The control of leptospires in animal host carriers may hold a key to breaking the chain of infection that perpetuates leptospirosis in man.

Canine Leptospirosis and Public Health

By ROBERT J. BYRNE, D.V.M.

SINCE the first report of canine leptospirosis in the United States in 1937 (*1*), the disease has been found with increasing frequency. Today, the effective detection and treatment of canine leptospirosis must be regarded as one of the most important problems challenging the veterinary profession.

Leptospira canicola, the organism responsible for the canine disease, can be transmitted to man by various methods. The resultant illness is a serious one and should be considered as a public health problem of importance. The various aspects of *Lept. canicola* infections necessary to an understanding of the problem will be considered here.

History

The first detailed description of the disease now believed to be human leptospirosis dates back to 1886 when Weil described the clinical disease syndrome which still bears his name. The disease was characterized by icterus, fever, hemorrhagic tendency, and a high mortality resulting from renal, hepatic, and vascular failure.

The search for the etiological agent of this so-called "Weil's disease" ended when Japanese (*2*) and European (*3*) workers independently isolated a spirochete, later designated as a *Leptospira* by Noguchi (*4*).

The first evidence of an animal-host carrier was obtained by Miyajima in Japan, who demonstrated that spirochetes were present in the tissues of field mice (*5*). The significance of such leptospiral carriers was dramatically illustrated in the rat infested trenches of World War I where over a hundred cases of human leptospirosis occurred (*6*). Since those early reports, new leptospiral hosts have been found, including almost every type of domestic animal, most rodents, and many wild animals. In addition to *Leptospira icterohemorrhagiae*, numerous other leptospiral serotypes pathogenic for animals and man have been identified and differentiated from each other by serologic techniques.

In 1931, Klarenbeek and Schuffner, in the Netherlands, isolated leptospires from the urine of a dog affected with nephritis (*7*). The leptospiral strain was found to differ, serologically, from *Lept. icterohemorrhagiae* and was designated as *Lept. canicola*. Shortly thereafter the first human infection with *Lept. canicola* was reported in that country (*8*). This leptospiral serotype was isolated from dogs in the United States by Meyer and associates in 1937 (*9*), and the first human case in this country was reported in 1938 (*10*).

Etiology

Members of the genus *Leptospira* are delicate filamentous organisms, tightly coiled, and usu-

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ally hooked at both ends. They are generally 6 to 14 microns in length, but individual organisms measuring up to 40 microns have been observed in laboratory cultures. They are difficult to stain and cannot be observed in the living state except by darkfield or phase-contrast microscopy. These spirochetes can be propagated in special laboratory media in which they may remain viable for a year or longer. Viability, as well as pathogenicity for certain animal hosts, may be maintained by serial passage in hamsters of infective blood or tissues. Since one leptospiral species cannot be differentiated from another by morphologic, cultural, or biochemical methods, classification is based on serologic methods involving cross-agglutination and absorption techniques.

Epidemiology

The widespread distribution of canine leptospirosis in the United States has been substantiated by numerous epidemiological surveys. The reported incidence has varied from 3 to 38 percent depending on the diagnostic technique used and the age of the dogs surveyed (*11–13*). Man and other susceptible hosts can become infected by direct contact with contaminated urine from infected dogs, by consumption of food or water so contaminated, or by close contact with surface water in which pathogenic leptospires are present. Infection can occur by entry of these organisms through a skin abrasion or cut, or through the unbroken mucosal surfaces of the conjunctiva, pharynx, or nasal passages.

Pathogenic leptospires are harbored in the kidneys of rodents and other mammalian hosts. These organisms display a characteristic affinity for the renal cortex where they may be found nesting in the lumina of the convoluted tubules. From these foci they may be excreted in the urine for long periods of time. Should such organisms find their way into a favorable environment—such as damp soil or a small body of fresh water—they may survive for as long as 22 days (*14*). Dr. D. W. Johnson of Australia in a personal communication reports survival of the organisms for as long as 7 weeks.

The possibility of transmitting this disease from dog to man is readily apparent. Dog handlers, kennelmen, and veterinarians are most subject to infection from exposure to contaminated urine. Cuts, abrasions, or scratches of the hands provide suitable routes of entry for these organisms. The fact that in many instances a dog's urine may be acidic is no assurance that infections cannot be acquired in this manner. Despite the preference of leptospires for an environment having pH values ranging from 6.8 to 8.6, these organisms are able to survive for short intervals in acidic urine, and upon invading a new susceptible host could multiply and produce disease.

Human *Lept. canicola* infections associated with swimming or wading in surface waters contaminated with dog urine have been reported (*15*). Of possibly greater epidemiological significance is the transmission of *Lept. canicola* infections from dogs to larger domestic animals and subsequent development of leptospiruria in these new hosts. The relatively large volume of infected urine excreted by these animals, cows and swine, for example, poses a far greater threat in the contamination of surface water than that excreted from dogs (*16*).

A constant reservoir of infection is maintained in the kidneys of the many urinary shedders among the canine population. This factor, coupled with the characteristic greeting behavior of dogs, insures the sustenance of *Lept. canicola*. Presumably, *Lept. icterohemorrhagiae* infections in dogs are contracted in this manner or when dogs kill and eat infected rats or other rodents.

The dog has been proved a host to several distinct leptospiral strains, some of which have yet to be reported in the United States. *Lept. canicola* has been universally incriminated as the most frequent leptospiral parasite of dogs, although occasional cases of *Lept. icterohemorrhagiae* infections have been reported. In the United States, serologic evidence indicates that about 90 percent of all canine leptospirosis involves *Lept. canicola* and 10 percent are probably due to *Lept. icterohemorrhagiae* (*17*).

Other leptospiral strains which have been reported in dogs are *Lept. pomona*, the principal causative agent of bovine and porcine leptospirosis in the United States; *Lept. hebdomadis* and *Lept. autumnalis*, the latter two serotypes being found most frequently throughout the Far

East. *Lept. australis* A, *Lept. medanesis*, *Lept. bataviae*, *Lept. grippotyphosa*, and *Lept. sejroe* have all either been isolated from dogs or there is serologic evidence suggesting their existence in this host. The importation of dogs from many parts of the world carries with it the possibility that new leptospiral strains may be introduced in the United States, thus presenting new disease problems among both animals and man.

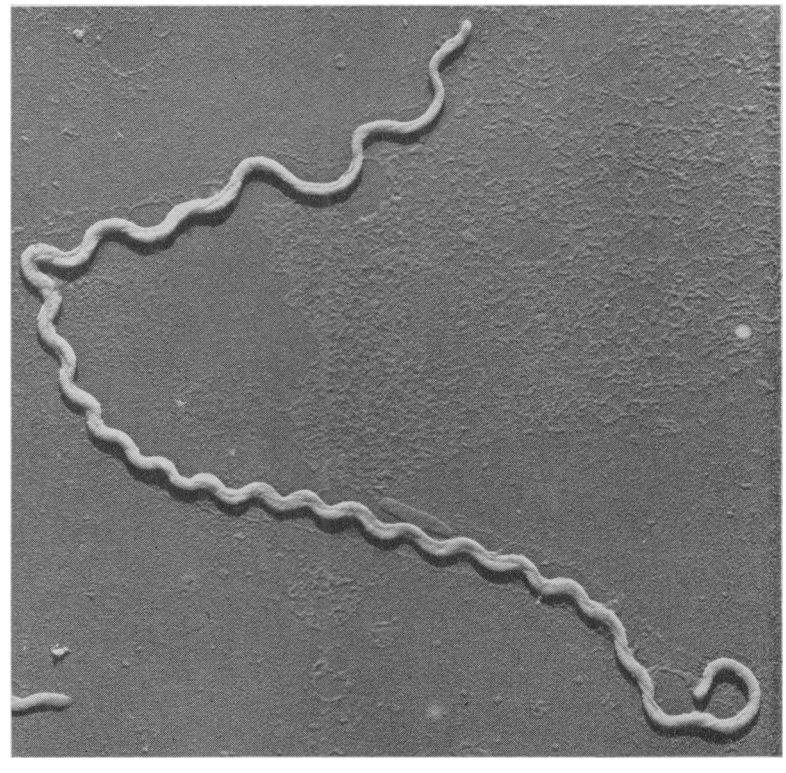
Clinical Aspects in Animals

Added to the other pathogenically unique effects which characterize leptospirosis are the particular syndromata produced by this disease in dogs. Based on experimental evidence and field observations, it is impossible to predict consistently the precise clinical response to leptospiral infection. Reactions following inoculations with living leptospires are variable—a dog may remain completely asymptomatic, or become jaundiced, develop a renal syndrome, or suffer a peracute fulminating disease resulting in death.

Acute canine leptospirosis resulting in either a severe icteric or hemorrhagic disease has been reported in epizootic proportions (*9*). The disease may appear in kennels and result in a high fatality rate, particularly among young dogs. These outbreaks are characterized by the high incidence of jaundice in affected animals from which the common designation, "canine yellows," has been derived.

An animal surviving the acute disease or experiencing a mild subclinical infection almost invariably becomes a urinary carrier. The apparent effect of the extended nesting of leptospires in the kidney tubules of dogs is a tissue response manifested finally by the development of interstitial nephritis. Should this process continue over a prolonged period of time, severe renal dysfunction may result with the development of a uremic syndrome known as "canine typhus" or "Stuttgart disease."

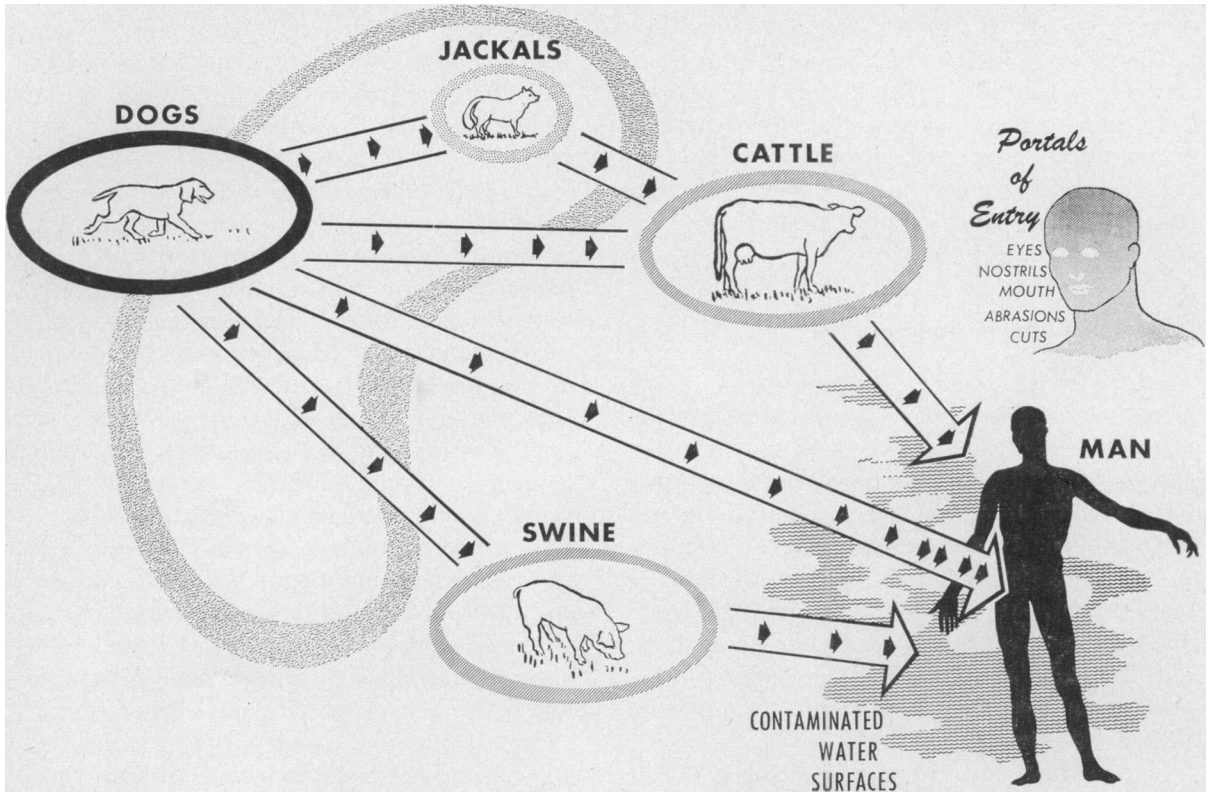
Numerous attempts have been made to outline the symptomatology of canine leptospirosis and to define and describe various forms in which the disease may manifest itself. These descriptions usually include a hemorrhagic type and a uremic type. Bloom (*18*) comments: "The clincial manifestations of canine leptospirosis are extremely variable and may be absent, latent, subclinical, atypical, mild or



Leptospira canicola magnified about 27,000X.

Photograph by Dr. Edgar Ribi, PHS, Rocky Mountain Laboratory, Hamilton, Mont.

Transmission of canine leptospirosis to animals and man.



severe. The clinically obvious disease may be peracute, acute, subacute, or chronic."

It would be equally accurate to describe the clinical disease from the bacteriological and pathological standpoint. This has been done by Stuart (*19*), who mentions three stages:

Invasive. After gaining entry, the leptospires multiply and find their way to all organs of the body. Direct isolations from the blood may be made at this time. This is the period of febrile illness and is generally accompanied by lethargy and anorexia. Jaundice, if it occurs at all, usually appears immediately at the end of this period. Serum titers do not usually reach significant levels at this stage.

Primary renal. The invasive stage may be followed a week later by a primary nephritic stage, which may be the first stage to be clinically detected. During this period leptospires have found their way to the kidney tubules, whereupon the spirochetes may be isolated from the urine. A diffuse or focal round-cell infiltration characterizes the interstitial nephritis that results from the kidney infection. The uremia which commonly occurs from this stage may result from nephron obstruction or other pathological changes, not clearly understood. Apathy, stomatitis, and thirst are the chief clinical symptoms manifested by affected animals. The blood-urea nitrogen level is generally elevated, and the leptospiral agglutination titers of the serum reach a high level.

Secondary renal. The primary nephritis stage may proceed, after a lapse of several months or years, into a secondary nephritic stage. This stage is characterized pathologically by chronic interstitial nephritis accompanied by fibrosis and clinically by uremia. Leptospiruria is rarely found, and it must be concluded that the kidney damage is not associated with a continuing infection. The serum agglutination titers tend to be of a low order during this stage.

Clinical Aspects in Humans

The basis for naming the human leptospiral diseases has included such considerations as geo-

graphic location or epidemiological and clinical similarities associated with infections by specific leptospiral strains or serotypes. For example, Weil's disease is associated with *Lept. icterohemorrhagiae* infections, and *Lept. grippotyphosa* is the etiological agent of mud fever. In Japan, akiyami, or autumn sickness, is caused by *Lept. autumnalis*. *Lept. canicola* infections in man have been described as canicola fever. Within some of these groupings extreme variations in the clinical manifestations are frequently found. The protean nature of the human leptospires is exemplified by the various symptoms of *Lept. canicola* infections.

As with other leptospiral infections, the onset of canicola fever is quite sudden and characterized by chills and fever, severe headache, stiff neck, and intense muscular pains.

In general, it is a relatively mild disease, but on occasions it may simulate classical Weil's disease and result in death. A grippe-like form of canicola fever has been described in which such respiratory symptoms as cough and bronchitis are observed. Ocular manifestations in the form of uveitis may occur long after the febrile stage of this disease has passed (*20*).

The ease with which leptospiral infections can mimic other diseases was demonstrated in an outbreak affecting 25 children in Georgia (*16*). These children went swimming in a small stream which was polluted with the urine of cows and pigs upstream and developed a disease initially diagnosed as dengue. It was not until the epidemiological and laboratory aspects of the outbreak were completed that *Lept. canicola* was established as the etiological agent.

Rosenberg (*21*), in his review article, states that approximately 50 percent of all cases of canicola fever are accompanied by meningeal symptoms. A study by Beeson and Hankey (*22*) indicated that 8 to 10 percent of all cases of aseptic meningitis are leptospiral in origin, and half of that number were canicola infections. This figure agrees closely with data obtained by other American and European investigators. Reference has been made to the resemblance of leptospiral meningitis to early poliomyelitis (*23*). Woodward (*24*) points out that leptospirosis must be considered in the differential diagnosis in any disease in which lymphocytes are found in the spinal fluid—such as lymphocytic choriomeningitis, mumps, herpes, poliomyelitis, Coxsackie disease and the various neurotropic encephalitides.

Laboratory Diagnosis

The reported incidence of leptospirosis often varies with the awareness of the disease. To confirm a diagnosis of leptospirosis in either man or animals, adequate laboratory support is essential. At present, this type of support is not always available. There are relatively few laboratories in the United States which have the necessary equipment and trained personnel essential to carry out this task. The laboratory diagnosis of leptospirosis is based either on the demonstration of the organism in the blood, cerebrospinal fluid, or urine during the course of disease, or by a rise in antibody titer between serum specimens taken during acute and convalescent phases, or by pathological findings at autopsy.

Leptospires appear regularly in the circulating blood during the first week of disease and may be isolated at this time by directly inoculating a few drops of blood into appropriate laboratory media. These cultures are subsequently examined at 2-week intervals by darkfield microscopy. If no leptospires can be demonstrated in the media after 28 days, cultures may be discarded as negative. Such techniques may also be employed in isolating leptospires from cerebrospinal fluid during the early stages of infection. It is difficult and often dangerous to base a diagnosis of leptospirosis on the direct darkfield examination of blood. The presence of artifacts in the form of fibrin shreds or other blood constituents may lead to a false diagnosis. Conversely, leptospires are ordinarily present in such small numbers as to be missed by direct examination.

The leptospiruric phase of the disease usually commences about 12 to 14 days after the onset of symptoms. The same precautions must be applied to the direct darkfield examination of urine as were cited regarding blood, although on occasions, large numbers of leptospires have been directly observed in the urine of dogs and other animals.

Attempts to isolate these spirochetes from urine are best made by inoculating freshly

voided or catheterized urine samples intraperitoneally into young guinea pigs or hamsters, bleeding these animals by cardiac puncture 4 to 6 days after inoculation and culturing media with their blood. These cultures are then handled in the same manner as those initiated directly from the patient's blood. Cultivation of leptospires directly from urine is usually not feasible, because of bacterial contaminants.

Serologic diagnosis is based on the demonstration of a rise in antibody titer between serum specimens drawn during the acute phase of disease and during convalescence. In the laboratory at the Army Medical Service Graduate School, a modification of the Schuffner-Mochtar agglutination-lysis test employing a battery of viable leptospiral type strains is used (*25*). In making a serologic diagnosis of leptospirosis, the value of paired serum specimens cannot be stressed too strongly. Single serum specimens, particularly those with a low antibody titer, are often of little value unless accompanied by a complete clinical history. A low serum titer may indicate a past leptospiral infection or a new infection in the early stage of antibody development.

Complement fixation has been employed in the diagnosis of human leptospirosis infection (*26*). Although it has proved of value in the diagnosis of leptospirosis per se, it is not sufficiently specific to give any clue as to the infecting strain or serotype. To date at our laboratory, this test has been of little value in the diagnosis of canine leptospirosis due to the occurrence of nonspecific reactions between antigens and the majority of canine serums.

The use of various types of macroscopic agglutination antigens in the serologic diagnosis of leptospirosis has been cited on numerous occasions. Although tests employing such antigens have had advantages in the ease and rapidity of performance, they are generally less sensitive than microscopic tests, and often the antigens have been found to be unstable. Recently a capillary-tube test for the diagnosis of leptospirosis was described by Stoenner (*27*).

Therapy

An effective course of treating human leptospirosis still remains a conspicuously unsolved problem. Hall and associates (*28*), in a study of 67 laboratory confirmed cases, concluded that none of the antibiotics employed in their study altered the course of disease or affected the duration of leptospiremia. Other workers (*29*) obtained similar results in dogs, hamsters, and guinea pigs when evaluating chloramphenicol, subtilin, and penicillin G. Gsell (*30*), however, reports favorable response in human leptospirosis to either aureomycin or terramycin if initiated on the first or second day of disease. Brunner and Meyer have reported that streptomycin (*31*) or aureomycin (*32*) given in adequate dosage will eliminate the carrier state in dogs and hamsters. These investigators suggest the administration of either of these antibiotics to dogs whenever there is a question of an animal being a carrier and transmitting the disease to other animals or man.

Control

The ultimate control of human canicola fever is based on the control of the animal leptospiroses. To achieve this end and to break the chain of infection that perpetuates the disease, it is essential that a vaccine for the prevention of canine leptospirosis be developed and made available for widespread distribution and use. Such a vaccine, of necessity, should meet the following requirements:

1. Elicit the production in the recipient of protective antibodies which will persist over a reasonable period of time, while at the same time insure that the vaccinated animals will not develop either clinical symptoms or leptospiruria subsequent to challenge. Bacteriological studies on both vaccinated animals and controls must be carried out to determine the degree of protection attained.
2. Exhibit minimal toxicity following administration.
3. Be polyvalent and give adequate protection against both *Lept. icterohemorrhagiae* and *Lept. canicola* in the United States. In certain other countries, additional leptospiral strains would have to be incorporated in such a vaccine.

Until canine leptospirosis is controlled, a large reservoir of infection remains among the dog population. The owners of these animals must be educated to this fact and to the danger

of acquiring canicola fever from close association with dogs.

Conclusions

Canine leptospirosis is widespread, and its control is a growing problem to the veterinary profession. Certain fundamental questions regarding epidemiological, clinical, pathological, and immunological characteristics of canine leptospirosis remain unanswered. Practicing veterinarians can do much to alleviate this situation by recording and reporting clinical cases of canine leptospirosis, particularly in those instances in which laboratory support has been made available.

Research activities must be directed toward the development of improved diagnostic techniques, further evaluation of therapeutic agents in the treatment of clinical leptospirosis, and development of adequate vaccines for the protection of man and animals.

The extent of human leptospirosis acquired from dogs remains undetermined. Education of the public to the danger of acquiring the disease, the development of adequate diagnostic laboratory facilities, and a constant awareness of the protean nature of the disease are the best means of bringing the problem into proper perspective.

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Warning on Salicylate Drug Labels

The Food and Drug Administration has asked drug manufacturers to label aspirin and other salicylate drugs with a warning to keep these products out of reach of children.

Accidental misuse of salicylate preparations prompted the new ruling. Although salicylates ordinarily are not toxic in amounts required for producing analgesic action, they can cause injury or death when taken in excessive quantities. Poisoning by salicylate preparations are responsible for about 100 deaths a year, mainly in children under 5 years of age.

Recommended statements on the labels are: "Warning—Keep out of reach of children" or "Warning—Keep this and all medications out of the reach of children."

In lieu of specific dose recommendations for children under 3 years of age, FDA recommends the statement: "For children under 3 years of age, consult your physician."

The ruling does not apply to oil of wintergreen (methyl salicylate), which already bears a warning statement; effervescent salicylate preparations (those that "fizz" when placed in water); or preparations of para-aminosalicylic acid and its salts, which are used only in the treatment of tuberculosis.

The advisory ruling, published in the *Federal Register* on October 15, 1955, is based on the recommendation of the FDA medical advisory panel consisting of pediatric experts and drug industry representatives. Six months are allowed for modifying present labeling.