

History of Leptospirosis and *Leptospira*

Ben Adler

Abstract *Leptospira* was isolated and identified as the causative agent of the severe human syndrome Weil's disease about 100 years ago almost simultaneously, but independently, by workers in Japan and Europe. Since that time leptospires have been isolated from almost all mammalian species on every continent except Antarctica, with leptospirosis now recognized as the most widespread zoonosis worldwide and also a major cause of disease in many domestic animal species. Recent advances in molecular taxonomy have facilitated the development of a rational classification system, while the availability of genome sequences and the development of mutagenesis systems have begun to shed light on mechanisms of pathogenesis that appear to be unique to *Leptospira*.

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1 History of Weil's Disease

The modern history of leptospirosis began in 1886 when Adolph Weil (Fig. 1) described a particular type of jaundice accompanied by splenomegaly, renal dys-

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Fig. 1 Portrait of Adolph Weil (1848–1916). Image courtesy of Wellcome Library, London



function, conjunctivitis, and skin rashes (Weil 1886). It was subsequently named Weil's disease. Although the etiology of the disease was unknown, it appeared to be infectious in nature and was often associated with outdoor occupations in which persons came into contact with water. Epidemics were common among sewer workers, rice-field workers, and coal miners.

However, it is apparent that leptospirosis had existed for millennia. Although it is difficult to draw firm conclusions from records before the advent of modern medical and scientific literature, it seems clear that at least some of the early disease outbreaks described in ancient texts were leptospirosis. For example, ancient Chinese texts carry accounts of "rice field jaundice", while in Japan syndromes clearly recognizable today as leptospirosis were termed "autumn fever" or "seven-day fever" (Kitamura and Hara 1918). In Europe, Australia and elsewhere, associations were recognized between febrile illness and particular occupations, giving rise to syndromes such as "cane-cutter's disease", "swine-herd's disease", and "Schlammfieber (mud fever)", well before the common etiology was recognized and identified (Alston and Broom 1958; van Thiel 1948). For a more detailed description of the early accounts of what were almost certainly large-scale outbreaks of leptospirosis, the reader is referred to Chapter 1 of Faine et al. (1999).

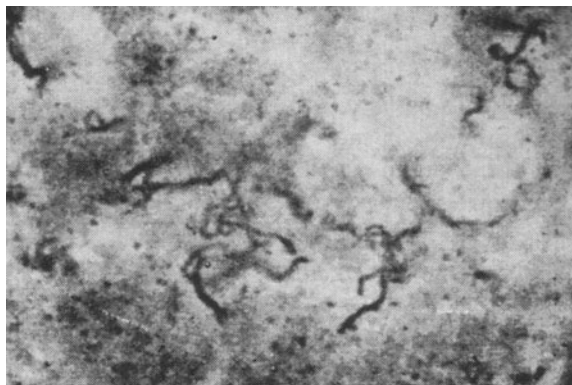
2 A Spirochete as the Causative Agent

Although *Leptospira* was first isolated independently and almost simultaneously in Japan and in Europe (see below), it is clear that the first demonstration of leptospire was made some years earlier by Stimson (1907), who used the recently described Levaditi silver deposition staining technique to observe spirochetes in kidney tissue sections of a patient described as having died of yellow fever (Figs. 2 and 3). It is probable that the patient was convalescing from Weil's disease when he contracted fatal yellow fever; spirochetes were observed in kidney, but not liver or heart, tissues. Stimson called the organism *Spirocheta interrogans*; the species name, which survives to this day, was suggested by the resemblance of the bacterial cells to a question mark, a feature that we now know to be due to the characteristic hooked ends of leptospire.

The first isolation of *Leptospira* followed just a few years later. In Japan, where Weil's disease was common in coal miners, Inada et al. (Fig. 4) injected guinea-pigs intraperitoneally with the blood of Weil's disease patients and succeeded in reproducing typical, acute leptospirosis in the animals (Inada et al. 1916). This and subsequent papers constituted a *tour de force* for the period; they defined transmissibility, routes of infection, pathological changes, tissue distribution, urinary excretion, leptospiral filterability, morphology, and motility. Signs in infected guinea-pigs included jaundice, conjunctivitis, inappetence, anemia, hemorrhages, and albuminuria. Disease was transferred in guinea-pigs for up to 50 generations. Spirochetes were observed in most tissues, with liver and kidneys containing the greatest numbers. These observations were extended to postmortem tissues from human cases, which revealed similar findings. These workers also showed that rabbits, mice, and rats were comparatively resistant to acute disease, even when injected with very large volumes of infected guinea-pig tissues.

Within a few months Inada and colleagues had succeeded in propagating the spirochetes in vitro in a medium made from emulsified guinea-pig kidney, and showed a preference for growth at 25 °C, with loss of viability at 37 °C.

Fig. 2 Stimson's original observation of spirochetes in kidney tissue. Reproduced from (Noguchi 1928), with permission from the publishers, University of Chicago Press



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NOTE ON AN ORGANISM FOUND IN YELLOW-FEVER TISSUE.

[By Asst. Surg. A. M. Stimson, Hygienic Laboratory, Public Health and Marine-Hospital Service.]

The spirochætal origin of yellow fever has been suggested by Schaudinn and by Novy, but so far as I know no organism belonging to the genus *Spirochaeta* has been reported as having been found in yellow-fever tissues. I have examined some tissues for this class of organisms, using the method of Levaditi, as employed for the demonstration of *Treponema pallidum* in syphilis. The available yellow-fever material was unfortunately limited to the tissues from one case, all other specimens having been fixed otherwise than in formalin, which is required by Levaditi's method. The brain, liver, heart, and kidneys were examined. Nothing of special interest was observed in the first three, but in the kidney a very definite organism was found, having the following characters: Color, opaque black, in sharp contrast to the surrounding tissues; general appearance strongly suggesting a *spirochæte*; often irregularly curved, but some individuals having a regular series of alternate curves, no other indication of segments being observed; one or both extremities often bent back in the form of a hook; entire length variable up to $14\ \mu$ or more; width estimated at $\frac{1}{2}\ \mu$; length of short curves, $1\frac{1}{2}$ to $2\ \mu$. It was confined to the cells and lumina of the tubules of the kidney, none being observed in the blood vessels, glomeruli, or interstitial tissue. While in some fields no organisms were present, in others large numbers were crowded together or scattered individuals were observed. The kidney from another case of yellow fever, where the tissue had been fixed in bichloride of mercury and acetic acid, was examined, and while no stained organisms were found, structures resembling those described were present in an unstained condition. The organisms were not found in kidney tissue from a patient dying of malaria, although the tissue was properly fixed and stained.

The object of this report is simply to invite attention to the findings in a single case, since no opinion as to the significance of this organism can be formed from such meager data. For convenience of reference I would suggest that the organism be called (*?Spirochaeta*) *interrogans*, the specific name being suggested by the form, somewhat resembling a question mark, which the organism frequently assumed in my preparations.

Fig. 3 Copy of Stimson's (1907) article in Public Health Reports. US Public Domain

The organism was named *Spirochaeta icterohaemorrhagiae*. One of the first isolates survives to this day and Ictero No. 1 was accepted by the Subcommittee on the Taxonomy of *Leptospira* in 1990 as the Type Strain of *Leptospira interrogans* (Marshall 1992).

Fig. 4 Portrait of Ryokichi Inada (1874–1950). Kindly provided by Prof. Shin-ichi Yoshida, Kyushu University



Remarkably, the Japanese group also conducted the first vaccination studies. It is worth quoting verbatim.

Guinea pigs were immunized with repeated injections of liver emulsion of the infected animal and later with a pure culture of the spirochete, which had been killed by carbolic acid [Author's note, phenol]. The animals thus immunized did not develop the disease on the injection of the spirochete, which, it was known, would produce the disease in healthy animals. Hence this method seems promising for the prevention of the disease in man. Our conclusion is that the flea and mosquito have no share in the infection.

Of course, in the absence of quantitative data it is impossible to assess the degree of protection.

Finally, Inada and colleagues demonstrated immune lysis of leptospire by patient serum within the guinea-pig peritoneal cavity (the so-called Pfeiffer's method) and showed passive protection of guinea-pigs by convalescent patient serum or immune goat serum, but only if it was administered before the onset of jaundice. The importance of early treatment before the onset of organ failure remains relevant today (see the chapters by [D.A. Haake](#) and [P.N. Levett](#) and [W.A. Ellis](#), this volume).

The 1916 paper of Inada et al. extended data that were first published in the Japanese literature in early 1915 which described their observation in November 1914 of leptospire in the liver of a guinea-pig injected with the blood of a Weil's disease patient. Of course, this work was not known in Europe where trench warfare in World War I resulted in large numbers of Weil's disease cases. Two German groups independently and almost simultaneously (October 1915) succeeded in transmitting the infection to guinea-pigs and demonstrating the leptospire in guinea-pig tissues (Hubener 1915; Uhlenhuth and Fromme 1915). The groups named the organism *Spirochaeta nodosa* and *Spirochaeta icterogenes* respectively. Some controversy followed about priority, but it is clear that the Japanese discovery pre-dates the European ones by about a year, a fact recognized by the Subcommittee on the Taxonomy of *Leptospira* in specifying Ictero No. 1 as the type strain.

3 Rats as Carriers of *Leptospira*

The key finding that rats were renal carriers of *Leptospira* followed within 2 years, also reported by the Japanese group (Ido et al. 1917). The investigation was prompted by the serendipitous findings of spirochetes in the kidneys of field mice by colleagues working on *tstutsugamushi* (now *Orientia tsutsugamushi*). Ido and colleagues observed and cultured spirochetes from the kidneys and urine of a range of species of house and wild rats and identified them as *S. icterohaemorrhagiae* based on specific Pfeiffer reactivity with immune serum. They also made the key observation that leptospire were restricted to the kidneys and that the rats appeared healthy, the first observation of the asymptomatic carrier state. The connection between rats and Weil's disease was clearly established, as in coal mines which were frequently infested with rats, and also with the following epithet: "Cooks working in kitchens frequented by rats often became ill with spirochetosis icterohaemorrhagica." Interestingly, the group also observed spirochetes in mouse kidneys, but they were much less virulent when injected into guinea-pigs. It is probable that they observed one of the several serovars that we now know to be carried by mice. The Japanese findings were quickly confirmed in Europe and the U.S.A (Noguchi 1917; Stokes et al. 1917).

The Japanese group also reported some interesting epidemiological observations. Weil's disease in Japan showed a clear increased incidence in spring and autumn, but in coal mines where there was no temperature fluctuation the prevalence was the same year round. While this difference may be explained partly by season-specific human activities, the point was noted that higher incidence corresponded to temperatures of 22–25 °C. In addition, the incidence in coal mines with neutral or alkaline soil and water was high, whereas in mines with acidic soil and water infection was rare, despite equally high levels of rat infestation.

4 Recognition of Leptospirosis in Animals and the Expansion of Serovars and Syndromes

The following decades saw major advances in the understanding of leptospirosis. Arguably, one of the more important was the recognition of leptospirosis as an infectious disease of almost all mammalian species, especially in an increasing range of rodent species, and the importance of domestic animals as a source of human infection (Alston and Broom 1958; van Thiel 1948). For example, Dutch workers reported the isolation of a canine strain, Hond Utrecht IV (Klarenbeek and Schuffner 1933), which remains the type strain for serovar Canicola. The disease in cattle was first reported in Russia in 1940, then referred to as “infectious yellow fever of cattle” (Semskov 1940). By the 1950s the range of serovars and host animals had expanded substantially (Alston and Broom 1958) and by the 1980s leptospirosis was well documented as a veterinary disease of major economic importance in dogs, cattle, swine, horses, and perhaps sheep (Ellis 1990). Current aspects of leptospirosis in animals are detailed in the chapter by W.A. Ellis, this volume.

At the same time as more and more serovars were isolated, it became apparent that severe Weil’s disease was not the most common presentation of leptospiral infection. This perhaps should not have come as a surprise. In fact, even the very early accounts described milder, anicteric cases of leptospirosis (Uhlenhuth and Fromme 1915). Thus, over the next few decades it became clear that leptospirosis in humans and animals varied from a mild febrile illness (so-called “influenza-like”) through to severe, often fatal infections characterized by liver and kidney failure and severe pulmonary hemorrhage (Bharti et al. 2003; Gouveia et al. 2008). It is clear that the infecting serovar is an important factor that determines the outcome of infection. For example, serovar Hardjo never causes fatal human infections. However, it is also clear that the host and other factors also play a role; even serovars most commonly associated with severe fatal disease commonly cause mild infections (Gouveia et al. 2008).

5 Nomenclature and Classification

The genus name *Leptospira* was first proposed by Noguchi (1918) in order to differentiate the Weil’s disease spirochete from others known at the time, especially *Treponema pallidum*, *Spirochaeta* and *Spironema* (later *Borrelia recurrentis*; the differentiation was based almost entirely on morphological characteristics. As new serovars were isolated they were given species status, e.g. *Leptospira pomona*, *Leptospira canicola*, *Leptospira hardjo*, *Leptospira copenhageni*, and so on. Species (serovars) with related antigens were grouped together in serogroups. Even with the limited taxonomic tools available for *Leptospira* at the time, it was apparent that there were not >200 species and so in 1982 the subcommittee on the

Taxonomy of *Leptospira* adopted the notion of two species of *Leptospira*, with *L. interrogans* containing the pathogenic serovars and *Leptospira biflexa* containing the saprophytic serovars (Faine and Stallman 1982). Interestingly, the saprophytic *L. biflexa* had actually been described before the first isolation of pathogenic leptospires (Wolbach and Binger 1914). The family *Leptospiraceae* was formally proposed in 1979 (Hovind-Hougen 1979), although Pillot had suggested this grouping in 1965, but without a valid publication. Hovind-Hougen (1979) also placed *Leptospira illini* in a new genus *Leptonema*. *Leptospira parva* was reclassified as the genus *Turneriella* in 2005 (Levett et al. 2005).

The advent of much more objective and rational molecular taxonomy brought major changes to the classification of *Leptospira*. Based on DNA–DNA relatedness, the former single species *L. interrogans* was divided into seven species (Yasuda et al. 1987). Subsequent new isolations and analyses have added several additional species of both pathogenic and saprophytic *Leptospira* (Adler and de la Peña Moctezuma 2010). The systematics of *Leptospira* is described in detail in the chapter by P.N. Levett, this volume, while a listing and description of leptospiral species and serovars is available at: <http://www.kit.nl/net/leptospirosis>.

6 Recent Developments

The last 10 years have seen a resurgence of activity into research on *Leptospira* and leptospirosis. The number of publications in this field in the last decade was double that of any previous decade and about the same as the total in the 50 years following the discovery of *Leptospira*. Major changes were made in taxonomy and identification, with the addition of several new species and the development of molecular typing tools such as MLST. Significant advances have been made in the understanding of the biology of *Leptospira* and the mechanisms of interaction of leptospires with the mammalian host at the cellular and molecular levels. Progress has been facilitated by the availability of whole genome sequences concomitant with improvements in bioinformatics, genome analysis, proteomics methods and in particular the development of mutagenesis systems for pathogenic *Leptospira*. All of these areas are explored in detail in the ensuing chapters of this volume.

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