Leptospirosis in California

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EVER SINCE Adolph Weil clinically differentiated leptospiral jaundice in 1886 (*1*), leptospirosis has been a source of confusion to the physician. It was another 30 years before the causative agent, *Leptospira icterohaemorrhagiae*, was isolated and described by Inada and co-workers (*2*). However, confusion remained; for as late as 1924, at the International Conference on Health Problems in Tropical America, only Aristides Agramonte spoke out against the theory of Noguchi and his followers that leptospires were the cause of yellow fever (*3*). Ironically, Noguchi died of yellow fever.

Leptospiral jaundice became known as "Weil's disease," and rats were considered the only important reservoir. Later, other serotypes, such as *Leptospira canicola* and *Leptospira pomona*, were isolated, and the clinico-epidemiologic patterns were thought to be sufficiently specific to justify such names as "canicola fever" and "swineherd's disease." Finally, Edwards and Domm (*4*), in their excellent 1960 review of clinical leptospirosis, pointed out that several of the recognized serotypes can produce leptospiral jaundice although the majority rarely, if ever, do. In addition, they noted no justification for the use of such terms as "canicola fever" based on the clinical syndrome presented, and they therefore recommended that the clinical diagnosis be limited to leptospirosis. At present, 100 serotypes and subserotypes are classified into 14 serogroups (*5*).

Molner and co-workers (*6*) found 228 cases of leptospirosis reported in the United States through 1945, beginning with a fatal case of jaundice described by Stimson in New Orleans in 1905. Eighteen of these cases were in California. The first two cases to be recognized in California, the 9th and 10th in the country, were reported by Ball (*7*) in 1933. The initial illness, in a man who exhibited fever and icterus, proved fatal after a cholecystotomy. The death certificate read, "septicemia with hepatitis and jaundice (organism not discovered)." Structures suggesting leptospires were seen in silver-stained kidney sections. Subsequently, leptospires were identified by direct dark-field examination of tissues from guinea pigs inoculated with kidney emulsion. The second case was quite similar, including the surgery performed, except that diagnosis was based on silver-staining alone, inasmuch as the body had been embalmed before autopsy.

Meyer and co-workers (*8*), in 1938, recovered *L. icterohaemorrhagiae* from rates and *L. canicola* from dogs in California. At the same time, these authors reported serologic evidence of human infections due to these serotypes. Bovine infection with *L. pomona* was described by De Lay and associates (*9*) in 1955. In the same year, Grossman and co-workers (*10*) diagnosed *L. pomona* in man by serologic means. With the exception of a suspected *Leptospira ballum* infection attributed to exposure to laboratory mice reported by Boak and co-workers (*11*), cases of leptospirosis in man in California have been assumed to be the result of infection with one of three serotypes: *L. icterohaemorrhagiae*, *L. canicola*, or *L.*

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pomona. Epidemiologic investigations and serologic tests have generally been limited to these three classic host-parasite relationships.

Differential Diagnosis

Primarily because of historical precedent, leptospirosis has not been emphasized in clinical differential diagnoses of fevers of undetermined origin, unless some evidence of icterus was present. The low incidence of classic Weil's disease, particularly in relation to the great numbers of cases of jaundice resulting from viral hepatitis and other agents, has reduced considerably the index of suspicion for leptospirosis. Also, the strong identification of icterus with leptospirosis has contributed immensely to the lack of recognition of a very common syndrome caused by leptospires, aseptic meningitis.

The frequent omission of leptospires from lists of agents producing aseptic meningitis in California is exemplified by the review of Kerr and Shaw (*12*) in 1950. However, during the same year a survey of 65 paired serums, from patients with central nervous system (CNS) disease, that were submitted to the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, revealed three cases of leptospirosis (*13*). These findings correspond with the results obtained by workers in other areas. For example, Gordon and Studdert (*14*), during 1959, found 8 cases of leptospirosis among 310 patients with "polio-like" illnesses in Southwest Scotland. These same investigators, from 1955 to 1964, diagnosed leptospirosis in 5 of 94 cases of aseptic meningitis in Carlisle, England.

During 1960, I studied 17 cases of leptospirosis in Florida. These cases had been uncovered by screening paired serums, from patients with CNS disease, submitted to the Veterinary Public Health and Virology Section, Bureau of Laboratories, Florida State Board of Health (*15*). Among the 17 cases, leptospirosis had been considered in the differential diagnosis in 8. Only three physicians were responsible for the diagnoses in the eight cases, all three having observed the disease previously. Other initial diagnoses included enterovirus, one; nonparalytic poliomyelitis, four; aseptic meningitis, two; and viral encephalitis, two.

There are several important reasons why the clinician should consider leptospirosis when confronted with a case of CNS disease that suggests a viral etiology. First, in contrast to the viruses, antibiotics are effective against leptospires. Second, the reservoirs of infection are markedly different, thereby affecting greatly the methods of prevention and control. Leptospirosis is contracted by either direct or indirect contact with urine from carrier animals. Also, early specific diagnosis of an index case may hasten recognition of an epidemic, thereby increasing the chances for satisfactory control.

Specific Diagnosis

The consideration of paramount importance to the clinician is whether or not the disease may be leptospirosis. Therefore, the simplest and most rapid tests are needed in the clinical laboratory to expedite a generic diagnosis (leptospirosis) and, ultimately, specific therapy.

In the past, microscopic agglutination employing live antigens was the method used most frequently for detection of serum agglutinins. However, the use of live organisms has two main drawbacks: (*a*) maintenance of several serotypes at a suitable stage of growth, and (*b*) danger of infection among laboratory personnel. Although microscopic agglutination is still the standard method, there are now agglutination tests which are simpler and safer.

One particularly useful method is the macroscopic slide agglutination test described by Galton and associates (*16*). The slide test uses 12 serotypic antigens combined into four pools for screening. Serum titers may be determined by the use of individual antigens present in the positive pool or pools. Antigens recommended for serologic screening are listed in table 1 (*5,16*). (The majority of these antigens are available from Difco Laboratories, Detroit, Mich.) A pool is indicated for only 12 of the 14 antigens included in the table. The remaining antigens, as well as possibly others not listed, may be substituted for serotypes incorporated currently in the pools or may be combined to form a fifth pool, depending upon epidemiologic considerations that will be discussed later.

In addition to determination of serum antibody titers, demonstration of leptospires in body

Table 1. Antigens recommended for serologic screening

Number of pool	*Leptospira*		Type strain
	Serogroup	Serotype and subserotype	
1	*icterohaemorrhagiae*	*icterohaemorrhagiae* (*icterohaemorrhagiae*).	M20.
0	*javanica*	*javanica*	Veldrat Bataviae 46.
1	*canicola*	*canicola*	Hond Utrecht IV.
1	*ballum*	*ballum* (*castellonis*)	Castellon 3.
2	*pyrogenes*	*pyrogenes*	Salinem.
0	*cynopteri*	*butembo*	Butembo.
3	*autumnalis*	*autumnalis* (*autumnalis*)	Akiyami A.
4	*australis*	*bratislava*	Jez Bratislava.
3	*pomona*	*pomona* (*pomona*)	Pomona.
2	*grippotyphosa*	*grippotyphosa*	Moskva V.
4	*hebdomadis*	*borincana*	HS–622.
3	*hebdomadis*	*wolffi*	3705.
2	*bataviae*	*bataviae*	van Tienen.
4	*hyos*	*hyos* (*hyos*)	Mitis Johnson.

tissues and fluids has been a standard diagnostic procedure. Direct examination by dark-field microscopy or silver staining of specimens, or both, have been the usual methods. Recognition of organisms by dark-field examination of fresh material is not a simple task, as there are many fibrillar structures that will easily confuse the unwary and lead to a false-positive diagnosis. A silver-stained preparation lacks the criterion of motility but does allow greater scrutiny of fixed morphology than direct examination of unfixed specimens.

With the advent of fluorescent antibody, microscopic examination has become a rapid and practical diagnostic tool (*17*). The ability to recognize the distinct structure of the leptospire with a specific stain eliminates the problems encountered with direct dark-field examination. Studies of liver biopsies, cerebrospinal fluid (CSF), or urine with fluorescent antibody should be included routinely in the clinical laboratory. Urine or CSF specimens should be centrifuged at 10,000 x g. to increase the density of organisms in the sediment.

The methods described are of primary value as an aid to the clinician, for they provide a prompt generic diagnosis rather than a serotype-specific diagnosis. There are numerous leptospiral serotypes, many of which give sufficient serologic cross-reactions in serums obtained during convalescence to make specific identification of the responsible serotypes difficult if not impossible. Human infections due to *L. icterohaemorrhagiae* (*8*), *L. canicola* (*8*), *L. pomona* (*10*), and *L. ballum* (*11*) have been reported in California, based on serologic evidence alone. Although the clinical and epidemiologic findings were consistent with a diagnosis of leptospirosis, the agglutination pattern suggested only the serotype responsible. A definite diagnosis of the serotype requires isolation of the organism. Isolation can be performed by direct inoculation of a simple medium, such as Fletcher's, with a few drops of

Table 2. Reported incidence of leptospirosis in man [1] and animals [2] in California

Year	Human	Bovine	Ovine	Swine	Equine
1955	4	-------	-------	-------	-------
1956	4	-------	-------	-------	-------
1957	6	-------	-------	-------	-------
1958	8	-------	-------	-------	-------
1959	3	44	0	9	3
1960	2	37	0	9	1
1961	4	66	2	5	3
1962	2	45	1	10	2
1963	4	69	1	1	2
1964	5	33	1	2	1
Average per year	4	49	0.8	6	2

[1] Cases reported to California State Department of Public Health.

[2] Cases diagnosed by Agricultural Veterinary Laboratory Services, California State Department of Agriculture. Data include only histopathologic evidence or isolations, or both, as serologic results are not available. No data are available prior to 1959. No estimate of incidence in canines available.

blood, urine, CSF, or tissue emulsion; or by injection of the material into a guinea pig or other suitable laboratory animal and recovery from the blood during the subsequent febrile response (*16*). Although blood collected during a febrile episode would be the most common source of isolation, in some cases leptospires may be found in the urine for a time after clinical recovery (*18*).

Any strains isolated may be submitted to the Veterinary Public Health Laboratory, National Communicable Disease Center, Atlanta, Ga., or the Division of Veterinary Medicine, Walter Reed Army Institute of Research, Washington, D.C., for typing.

Potential Incidence

Each year, leptospirosis is diagnosed in man and animals in California (table 2). However, the recognized incidence in man is, undoubtedly, considerably less than the actual incidence for several reasons in addition to failure to report proved cases.

As indicated earlier, generally leptospirosis is not yet considered in cases of aseptic meningitis. Magoffin and Lennette (*19*), in a study of specimens from 1,259 patients with clinical nonparalytic poliomyelitis and aseptic meningitis (submitted to the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, from 1956 through 1960) reported that a specific viral agent was involved in only 55 percent. During the same period, 23 cases of leptospirosis were reported. Thus, it seems reasonable to suggest that, of the 575 illnesses lacking a specific diagnosis in the study, some could have been leptospirosis.

Although transmission of leptospires from infected reservoir hosts does occur throughout the year, epidemics in the United States have occurred almost exclusively during the summer months (*16*). The explanation is simple. All the epidemics occurred after groups of persons swam in contaminated waters, such as farm ponds or streams. The fact that the "epidemic season" for leptospirosis parallels that for several of the viral CNS diseases may suggest why an epidemic of leptospirosis has not been recognized in California. Comparison of histories obtained from patients with CNS disease of suspected viral etiology would probably fail to incriminate a common source, such as a "swimming hole," because the key questions needed would not be asked in epidemiologic investigation of the other agents.

Limitation of epidemiologic and laboratory studies to the three classic host-parasite relationships—*L. icterohaemorrhagiae* from rats, *L. canicola* from dogs, and *L. pomona* from domestic livestock—has certainly limited recognition of cases. Relying on earlier work, the California State Department of Agriculture assumes that *L. pomona* is the main offender in livestock outbreaks, according to a 1965 personal communication from W. W. Worcester. This assumption has been contradicted by the recent studies of Carroll who isolated *L. canicola*, *L. grippotyphosa* (*20*), and *L. icterohaemorrhagiae* from dairy cattle (personal communication, 1965). His isolations of these serotypes are the first reported from cattle in California. In addition, this was the initial recovery of *L. grippotyphosa* in the State. There is ample evidence that the strict host-serotype relationships, long believed to exist, break down frequently. For example, *L. pomona* has been isolated from canine carriers (*21*).

The human case reported by Boak and associates (*11*) suggested that *L. ballum* was present in laboratory mice used in California. This serotype has been recovered from a western harvest mouse (*Reithrodontomys megalotis*) in Butte County (*22*). Although this single isolation does not indicate the extent to which *L. ballum* is distributed in the State, it has been found in six other rodents, five mammalian predators, and one reptile in the United States (*22*). There may be numerous heretofore unrecognized carrier hosts and leptospiral serotypes present in California.

Although this paper discusses problems affecting the recognition of leptospirosis in California, similar conditions can be found throughout the United States. Leptospirosis in man has been detected in 46 States (*23*). It probably occurs in the remaining four States as well, inasmuch as animal reservoirs have been recognized in at least two (*23*). Epidemiologists and public health laboratory workers in other areas may well compare their situations to California.

The public health laboratory is in an excellent position to lead the way in the diagnosis of leptospirosis. For several years, it has been the practice of the Florida State Board of Health to screen all serums from cases of CNS disease which were negative in the virus battery. Since September 1966, the California State Department of Public Health has been testing all serums from patients with a clinical diagnosis of aseptic meningitis. Reports of leptospiral agglutinin titers from this laboratory will permit epidemiologists to clarify the picture in California. If similar programs were initiated throughout the country, a truer estimate of the public health importance of leptospirosis could be obtained.

Summary

In addition to classic Weil's disease (leptospiral jaundice), leptospirosis is probably an important segment of the group of diseases producing aseptic meningitis in California. Prompt generic diagnosis by agglutination or fluorescent antibody tests will allow initiation of specific therapy. The battery of antigens and antiserums employed in laboratory tests should include at least the five serotypes now recognized in the State—*Leptospira icterohaemorrhagiae*, *Leptospira canicola*, *Leptospira pomona*, *Leptospira grippotyphosa*, and *Leptospira ballum*—as well as representatives from other serogroups, in order to detect as many infections as possible. Isolation should be considered if a serotype-specific diagnosis is desired.

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Program Notes

Aerial Spray Checks Encephalitis

City health officials of Dallas, Tex., were informed of the first possible occurrence of encephalitis for 1966 during the first week of August. Suspected cases were among Parkland Hospital patients. The first case was confirmed by the State health agency's laboratory on August 9 as St. Louis encephalitis.

Specialized teams from the Public Health Service's National Communicable Disease Center in Alanta, Ga., identified the encephalitis vector as *Culex quinquefaciatus* and recommended aerial spraying.

Six U.S. Air Force spray planes were sent immediately to Dallas upon request of the State Health Commissioner. Spraying, begun on August 19 and concluded August 27, included the residential area of Dallas and Dallas County. This spraying was the first use of the modernized aerial spraying technique in a metropolitan area for the control of an epidemic of mosquito-borne disease. Effectiveness of the spraying was immediately apparent because of the insect kill and the use of dye cards as coverage indicators.

As of October 15, a total of 180 cases had been reported from Dallas: 83 confirmed, 50 presumptive, 18 inconclusive, 21 negative, and 8 pending. Some had occurred as early as July, but the maximum number occurred in mid-August. Through October 15, a total of 19 deaths had been attributed to the epidemic.

Mobile Dental Unit Serves Children

The Illinois Department of Public Health has developed a mobile dental unit for use in a statewide program to provide dental care and dental health education to children in low-income and migrant families.

During the summer months of 1966, the unit traveled to migrant labor camps. The clinical dentist in charge of the mobile dental office provided on-spot care to the children. During the school year, the unit visited schools upon request and provided care to children who would not otherwise receive it.

It is expected, said Dr. Franklin D. Yoder, director of the Illinois Department of Public Health, that the service will be expanded if the need becomes evident.

New Affiliation of N.Y. Hospital

The New York State Rehabilitation Hospital at West Haverstraw began an affiliation with Columbia University's College of Physicians and Surgeons on January 1, 1967.

The hospital's facilities are thus available for undergraduate and graduate medical students of Columbia, and the resources of Columbia and its faculty are open to the hospital. Students do clinical work at the hospital under the supervision of faculty members.

The hospital provides clinical training for students of more than 25 other schools, none of which will be affected by the affiliation with Columbia. A 25-year-old affiliation with the New York University College of Medicine, however, has been terminated.

Agreement on Salinity Standards

Representatives of the seven Colorado River States recently reached an agreement on guidelines for water salinity standards. Utah's water quality standards, including salinity parameters, were the basis for discussion by these representatives of standards for the Colorado River. Lynn Thatcher, head of the division of environmental health of the Utah State Department of Health, was chairman of the meeting held January 13, 1967.

The increasing amounts of salinity in water represent a generally unrecognized pollution danger, according to researchers at Utah State University. For urban use, waters containing 500 mg. or more of salt per liter are considered questionable; those containing 1,000 mg. are objectionable and generally not acceptable. And heart patients, according to the American Heart Association, should drink water containing no more than 20 mg. of sodium per liter.—*Your Health* (Utah State Department of Health), January 1967.

Plague Control in New Mexico

The New Mexico Department of Game and Fish recently issued an order prohibiting hunting and trapping of rabbits in De Baca County. In an investigation of a die-off of jackrabbits, cottontail rabbits, and jack rats in the county, *Pasteurella pestis* was isolated in the specimens examined, and plague infection in a rabbit was confirmed.

Since 1949, there have been 22 cases of plague in human beings in New Mexico. In five of these cases, infection developed following contact with rabbits.

Hepatitis From Illicit Drug Use

Serum hepatitis in a 20-year-old woman was reported to the Utah State Department of Health on January 13, 1967. This patient had never had a blood transfusion but admitted to illicit use of a drug. She had taken methedrine, a stimulant similar to benzedrine, intravenously at a party.

An investigation of the woman's contacts revealed 16 persons who regularly or occasionally used drugs intravenously. Of this group, 10 had developed hepatitis within the 6 months before the investigation. All 16 of the young adults, aged 18 to 26, had attended a party between October 27 and 29 and used methedrine intravenously with the same needle and syringe.

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