to a possible source of infection may provide a clue to the recognition of these diseases when they occur in children. Rocky Mountain spotted fever, murine typhus and rickettsialpox are transmitted to children by invertebrate vectors. However, the child frequently may be unaware that he has been the accidental host of vectors of the last two diseases. Since Q fever is transmitted by air-borne dust, this disease should be considered in the diagnosis of illnesses resembling atypical pneumonia that occur among children directly or indirectly associated with livestock. Diagnosis of these rickettsial diseases may be difficult, even with the aid of laboratory tests, if patients have been treated early with broad-spectrum antibiotics.

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EPIDEMIOLOGIC ASPECTS OF LEPTOSPIROSIS

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More than 70 years have passed since Weil first described several cases of leptospirosis in humans although he had no knowledge of the etiologic agent. In 1905, Stimson,1 in New Orleans, first observed leptospires in kidney sections from a patient believed to have died of yellow fever. A few years later (1915) pathogenic leptospires were isolated first from patients with Weil's disease in Japan by Inada et al.2 and independently in Germany by Uhlenhuth and Fromme3 in the same year. About the same time the Japanese workers4 found that the rat (Rattus norvegicus) is a carrier of Leptospira icterohaemorrhagiae. Since this early work, extensive investigations have shown that leptospirosis occurs in humans and animals in all parts of the world and is not a single disease but a group of diseases caused by a variety of leptospiral serotypes. Possible explanations for the wide distribution of these diseases may be (1) that they are insidious infections which have appeared gradually and become established almost unnoticed,5 or (2) that they have been present for many years and remained largely undetected because of the variable masking symptoms and the problems associated with laboratory diagnosis. Although considerable attention has been directed toward studies of leptosporal infections by European and Asian investigators since the early 1930's much of our knowledge regarding the epidemiology, public health importance and distribution of these diseases in the United States has been gained only during the past decade.

The epidemiology of the leptospiroses has been shown to follow a characteristic pattern based, in part, upon the fact that
they are zoonoses, diseases transmitted from animal to animal and from animal to human. The chain of transmission, with rare exception, stops with human infection.

For many years rats and dogs were considered to be the primary animal carriers but as the search for leptospires continues the host range broadens not only among domestic animals but in a variety of feral mammals. Leptospirosis now constitutes a major problem in cattle and swine, and in some areas sheep, goats and horses become infected. The rat is one of many rodent carriers, including mice, voles, and shrews. In addition bats, mongooses, bandicoots, jackals, foxes, opossums, raccoons, skunks, and wildcats have been found infected. In these host animals, leptospires become localized in the kidneys and may be found in the lumina of the convoluted tubules. They may be shed in the urine for long periods.

Each leptospiral serotype usually is thought to have a primary animal host but they may infect other animals, and a “so-called” primary host for one serotype may become infected with other serotypes or even harbor two types at one time. A classic example of this is L. canicola, found principally in dogs; it has been isolated from cattle, swine and jackals, and serologic evidence suggests it may infect raccoons, while dogs have been found to harbor at least nine other serotypes.

Differentiation of the rapidly increasing number of pathogenic leptospiral strains is highly important from an epidemiologic and epizootiologic point of view. In the early 1930’s, it became apparent to the Dutch workers that classification of leptospires must be based upon serologic analysis. During the next 20 years these investigators studied antigenically distinct strains isolated in various parts of the world and developed technics for serologic identification. In 1954, Wolff and Broom published a suggested classification scheme which included 34 leptospiral serotypes isolated from man and/or animals. In the 3 years since this report, approximately 25 additional serotypes have been described in Australia, Africa, India, Europe, and the United States.

The primary problems in the United States appear to be with the more common types, L. icterohemorrhagiae, L. canicola and L. pomona in domestic animals and humans. However, seven other serotypes have been isolated and serologic findings suggest the presence of at least two others. The cause of Fort Bragg fever was identified after an 8-year period as L. autumnalis. Six years later the first animal host for this type in the United States was detected when the organisms were isolated from the kidneys of raccoons trapped in southwest Georgia. L. ballum has been found frequently in rural house mice and opossums and occasionally in rats and laboratory mice. Recent evidence has shown that one proved case in a human and three probable cases due to L. ballum contracted from Swiss white mice occurred among laboratory workers at the Rocky Mountain Laboratory, Hamilton, Montana. Serologic evidence suggests the presence of L. bataviae infection in humans, L. sejroe in cattle and L. grippotyphosa in humans and cattle. It is interesting that during recent cultural studies on wild mammals at the Communicable Disease Center, Newton, Georgia Field Station, L. grippotyphosa was isolated from raccoons trapped within 50 miles of a Florida farm on which cattle showed antibodies to L. grippotyphosa in 1952. In addition, these studies have revealed the presence of L. pomona, L. australis A, two serotypes that belong to the mitis-hyo sero-group and a member of the hebdomadis serogroup in wild animals.

In the transmission of leptospiral infections to humans, these animal carriers which may become urinary shedders after acute, mild or more frequently inapparent infection, serve as important foci. Infections of humans and other animals results from direct or indirect contact with infected urine of these shedders. For example, direct contact may occur when individuals care
for sick animals, fondle a pet dog or handle the tissues of infected animals in abattoirs. Indirect contact occurs when the organisms are excreted in water or moist soil and individuals are subsequently exposed while swimming, or working or otherwise coming in contact with the contaminated environment.

Although arthropod vectors have not been incriminated as yet in the transmission of leptospirosis in nature, several investigators\textsuperscript{31-34} have been able to infect ticks by allowing them to feed on infected guinea pigs or hamsters. These experimentally infected ticks transmitted the disease to normal animals. However, recently \textit{L. grippotyphosa} was isolated from the European tick \textit{Dermacentor marginatus} S. from cattle in Russia where isolated cases of leptospirosis had occurred among farm animals.\textsuperscript{34}

During the acute phase of leptospirosis in lactating animals, leptospires may be shed in the milk but no cases in humans have been attributed to drinking infected milk. This may be explained by Kirschner's\textsuperscript{35} observation that whole milk is leptospirocidal and the organisms will survive in it for only a few hours.

The leptospires usually enter the body through the mucous membranes of the conjunctivae, nose or mouth. It is doubtful that these organisms penetrate the intact skin and it is unlikely that the digestive tract is an important portal of entry since the pH of the stomach is usually such that they may be quickly destroyed.

Environments that favor the survival of leptospires outside the body include moist soil, stagnant ponds of slow-moving streams that are neutral or slightly alkaline and temperatures of 22\degree C or more. When these conditions exist in nature, leptospires may survive several weeks.\textsuperscript{36,37}

It is under such conditions that several large outbreaks have occurred in the U. S. after swimming in contaminated water. Since 1940, there have been four outbreaks in Georgia,\textsuperscript{38-40} one in Alabama,\textsuperscript{41} and one in Wyoming\textsuperscript{42} involving more than 150 individuals. Each of these water-borne leptospiral outbreaks followed a similar pattern. They occurred in the late summer during drought periods; there was presumed contamination of a stagnant pond or slow-moving creek by urine from infected animals and transmission to humans by immersion in the contaminated water. The patients were young, primarily children ranging from 5 to 16 years of age with some young adults. Similar water-borne outbreaks in young people have been reported in many other areas of the world.\textsuperscript{43-46}

The leptospiroses are frequently referred to as occupational diseases. Certainly opportunities for exposure are encountered more frequently by veterinarians, abattoir workers, sewer workers, dairy workers, animal husbandrymen, poultry and fish house workers and swine herdsmen here in the United States. In Europe, Asia and Australia, leptospirosis is an important health and economic problem among agricultural workers, particularly in the rice and cane fields.\textsuperscript{47,48} The apparent lack of this problem among agricultural workers in the United States may be attributed to higher living standards and to mechanization of industrial and agricultural operations. For example, in Italy the flooded rice fields are worked by hand laborers in their bare feet; here the work is done mechanically. In the United States also, protective clothing, boots or heavy shoes are usually worn to perform other tasks on farms requiring contact with contaminated soil.

As a result of these environmental and occupational factors the epidemiologic pattern of human leptospiro infections has certain characteristic features related to age, sex, and season. Although these infections may attack individuals of all ages, conditions are most favorable for infection of young adults.\textsuperscript{49} Beeson and Hankey\textsuperscript{50} observed that the leptospiroses occur most frequently in the United States in males above the age of 15 years due to the occupational factor. In a series of 24 cases reported by them the age range was 10 to 55 but 19 (79\%) were less than 30 years of age and only 5 of the patients were female.
A distinct seasonal incidence was observed with 10 (41%) of the cases occurring in August. Molner et al.\textsuperscript{51} reported a similar age, sex, seasonal distribution among 78 patients studied in the Detroit area. In this series, 70 (90%) of the patients were more than 20 years of age and 73 (93%) were male, providing further evidence of an occupational relationship. Although sporadic cases occurred throughout the year, a definite increase was noted from August through November. During the past 3 years, information obtained regarding 94 cases of leptospirosis in 27 states,\textsuperscript{52} revealed patients from 2 to 64 years of age but the majority were between the ages of 30 and 39. There were only 10 (12%) females in the group. The highest incidence occurred in August and September.

These observations regarding age, sex, and seasonal distribution of the leptospiroses in the United States are in accord with the findings of European investigators with possibly one exception. In certain agricultural areas where the field workers are predominantly women, the number of cases may be more numerous in females.\textsuperscript{47}

Sporadic cases in children are reported throughout the world\textsuperscript{53-57} but, as may be expected, they are in the minority. Those that occur may be attributed usually to contact with a pet dog or with other domestic animals or rodents about the home or to recreational water accidents. Information obtained at the Communicable Disease Center\textsuperscript{52} regarding the occurrence of 94 cases revealed eight patients between 2\textsuperscript{1} and 13 years of age. Of these, three had been swimming, two had had contact with domestic animals, two with rats and a 13-year-old Negro boy had worked for 6 days as a helper in a veterinary hospital. L. canicola was isolated from hamsters inoculated with urine from this boy.

Since it has been estimated that 25% of the dogs in this country have or have had leptospirosis and 25 to 50% of these become temporary carriers, the opportunities for exposure among children would be expected to be high. However, Broom\textsuperscript{5} observed a low infectivity rate among dog owners and their families. Recent investigations in the Communicable Disease Center, Leptospira Research Laboratory on leptospirosis in dogs in the Atlanta area failed to detect leptospiral antibodies in serum from about 50 human household contacts of 10 cases of canine leptospirosis proved by isolation of L. canicola.

An unusual family outbreak was reported recently by Haunz and Cardy.\textsuperscript{58} The family, including parents and seven children 5 to 16 years of age, lived in a converted boxcar without sanitary facilities. Drinking water was kept in a bucket and the family dog occasionally drank from this bucket. The dog was necropsied and leptospires were demonstrated in sections of kidney tissue. All members of the family became ill within a period of 1 month.

In 1948 Molner et al.\textsuperscript{51} summarized the reported cases of leptospirosis in the United States from 1905 to 1948 according to geographic location. During this 43-year period there were 220 cases in 24 states, 8 in which location was not specified and an additional 78 cases which these authors reported from Michigan. In contrast, a summary of cases detected through serologic tests in the laboratories of the Communicable Disease Center during a 4-year period (1953-1956) plus those reported to the Communicable Disease Center by the State Health Departments during this time revealed a total of 392 in 39 states.\textsuperscript{52}

A similar contrast has been noted in the distribution of bovine leptospirosis in the United States. A summary of animal morbidity reports to the Communicable Disease Center, published reports and positive serum samples examined by laboratories of the Communicable Disease Center revealed its occurrence in 42 states in 1956 compared with occurrence in 12 states reported by York\textsuperscript{49} in 1951. In 1954 the United States Department of Agriculture, Agricultural Research Service,\textsuperscript{60} estimated that animal losses from bovine leptospirosis were more than 112 million dollars or 25 million dollars greater than losses from bovine brucellosis. Conditions considered responsible for these losses are abortions, deaths, lowered milk
production and stunting of young animals.

It should be mentioned that abortion due to leptospirosis has been found occasionally to occur naturally in humans. Reported human abortions have occurred during the fourth and sixth month of pregnancy.61-63

Although in recent years there has been an increase in reported cases of leptospirosis in humans in the United States, our knowledge of the true incidence of leptospiral infections is limited. Rarely are leptospires isolated from humans in this country, as few medical and public health laboratories provide leptospiral diagnostic services. For this reason some of the pertinent factors involved in the laboratory confirmation of the diagnosis of leptospirosis will be mentioned. Of course, isolation and identification of the organism from patients with suspected leptospirosis should be the ultimate aim; as only then can the infecting serotype be determined with certainty. The most reliable and simplest method of recovering leptospires is by direct culture of blood into a suitable medium during the febrile stage of illness. The organisms usually appear in the urine during the second week and may persist for 30 days or longer. If free of contamination the urine may be cultured directly; otherwise animal inoculation is necessary. This is a costly, time-consuming procedure and far less productive. When necessary, weanling hamsters or guinea pigs are usually employed as test animals. Leptospires may be recovered from 1-day-old chicks but these animals appear to be slightly more refractory to small numbers of organisms than hamsters64 or guinea pigs.

During leptospiremia, leptospires may be found by darkfield examination of the blood or they may be detected in the urine after the first week of the disease. This method so frequently results in failure or misdiagnosis that it should never be used as the only test.

Leptospires may be demonstrated in tissue sections stained by a silver impregnation method.

Since isolation of leptospires from blood is usually possible only during the acute phase of the disease, laboratory diagnostic aid frequently is dependent upon serologic demonstration of antibodies in the serum of the patient. A variety of tests have been developed for the serodiagnosis of leptospirosis. Probably the most widely used test has been the live antigen microscopic agglutination test. Although this test is time-consuming, hazardous, and the sensitivity of the living antigen is difficult to standardize, it still is considered the reference test for evaluation of other tests. The microscopic agglutination test with killed antigens is less hazardous and the antigens usually remain stable for at least 2 weeks. Results with the two tests compare favorably.65

Within recent years several macroscopic agglutination tests have been developed66-68 which are performed easily and rapidly. The antigens are stable for at least 9 months and results have been highly satisfactory in comparative testing with the microscopic methods. All of these tests are usually serogroup specific which means that a battery of antigens should be employed.

Other tests include the sonic-vibrated leptospiral complement fixation test,69 the whole antigen complement fixation test,70 the erythrocyte sensitizing substance (ESS) test71 and the hemolytic test (HL).72 These tests tend to be somewhat genus specific and require fewer antigens to detect leptospiral antibody. However, they are more difficult to perform and would not be practical for use in small laboratories.

In cases of leptospirosis antibodies generally appear from the sixth to the twelfth day of disease and increase rapidly, reaching maximum titers by the third or fourth week. Low agglutinin titers may persist for months or years. It is important that at least two specimens be examined, the first during the first week of illness and the second 10 days to 2 weeks later.

While serodiagnostic tests are of value in confirming leptospiral infection, dependence should never be placed entirely upon serologic reactions of the patient's serum to determine the infecting serotype. This may be done with certainty only by isolation
and serologic identification of the leptospires.

In summary, the leptospiroses are a group of diseases caused by a variety of leptospiral serotypes. They are associated with many animal hosts and are transmitted from animal carriers to other animals and to man. Transmission occurs by direct contact with infectious urine and with tissues of infected animals or indirectly through contact with contaminated water. Mucous membranes or abraded skin are the usual portals of entry.

Outbreaks have occurred in the United States and most other parts of the world as a result of swimming in ponds or slow-moving creeks contaminated by domestic or wild animal shedders. These outbreaks are usually observed during the late summer and involve primarily adolescents and young adults. Sporadic cases occur frequently from occupational exposures among veterinarians, abattoir workers, sewer workers, dairy workers, poultry and fish house workers and animal husbandrymen. In Europe, Asia and Australia it is endemic among agricultural workers particularly in the rice and cane fields. In those cases attributed to occupational exposures, the disease is most common in young males (20-39 years) except in certain European agricultural areas where women are employed in the fields.

The disease is not common in children but sporadic cases do occur.

Evidence was presented which indicates an appreciable increase in human cases of leptospirosis in the United States since 1948 and the rapid spread of bovine leptospirosis since 1951.

The laboratory diagnosis of leptospirosis was discussed and some of the problems and pitfalls pointed out.

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