Current Status of Murine Typhus

1976

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CURRENT STATUS OF MURINE TYPHUS

BY

DOROTHY WILSON FREEMAN
B.S., Florida Technological University, 1970

RESEARCH REPORT

Submitted in partial fulfillment of the requirements for the degree of Master of Science in the Graduate Studies Program of Florida Technological University

Orlando, Florida
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**INTRODUCTION**

**Rickettsial Diseases of Man**

The rickettsial diseases of man can be categorized into five groups: (1) the typhus group, including epidemic typhus and murine typhus; (2) the spotted fever group, including American spotted fevers, Boutonneuse fevers, Siberian tick typhus, Queensland tick typhus, and rickettsialpox; (3) tsutsugamushi disease; (4) trench fever; and (5) Q fever. With the exception of Q fever each disease is transmitted to man by an arthropod vector; all have an animal reservoir (Philip 1966).

The three most important rickettsial diseases in the United States are Rocky Mountain spotted fever, murine typhus, and Q fever (Woodward 1973). Much of the field and laboratory work that has resulted in the control of murine typhus was performed in the United States where the disease is concentrated in the southeastern states (White 1965b).

**Murine Typhus**

Murine typhus is a serious but rarely fatal febrile disease of worldwide distribution (Philip
Other names of the disease are: endemic flea-borne typhus (Benenson 1970); Tabardillo (Mexico); shop typhus (Southeastern Asia); Manchurian typhus; Toulon typhus; Moscow typhus; and red fever of the Congo (Burrows 1968). The etiological agent is Rickettsia typhi, formerly known as R. prowazekii var. mooseri, R. muricola, and R. mooseri (Burrows 1968).

The reservoirs of murine typhus are typically domestic rats (Rattus rattus and Rattus norvegicus) and the vector is usually the oriental rat flea (Xenopsylla cheopis). Fleas acquire the rickettsiae from the circulating blood of infected rats which show no signs of illness. The fleas remain infective throughout their one year life span, transmitting the rickettsiae to other rats and to man by feces. The classic mode of infection occurs when the flea takes a blood meal from an infected rat. The ectoparasite defecates the rickettsiae, which contaminate the bite site or any other fresh skin wounds. Human infection usually results from rubbing the flea feces into the skin while scratching (Philip 1966, Benenson 1970). Inhalation of dried infective flea feces can also be a mode of transmission (Wisseman et al. 1962, Benesin 1970).
The clinical features of murine typhus are similar to but milder than those of epidemic louse-borne typhus. After an incubation period of six to 14 days, an individual has muscular pains, shivering, loss of appetite, fever above 102°F, which lasts approximately 14 days, and a macular rash which appears on the trunk of the body at the end of the first week. Complications and fatalities rarely occur (Philip 1966, Benenson 1970).

Immunity is conferred by one attack (Benenson 1970), and cross-immunity can occur in persons who have had epidemic louse-borne typhus (Philip 1966). *Rickettsia typhi* is closely antigenically related to *Rickettsia prowazeki*, the etiological agent of the more serious epidemic louse-borne typhus (Burrows 1968). A vaccine against murine typhus has not been developed because attenuated vaccines of *R. prowazeki* (strain E) provide resistance to murine typhus (Philip 1966).

Laboratory diagnosis of murine typhus as well as other rickettsial diseases can be determined by two methods: (1) demonstration of rising antibody titer in serial serum specimens and (2) insolation and identification of the causative agent (Philip
Statement of Problem and Objectives

Three decades ago murine typhus was considered to be a serious public health problem in the United States with the highest incidence of the disease occurring in the southeastern states (Miller and Beeson 1946, Pratt 1958, White 1965a, White 1965b). The requirement for reporting cases of murine typhus to local health authorities went into effect in 1920 (White 1965b). A total of 31 cases was reported that year (Table 1). The number of reported cases reached a maximum of 5401 in 1944. Following that peak year a steady decline of reported cases has occurred. Approximately 35 murine typhus cases per year have been reported for the past 15 years.

Currently murine typhus is categorized as a notifiable disease of low frequency by the Center for Disease Control (1975). Yet, the disease is still considered to be widespread in nature (Adams et al. 1970). The most effective control measure for the vectors of the disease is DDT (Philip 1966).

The purpose of this study is to examine the nature and history of murine typhus. Explanations will be sought to account for the dramatic decrease
in number of cases reported and for the continued maintenance of the present low level of incidence in the United States.
HISTORICAL ASPECTS

Early Developments

Murine typhus was first described in the United States in 1913 when six cases were reported in Atlanta, Georgia (Paullin 1913). Diagnosis of these cases was based only on clinical findings. Shortly thereafter the disease appeared in North Carolina and Texas (Miller and Beeson 1946).

In 1910 Brill (1910) described a typhus-like disease occurring endemically in New York, New York. In 1912 he observed a cross-immunity between this disease and epidemic typhus (Anderson and Goldberger 1912). Zinsser (1934) hypothesized that the disease was a recrudescence of epidemic typhus. Plotz (1943) demonstrated the immunologic identity of Brill's findings with epidemic typhus by using the complement fixation test with rickettsial suspensions as antigens. For years murine typhus was erroneously called Brill's disease in the southern states because of the similar clinical features (Miller and Beeson 1946, White 1965b). Brill's disease is currently known as Brill-Zinsser disease (Joseph 1970).
Maxcy's (1926) epidemiological studies in the southeastern states indicated that murine typhus was a milder disease than epidemic typhus. He found that it occurred in the absence of body lice, the vector of epidemic typhus, and that it occurred more commonly in summer and fall as opposed to winter and spring, when epidemic typhus appears. He suggested that the reservoir was a rat or mouse, as opposed to man which is the reservoir for epidemic typhus, and that a blood sucking parasite was the vector.

Maxcy's hypothesis was substantiated in 1931 by the experimental work of two, independently operating groups: Dyer, Rumreich, and Badger in Baltimore, Maryland, and Moosser, Castaneda, and Zinsser in Mexico City, Mexico (Pratt 1958, White 1965b). The Baltimore group produced evidence that the oriental rat flea (*Xenopsylla cheopis*) was the vector of the disease (Dyer et al. 1931). The Mexico City group produced evidence that indicated that the domestic rat was the reservoir (Moosser et al. 1931). Since then the disease has been known as murine typhus (White 1965b).

The first specific serological test for murine typhus was the complement fixation test developed in 1941 (Bengston 1941). Prior to this time the
non-specific Weil-Felix test had been used in both experimental clinical work (White 1965b).

**Control Programs**

In 1945, following a peak year in which 5401 cases of murine typhus were reported, the United States Public Health Service began the first comprehensive typhus control program in nine states in which murine typhus was highly endemic (White 1965a, White 1965b). This program involved expansion of rat proofing of buildings, poisoning and trapping of rats, and dusting of rat runs with DDT. Subsequent evaluations of rat poisoning and DDT dusting programs indicated a significant reduction in the number of fleas, mites, lice, typhus antibodies in rats, and murine typhus cases reported (Morlan and Hines 1951, Smith 1958). Other factors, such as improved garbage collection and disposal, increased reliance of private industry on pest-control companies, intensified sanitation programs, and the development of effective anticoagulant rodenticides, also played a part in reducing the incidence of the disease (White 1965a). The USPHS control was terminated in 1952 following a nearly 15-fold decrease in number of cases reported (White 1956b).
In contrast, a four-year epidemiological study conducted by Fox and Garcia-Moll (1961) in San Juan, Puerto Rico indicated a dramatic decrease in reported cases as well as in rat flea populations in spite of unsuccessful rat control measures, low level sanitation practices in many areas, and the lack of a DDT dusting program. They also observed that as mite ectoparasites increased, rat flea ectoparasites decreased. This decline in incidence still remains an enigma which led to White's hypothesis (1965a) that factors as yet unknown can affect the epidemiological profile of murine typhus. Nevertheless, the control of fleas by dusting rat runs with DDT is considered by most workers to be the best method of controlling murine typhus (Philip 1966). However, all major uses of DDT in the United States were banned by the Environmental Protection Agency effective December 31, 1972 (Council of Environmental Quality 1972). Arthropod and rodent control departments of the Florida Division of Health currently use 2% heptachlor or 5% chlordane for dusting rat runs for elimination of ectoparasites; upon restriction of use of chlordane, 5% malathion will probably be used; the anticoagulant, dicumoral,
is used as a rodenticide (Whittaker pers. comm.).

Treatment

Coincidental with the initiation of the USPHS typhus control program was the development of chloramphenicol and tetracycline, broad-spectrum antibiotics which proved to be highly effective in treating rickettsial diseases (Ley and Smadel 1954, Pratt 1958). The first antibiotic to be clinically used for rickettsial diseases was chloramphenicol which was administered in La Paz, Bolivia in 1947 for treating of epidemic typhus (Payne et al. 1948). Both chloramphenicol and tetracycline are rickettsiostatic and the eventual recovery from the disease is dependent upon the immune response of the individual (Anigstein et al. 1948, Wong and Cox 1948, Smadel et al. 1949, Snyder et al. 1950). The use of broad-spectrum antibiotics has dramatically reduced the prolonged febrile courses of rickettsial diseases and the frequent deaths which resulted (Ley and Smadel 1954).

Current treatment for murine typhus is the same as for epidemic typhus. Administration of drugs of the tetracycline group (Terramycin, Achromycin, Aureomycin) or chloramphenicol (Chloromycetin) produce
equally effective results. Recommended dosage for adults is an initial dose of 2 gm followed by 2 gm daily in divided doses. Antibiotic treatment should continue until at least the 10th day after onset of symptoms and for a minimum of 48 hours after the fever has subsided (Philip 1966).

**Current Diagnostic Methods**

The complement fixation serologic test is the most practical diagnostic method for differentiating rickettsial groups (Joseph 1970). However, for within-group differentiation, such as between murine typhus and epidemic typhus, species specific antigens must be used. These are prepared by removing soluble group specific antigens from the rickettsial organisms by repeated washing which leaves the firmly attached species-specific antigens on the cell wall (Philip 1966). Since this is a time consuming and expensive procedure, most commercial complement fixation preparations contain soluble group specific antigens (Joseph 1970).

Complement fixing antibodies can be detected about seven to nine days after onset. A peak titer occurs between the 12th and 16th days. The titer declines slowly during the following three to six
months and remains at a comparatively low level for years. Diagnosis is based on a four-fold or greater rise in titer between acute and convalescent phase serum specimens, or on a decline in titer between paired sera taken at four to six weeks and 12 to 14 weeks after onset, or on a titer greater than 1:160 for a single convalescent phase serum sample. Complement fixation antibodies occur in significant titer for many years after rickettsial infection or immunization (Joseph 1970).

Broad-spectrum antibiotics may partially or completely inhibit complement fixation antibody formation (Lynnette et al. 1952). For this reason considerable significance has been placed on the Weil-Felix agglutination reaction, one of the earliest devised serological tests for rickettsial diseases (Sonnenwirth 1970).

Sonnenwirth (1970) discussed various aspects of the Weil-Felix test. Nonspecific antigens, designated OX-19, OX-2, and OX-K of the O variant of nonmotile strains of the bacterial species, *Proteus vulgaris*, are agglutinated by antibodies produced as a result of certain rickettsial diseases. A fourfold rise in titer is obtained for both murine and epidemic typhus
with Proteus OX-19 antigens. Variable rises in titer are obtained for Rocky Mountain spotted fever with Proteus OX-19 antigens. Murine typhus, epidemic typhus and Rocky Mountain spotted fever can produce less than fourfold rises in titer with Proteus OX-2 antigens, however the latter can also produce a fourfold rise with this antigen. Only tsutsugamushi disease produces a positive reaction with Proteus OX-K antigens. Because of the similarities in rise in Proteus OX-19 titers, the Weil-Felix test cannot be used to differentiate between murine typhus, epidemic typhus, and Rocky Mountain spotted fever.

Antibodies to Proteus OX-19 can be detected during the second week of murine typhus. Peak titers of about 1:640 to 1:1280 occur late in the third week of illness; the titer then declines rapidly (Joseph 1970). Presumptive diagnosis is based on a fourfold or greater rise in titer between acute and convalescent phase serum specimens; significance is placed on a titer of 1:160 or greater in a single serum sample (Sonnenwirth 1970). Sonnenwirth (1970) further stated that low titers showing little change usually indicate past Proteus infections.

Isolation and identification of R. typhi can
be accomplished by inoculating an adult male guinea pig with blood taken from the patient during the febril phase. However, this method of diagnosis is not routinely used in clinical laboratories. Subpassage of peritoneal fluid, the tunica vaginalis, and splenic tissue results in increase in rickettsial concentration. This allows the rickettsiae to be demonstrated in impression smears of the spleen and testicular tissues (Joseph 1970).

Host reactions in infected male guinea pigs have been used to differentiate between epidemic typhus, murine typhus, and Rocky Mountain spotted fever. Murine typhus produces the characteristic Neile-Mooser reaction. This is an inflammatory reaction of the tunica vaginalis which results in a nonreducible scrotal swelling. The inflammatory exudate consists of Mooser cells which are large mononuclear serosal cells filled with intracytoplasmic rickettsiae. Epidemic typhus rarely produces scrotal swelling and does not produce Mooser cells. Rocky Mountain spotted fever produces reducible scrotal swelling and large mononuclear cells with rickettsiae visible in both the cytoplasm and nucleus (Philip 1966).
Correlation Between Temperature and Prevalence

Hill and Morlan (1948) showed correlation between the seasonal occurrence of murine typhus and the seasonal prevalence of the oriental rat flea. Stewart and Hines (1954) observed a peak in cases reported in the summer in rural areas, but an even distribution of cases throughout the year in urban areas. Smith (1957) demonstrated a correlation between the monthly abundance of the oriental rat flea and the monthly incidence of murine typhus antibodies found in a sample of both species of domestic rats. Mohr et al. (1953) found that murine typhus was widespread in rats in rural areas where the average January temperature was 47° F or greater, but was not found in rural areas where the average January temperature was below 40° F even though the disease occurred in rats in northern urban areas in heated buildings.
WHO Statistics

Between 1969 and 1973 a total of 1309 cases of typhus classified as either murine or endemic was reported to the World Health Organization (Table 2). During this five year period Israel reported 521 cases, which constituted 39.8% of the worldwide incidence; this is the equivalent of 17.966 cases per 100,000 population. The Maltese Islands reported 107 cases (8.2% of the worldwide incidence) which is equivalent to 33.334 cases per 100,000 population. The United States reported 153 cases (11.7% of worldwide incidence); the equivalent being .075 cases per 100,000 population. Since some reporting countries did not specify the exact number of cases, these data represent low extremes.

USPHS Statistics

During the past seven years 86.9% of the reported cases in the United States came from the south Atlantic, east south central, and west south central areas (Table 3). This distribution was shown by White (1965b).
During these years, 69.7% of the total cases occurred in Texas. In 1974, 26.9% of the reported cases came from California.

**Inaccuracies in Reporting**

It appears that the number of cases of murine typhus reported to the USPHS does not reflect the actual prevalence of the disease. Several studies support this conclusion. Hill and Ingraham (1947) showed that although only 61 cases were reported in 1943 in Coffee County, Alabama, 211 individuals claimed to have had the disease. Complement fixation and/or Weil-Felix tests were positive for 135 of the 211 individuals. This indicates that only 45.1% of the actual cases of murine typhus were reported. In 1945 complement fixation tests performed on 4219 food handlers in San Antonio, Texas, proved positive for 3.5% (Davis and Pollard 1946). From this sample they estimated that approximately 700 cases per year occurred between 1935 and 1945; the highest reported incidence was 91 cases in 1944. A survey conducted in four counties in southwestern Georgia revealed that only about 33% of the cases which occurred in 1945 were reported to health authorities (Williams 1949). Quinby and Shubert (1953) studied 351 reported
and 99 unreported cases which occurred in eight southern states between 1948 and 1951. Only 58% of the reported cases were positive for complement fixing antibodies, and 33% of the unreported cases were positive.

It appears that the United States prior to and during the peak years of murine typhus incidence the disease was under-reported and following the peak years it was over-reported (Pratt 1958, Burrows 1968). Burrows (1968) stated that over-reporting resulted largely from misinterpretation of low-titer Weil-felix reactions.

**Maltese Islands Epidemiological Profile**

A murine typhus epidemiological profile somewhat similar to that of the United States occurred on the Maltese Islands. Vasallo (1970) discussed incidence between 1944 and 1967. Sixty-five cases were reported in 1944 (Table 4). A maximum of 135 reported cases occurred in 1945, followed by an abrupt decline to 35 cases in 1946. Mini-peak years occurred in 1950 and 1955 with 57 and 30 cases reported, respectively. A leveling off period, with an average of no greater than 14 cases per year, occurred between 1956 and 1967.
Vasallo (1970) suggested that the abrupt appearance of murine typhus on the Maltese Islands resulted from introduction of the disease during wartime conditions. He believed that ships bearing troops and cargo from North Africa were the probable source of entry for rats bearing fleas infected with murine typhus and bubonic plague. The presence of bubonic plague emphasized the need for intensified rodent control. Debris was removed and liberal amounts of DDT powder and anti-flea emulsion were used. Although Vasallo (1970) considered murine typhus to be a minor contemporary health hazard on the Maltese Islands, more recent WHO statistics indicate that 1972 and 1973 were mini-peak years with each having 32 reported cases (Tables 2 and 4). These islands, therefore, had the highest incidence of the disease per 100,000 population in the world.
A recent study of localized outbreaks of murine typhus was made by Miller et al. (1974) at the 12th USAF Hospital, Cam Ranh Bay, South Viet Nam from July 1968 through June 1969. Fifty-eight male military personnel were infected. Diagnosis was based on a greater than threefold rise in complement fixation antibody titer observed in paired sera collected at 7 and 14 day intervals. Weil-Felix OX-K, OX-19, and OX-2 tests were also performed. The OX-19 and specific antibody titers were usually in close agreement in degree of dilutional rise. However, the maximum rise in titers, which never occurred until at least 14 days after onset of illness, varied greatly.

Miller et al. (1974) described a typical case history. An acutely ill patient was admitted to the hospital after a four day illness characterized by headache, muscular pains, chills, and fever. Arthralgia, cough, chest pain, and nausea soon developed. A macular rash appeared over the abdomen on the fifth day and lasted four days. Twice daily
his temperature reached 104° F. With the appearance of the rash 500 mgm tetracycline was administered every six hours. Following the tetracycline therapy his temperature became normal within 24 hours and all symptoms disappeared within 48 hours. The patient returned to duty less than two weeks following the onset of illness. This dramatic shortening of the duration of illness was attributed to tetracycline therapy.

**Diagnostic Problems**

Murine typhus can be difficult to diagnose. Mellin et al. (1970) illustrated this point in the case history of a merchant seaman who recently arrived from Mexico, and was admitted on the 11th day of illness to a hospital in Baltimore, Maryland. The initial diagnosis was urinary tract infection. One week later the diagnosis was changed to an influenza-type disease. Although many of the symptoms of murine typhus were evident, with the exception of a skin rash, a rickettsial disease was not suspected until an elevated *Proteus* OX-19 was observed. A fourfold complement fixation antibody titer rise led to the confirmed diagnosis of murine typhus. The patient recovered after treatment of 2 gm tetracycline daily for 10 days.
Of 28 confirmed cases of murine typhus in Texas in 1969, influenza was the initial diagnosis in 22 instances. Weil-Felix tests were performed when the disease continued in spite of antibiotic therapy. Murine typhus was then considered and tetracycline was prescribed in 21 cases. Examination for rash was not made until late in the course of illness. The cases were confirmed by complement fixation convalescent titer of 1:64 or paired sera threefold titer rise (Older 1970).

Miller et al. (1974) recommend tetracycline therapy when murine typhus is suspected in the areas of known high incidence and whenever a fever remains of unknown origin after 72 hours of careful investigation.
Other Reservoirs and Vectors

Murine typhus may be widely distributed in nature (Adams et al. 1970). Animals other than domestic rats can serve as reservoir hosts (White 1965b). Some apparently naturally infected animals having positive sera for murine typhus are: opossum, cottontail rabbit, fox squirrel, house mouse, rice rat, cotton mouse, old-field mouse, cotton rat, dog, skunk, and blue jay (Morlan et al. 1950). Some laboratory infected animals are: gray squirrel, swamp rabbit, and chipmunk (Brigham 1938).

The Oriental rat flea (X. cheopis) is considered to be the most important vector, both from rat to rat and from rat to man, however, the tropical rat mite (Ornithomyssus bacoti), the rat louse (Polyplax spinulosus), and the flea (Nosopsylla fasciatus) are thought to spread the disease from rat to rat (Philip 1966). Reiss-Gutfreund (1966) isolated R. typhi from Hyalomma ticks removed from cattle in Ethiopia and from body lice (Pediculus humanus humanus) from two hospitalized cases of unspecified typhus in the same
country. Laboratory infection of *P. humanus humanus* with *R. typhi* has been demonstrated (Philip 1966).

Adams et al. (1970) suggested that opossums and their ectoparasites are responsible for sporadic outbreaks of murine typhus in Los Angeles and Orange Counties, California. Three cases of the disease occurred in these adjacent counties in 1967. An epidemiological survey revealed that the three individuals lived in association with dogs and cats, and that opossums occurred in the immediate environment. Field specimens were collected over a four month period during spring and summer of that year. Ectoparasite surveys showed that although *Rattus rattus* and *R. norvegicus* were present, *Xenopsylla cheopis* did not occur in this foothill area. The predominant ectoparasite on dogs, cats, and opossums was the cat flea (*Ctenocephalides felis*). None of the 104 *R. rattus* and *R. norvegicus* captured were serologically positive for *R. typhi* antibodies, however, eight of 75 opossums (*Didelphis marsupialis*) and one of seven skunks (*Mephitis mephitis*) had low titers of 1:8 to 1:32. *R. typhi* was isolated from the spleen of one opossum. The predominant ectoparasite on opossums was *C. felis* and on skunks
was a louse (*Pulex simulans*).

Over the previous 20 years there had been a shift in the distribution of murine typhus cases from urban Los Angeles areas where *R. norvegicus* was known to be sero-positive for *R. typhi* to the suburban foothill areas of Los Angeles and Orange Counties. Adams et al. (1970) suggested that a transmission cycle other than the classic rat-flea one exists. They implicated *C. felis* as the vector from animal to animal and animal to man.

Older (1970) also thought *C. felis* was a vector of murine typhus. During 1969, 28 confirmed cases of murine typhus were reported in Texas. Twelve of these led to an epidemiological study. Ten of these cases implicated *C. felis* as the vector. Two of these 10 implicated opossums as reservoirs; two implicated grass fleas, probably *C. felis* as the vector with reservoir unknown; and, six suggested domestic cats as reservoirs. Older (1970) assumed that cat fleas acquired *R. typhi* from infected rats. Two of the cases studied suggested contact with cats.
DISCUSSION

Since murine typhus is considered an enzootic disease in numerous naturally occurring animals (Morlan et al. 1970) and since DDT, the most effective ectoparasite control measure has been banned, it is remarkable that so few cases are reported in the United States. A possible explanation for the low number of reported cases is misdiagnosis due to failure to recognize the signs and symptoms of the disease.

White (1965b) observed that the infection rate for whites is about eight times greater than for blacks. Of 126 cases of murine typhus studied by Miller and Beeson (1946), rash was observed on 90% of the 58 white individuals and on only 43% of the 68 Negros. A possible explanation for the low incidence of murine typhus reported in blacks is that the rash may be more difficult to detect.

Older (1970) stated that of the 28 cases of murine typhus reported in Texas in 1969, rash was observed on only 25%. However, in these cases examination for rash often was not performed until
late in the course of illness. Because influenza was
the erroneous original diagnosis in 78% of the cases,
he recommends that murine typhus be a part of the
differential diagnosis when symptoms of influenza are
present.

In the one case history described by Mellin et
al. (1970) no skin rash was observed even after
careful repeated examination. Because of this and
because of the rarity of murine typhus in the United
States the ailment was initially diagnosed as a
urinary tract infection. One week later, the
diagnosis changed to an influenza-type illness.
Consequently, they recommend that physicians be alert
to the possibility of a murine typhus diagnosis.

A rash was observed on only 38% of the 58
patients studied by Miller et al. (1974). All
patients were subjected to a battery of diagnostic
procedures, including Weil-Felix and complement
fixation tests. Therefore, it is assumed that the
initial diagnosis in each case was murine typhus.
Tetracycline was administered to 57% of the
individuals upon laboratory diagnosis or strong
clinical evidence. Neither the number of tetracycline
treated patients having a rash nor the complement
fixation titers of tetracycline treated cases were given.

The widespread use of tetracycline is another possible explanation for the low number of murine typhus cases reported. This highly effective, broad-spectrum antibiotic is currently a drug of choice, second only to penicillin in the treatment of syphilis by various county health departments of the Florida Division of Health; it is administered in the same dosage as prescribed for murine typhus (Abel pers. comm.). Nationwide, tetracycline has been among the 50 most prescribed drugs since 1966, ranking fourth in 1973 and sixth in 1974 (Pharmacy Times 1975).

Older (1970) suggested that tetracycline may have been administered to cases of murine typhus which were misdiagnosed as influenza. Since the initial signs and symptoms of murine typhus are similar to some common ailments for which tetracycline is prescribed, the disease could be treated properly, although misdiagnosed, and never reported to health authorities. Also, early administration of tetracycline or other rickettsiostatic antibiotics could obscure the clinical signs and symptoms.

Available evidence does not indicate whether the absence of rash results from antibiotic therapy,
failure to detect apparent clinical signs, or a phenomenon of the disease process.

In an effort to ascertain if cases of murine typhus had gone undetected, Adams et al. (1970) performed complement fixation tests on 306 persons who lived in endemic areas and who had recorded histories of febrile illness. All cases proved to be negative for murine typhus. Although this sampling tends to indicate that missed cases are rare, no statement was made if the 306 cases received antibiotic therapy. Lynnette et al. (1952) claimed that broad-spectrum antibiotics may partially or completely inhibit complement fixation antibody formation.

Inaccuracies in USPHS murine typhus statistics (Davis and Pollard 1946, Hill and Ingraham 1947, Williams 1949, Quinby and Shubert 1953) blemishes the epidemiological profile. Several factors could have contributed to the inaccuracies. Of major importance is that the complement fixation test, the first specific one for murine typhus detection was not developed until 1941 (Bengston 1941). Prior to this time diagnosis was based on clinical findings or the non-specific Weil-Felix test. All confirmed diagnoses
were based on the Weil-Felix test (Miller and Beeson 1946). Presently, confirmed diagnosis is based on a group specific complement fixation test (Joseph 1970).

Another factor contributing to inaccuracies is the use of different standards for determining a positive identification. The current bases for a confirmed diagnosis are a fourfold rise in complement fixation titer in paired sera and/or a 1:160 titer for convalescent phase serum (Joseph 1970). Cases reported by the Texas State Health Department are confirmed by a threefold rise in titer or a 1:64 convalescent phase titer (Older 1970).

Another factor affecting statistics is failure to report murine typhus to health authorities (Williams 1949). This could result from failure of a patient to see a physician while ill or from failure of the attending physician to notify proper authorities.

Of considerable interest are the WHO statistics on incidence of murine typhus in Israel and the Maltese Islands between 1969 and 1973 (Table 5). In 1972 Israel reported 187 cases, the equivalent of 6.45 cases per 100,000 population; in 1972 and also in 1973 Malta reported 32 cases, the equivalent of 9.97
cases per 100,000 population. These figures exceed the 4.00 cases per 100,000 population reported in the United States in the peak year of 1944. However, 90% of the 5401 cases reported in the United States in 1944 were concentrated in the southeastern states (White 1965b). Therefore a density greater than statistically recorded existed.
SUMMARY

Murine typhus is a serious but rarely fatal febrile disease. The classic mode of transmission is to man from rat reservoirs via rat flea vectors. The disease was first described in the United States where much of the subsequent research has been done.

During the 1930's and 1940's murine typhus was a significant public health problem in the southeastern states. The rapid decrease in reported cases correlates with the initiation of the USPHS typhus control program, which included the use of insecticides, and with the development of broad-spectrum antibiotics. At present, murine typhus is considered to be a worldwide disease of low frequency. In the United States, it continues to be concentrated in the southeastern area.

Possible explanations for the low frequency of reported cases are misdiagnoses coupled with the widespread use of tetracycline. Many of the clinical signs and symptoms of murine typhus are quite similar to those of influenza-like disease for which tetracycline is often prescribed. Clinical
misdiagnosis, which may occur when the classic rash of the disease is not apparent, can be avoided by confirming diagnosis with the complement fixation serological test.

The late development of the complement fixation test, almost 30 years after the disease was first described, was a major contributing factor to the inaccuracies incorporated into the USPHS murine typhus statistics. Other factors contributing to a faulty epidemiological profile are the use of different standards for determining positive identification and the failure in reporting the disease.

The current status of murine typhus in the United States is that of a relatively insignificant disease. USPHS control measures, development of rickettsiostatic antibiotics, and improved insecticides and rodenticides have dramatically reduced the incidence of the disease. However, control measures should not be relaxed.
### TABLE 1. *Murine typhus in the United States*<sup>a</sup>

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^bPopulation data from National Geographic Society 1970.

^cSymbols: + = positive incidence, total number of cases not given; - = not reporting; * = negligible, less than 5%.

^dLow extreme.

^eConflict with Center for Disease Control.
TABLE 3. Distribution of murine typhus cases in the United States \(^a\)

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\(^a\)From Center for Disease Control 1968-1974.
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^b^Population data from National Geographic Society 1970.
LITERATURE CITED


Center for Disease Control. 1969. Morbidity and mortality report, annual summary. 18: 4-6


