaise, sweats, joint tenderness, pain in the eyeballs, and nausea and vomiting often accompany the fever and headache. Physical signs are very slight or even absent, the chief finding being a patchy pneumonitis generally detected only by x-ray; this sign is especially characteristic of the American variety of "Q" fever (96). No rash is present as in other rickettsial diseases, and as we mentioned elsewhere, there is no agglutination of any of the strains of Proteus bacillus in the Weil-Felix reaction. The blood picture is usually one of a slight leucocytosis. Recovery from the disease is usual. Derrick (41), in his series of cases in Australia, reported no fatalities.

As in the treatment of the other rickettsial diseases, there is no specific therapy for "Q" fever. The treatment is entirely symptomatic and supportive. Maintenance of body fluids and chlorides, as well as an adequate diet intake, are essential aids. In as much as the disease is rather mild and self-limiting and no complications have been reported, there seems

to be no special demand for additional treatment outside of that mentioned above.

Bengtson (13) has prepared vaccines against "Q" fever which are quite effective in preventing the infection in laboratory animals, but, as yet, no human vaccines have been reported in use. She has also devised a complement fixation test which is specific for "Q" fever, and is consequently of value in the diagnosis of the disease (11).

With the close of World War II, we can now expect to find further investigations into this new and opportunity-filled field of research, the epidemiology of "Q" fever being especially in need of further study.

TRENCH FEVER

Trench fever, also known as Five Day fever and Wolhynian fever, is generally thought to have first occurred during World War I. However, Sir Arthur Hurst, in a recent article (86), believed that the disease had been endemic in parts of Poland for many years previous to this time, but was regarded by the physicians there as a form of malaria or influenza. It was also known in the seventeenth century as Five Day fever according to a passage in the German poem, "Meister Isengrimus" (171). In addition, reference to a "febris quintana" appeared in Russian literature a century or more ago, and Moldavia fever was described by Dehio as having occurred in the Russo-Turkish War in 1877 which no doubt was trench fever. The first known German clinical observations on trench fever were made by His in February, 1916; he gave it the name of "febris wolhynica", having observed it first among German soldiers in the Volhynia province in Poland (86). Trench fever first appeared in the French and British armies in France and Flanders in 1915, probably having been conveyed by louse infested German soldiers coming from the eastern to the western front. It was first noticed by Graham (69) in British troops in the summer of 1915,

and also by Hurst in Salonika in the latter part of the same year. Graham (70) (71) was the first to recognize the specific nature of the disease, but was followed shortly afterwards by Hunt and Rankin (85), who gave a more complete clinical report of the disease than did Graham. It was in their paper that the name "Trench fever" first appeared, having been adopted from the soldiers in the trenches who first used the term. Another group of investigators, McNee, Renshaw, and Brunt (114), about this same time (1915), began their study on the essential pathology of the disease; they were finally successful in transmitting the disease from man to man.

In 1916 it was shown by Topfer (32) and later confirmed by Arkwright and co-workers (4), Jungmann and Kuczynski, and Munk and da Rocha-Lima (32) that lice which had fed on trench fever patients contained very large quantities of rickettsia bodies in the midgut. Da Rocha-Lima found that these bodies were lying on the surface of the epithelium (extracellular) and were not in an intracellular position like the Rickettsia prowazeki in typhus-infected lice. These earlier investigations, in addition to later confirmatory evidence, establish, for the present at least, the extracellular rickettsia, to which the name Rickettsia

quintana is assigned, as the causative organism of trench fever. Since World War I, trench fever had disappeared, and opportunity for intensive study had not been present until its recurrence, on a much smaller scale however, with the present war. As a result, its true relationship to the other rickettsial infections is not yet known.

The method of transmission of this disease remained unknown until 1916 when, through the experimental work of Hunt and McNee (84), evidence was presented that suggested the body louse as the transmitting agent. This was collaborated by the work of Hurst (87) (88) in Salonika who likewise produced suggestive evidence in favor of louse transmission. Nearly two years elapsed before the systematic experiments of the American Trench Fever Commission in France and the British Trench Fever Commission in London showed conclusively that the body louse transmitted the disease (169). About this same time Davies and Weldon (38) proved the body louse to be the transmitting agent by subjecting themselves to lice which had fed upon trench fever patients; they became ill with trench fever twelve days after exposure to the lice. In additional investigation on the transmitting agent, Byam and co-workers (24) found that the infected lice must be crushed and scratched into the

skin before the disease could be contracted.

Clinically, trench fever is characterized by paroxysms of fever which tend to occur at regular intervals (usually four to five days), the intervening period being apyretic, by local pains particularly of the shin bones, by an erythematous rash, and by enlarement of the spleen. It usually begins with an abrupt onset without premonitory symptoms, but may occasionally be preceded by a feeling of malaise a day or two before. The earliest complaint is generally a severe frontal or retro-orbital headache which is rapidly followed in a few hours by pain in the lumbar region of the back, gradually extending down into the legs after two or three days. The fever that occurs in this disease may be one of three types (91):

1. The first type is characterized by paroxysms of fever lasting one or two days and recurring at intervals of four to six days; the intermission usually lasts about five days. These paroxysms may number up to a dozen or so.

2. The second may be an undulating type of fever, the waves recurring with a periodicity of four to ten days.

3. Rarely, the third type fever may similate typhoid.

The fever usually ranges from 102° to 104° F. In the early stages of the disease, pains occur in various parts of the body, but later on they tend to localize

in the shin bones, which is an important diagnostic feature of trench fever. The severity of the pain in the tibia caused the soldiers to name it "shin-bone fever". The characteristic rash usually appears during the first twenty-four to forty-eight hours, and thereafter comes and goes with the fever. It is present in the majority of cases, being usually macular in type, with occasional cases showing papules. The distribution is generally over the lower thorax and abdomen. Enlargement of the spleen is observed in forty to fifty per cent of the cases. Nausea and vomiting may occur. Occasionally herpes labialis accompanies the disease. Although catarrhal irritation of the upper respiratory tract may occur, it is rarely severe. The patient occasionally complains of profuse sweating and lacrimation. The blood picture is characterized by a leukocytosis which reaches 25,000 to 30,000 at the height of the attack, and which is followed by normal ranges during the intervals. The differential count at the height of an attack shows a pronounced deviation to the left with an increase in the lymphocytes and monocytes. Eosinophils are often absent in the paroxysms, but are increased in the intervals. The incubation period of trench fever varies from five to twenty-five days. Relapses are quite frequent in trench fever,

and they are prone to occur several weeks or several months after apparent recovery.

The pathology of trench fever is not very well known; fortunately for the patients and unfortunately for the pathologists, no postmortem studies have been made since the disease is never fatal. Macules taken from the skin during their appearance have shown no specific changes.

Diagnosis of trench fever in epidemics is readily made on the basis of the symptomatology mentioned above. Of prime importance is the behavior of the fever together with the characteristic pains in the tibia and lower spine. In the differential diagnosis, the typhoid type of trench fever is differentiated from true typhoid fever by the presence of a negative Widal reaction in addition to the characteristic moderate leucocytosis in contrast to the leucopenia of typhoid. Relapsing fever and malaria are best ruled out by examination of blood smears for their specific etiologic agents. As mentioned previously, the Weil-Felix reaction is of no importance in the diagnosis of trench fever since there has been no report of agglutination of any of the X strains of Proteus bacillus by serums of trench fever patients.

Trench fever has no mortality, but the morbidity rate is high during epidemics as was shown during World War I. At that time, it was calculated that an army of one million men would lose 45,000 casualties from trench fever, and that eighty to ninety per cent of them would be unfit for duty for at least three months and the rest for six months (86). As yet no reports have been received from the present war, but it is anticipated that the morbidity rate is very much lower due to the change in type of warfare and better knowledge concerning louse control and eradication.

There exists no specific or well-established treatment against trench fever, and the various drugs and chemicals used up to date (salvarsan, mercury, quinine, methylene blue, salicylates, sulfas) have not changed or shortened the course of the disease. No serum treatment has ever been tried as far as reports in the literature reveal. Of course, symptomatic treatment is indicated. Prolonged bed rest, good diet, and hygienic surroundings are also in order.

Prevention of the disease is primarily a question of efficient eradication of body lice. With the advent of D.D.T. powder and other chemicals as highly efficient delousing agents, there is a good possibility that trench fever may be eliminated entirely.

CONCLUSION

We have pointed out the important strides that have been taken in the last few decades toward completely understanding the rickettsial diseases both individually and as a group. However, there is still much investigation to be done before all of the true facts concerning the rickettsias are known.

These diseases provide a great opportunity in the field of research for both new and experienced investigators. The therapeusis of rickettsial diseases is an especially inviting field for experimentation and research in as much as no specific therapy exists for any of the rickettsial infections. Much also remains to be done on the epidemiology of these diseases.

Also, because of the increasing importance which the rickettsial diseases are assuming, as best exemplified by our experiences with them in World War II, it is important that we have, at least, a speaking knowledge of these diseases. If a step toward the better understanding of these diseases has been accomplished through the presentation of this paper, then its purpose will have been fulfilled.

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