HISTORICAL PERSPECTIVES IN LEPTOSPIROSIS

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The nineteenth century brought rational insight in the cause and transmission of infectious diseases. It was the dawn of microbiology as a science with the discovery of microbes as causative agents of infectious diseases. There are plenty of reports in the 19th century of outbreaks of icteric fevers. These were described under a variety of names such as Griesinger’s bilious typhoid, bilious or hepatic fever, hepatic typhoid, icteric typhoid, catarrhal icterus and febrile icterus. Some of these epidemics may have been leptospirosis. In 1886, a disease entity was described that got no name but was named after the man who defined it: Weil’s disease. Yet, at that time the difference between leptospirosis, yellow fever and other diseases with icterus was by no means clear. The similarity was such that leptospirosis was sometimes called the yellow fever of the temperate zones. Yellow fever was recognized already for a very long time in the tropics and hugely feared as it caused devastating epidemics. Even before the causative agent was discovered, it was found that yellow fever was transmitted by mosquitoes and that the disease could be effectively controlled by destroying mosquitoes and their breeding places.

Early views

Physicians were well aware in the 19th century that diseases occurred in relation to certain local conditions. The icteric infectious disease that was later to be called Weil’s disease was known to occur in relation to exposure of humans to water, marshy land, wet soil or mud. The association between environmental conditions (such as water, rainfall, seasons and certain activities like swimming) and disease were already recognized before the causative leptospires were known. One of the explanations of Weil’s disease was the idea of a miasma, a soil and climate-related cause of disease. Miasma was a sort of gas, generated by decaying organic matter and oozing out of marshy land that could cause disease. Those who held this view found support in the fact that hygienic measures were effective. They noticed that the disease could be prevented by avoiding bathing or swimming in places, where Weil’s disease was known to occur or by draining water from mines where miners were known to contract the disease. These hygienic actions would prevent contact with the harmful local miasma. The etiology was to be found in the influence of a local miasma whose specific qualities would lead to Weil’s disease in the temperate zones and a similar disease, yellow fever, in the tropics. The miasma theory soon faded away.

Spirochaetes as causative agents

Since the description of Weil’s disease, a search was made for its microbiologic cause as by that time the notion of pathogenic micro-organisms causing disease was accepted. Spirochaetes had already been discovered to cause diseases. In 1879, borrelias were discovered to be the cause of relapsing fever. In 1905, treponemes were found to be the cause of syphilis. It is to be kept in mind that at that time, widely spread syphilis was an enormously important disease, a real scourge for mankind. So, spirochaetes were at the centre of attention as a possible cause of disease. However, it took a decade before leptospires were found to be the cause of Weil’s disease, first by Japanese and then, independently and almost simultaneously, by German investigators. Kuenen cites...
Japanese investigators who attributed the delay in finding lepto-
spires since the discovery of borrelias and treponemes among others to the fact that lepto-
spires circulate during the first phase of the disease only for a few days in the patient’s blood. During that short period they can be found relatively easily before they disappear, into the kidneys and liver and other inner organs. In 1915, spirochaetes, later to be
identified as lepto-
spires, were discovered by Japanese
investigators in field mice and rats.  

Leptospires and other diseases

The discovery of lepto-
spires causing Weil’s disease led to an intensive search for spir-
choetes in yellow fever. Mochtar 8 sums up a number of investigators who claimed to
have isolated lepto-
spires from cases thought to be yellow fever. It proved even possible to transmit lepto-
spires by mosquitoes to experimental animals. In view of the resemblance between the
diseases, it seems in retrospect likely that the lepto-
spires were actually isolated from leptospirosis patients “concealed” among the yellow fever patients or perhaps mixed infections. 6,7

The observed transmission was possibly mechanical with blood containing lepto-
spires sticking to the stinging
mouthparts of the mosquitoes. Numerous later experiments excluded a role for mosquitoes as transmitters of leptospirosis. 5,8 The true causative agent of yellow fever, a flavivirus as we know now, was discovered more than ten years after the “isolation of lepto-
spires”. As yellow fever, dengue and Phlebotomus fever (pappataci fever) were considered to be closely related and the search was on for lepto-
spires. After many observations and experiments it was concluded that dengue and Phlebotomus fever were not caused by lepto-
spires and that it was unlikely that mosquitoes and sand-flies could transmit lepto-
spires. 8 It was later discovered that dengue and sand-fly fever are caused by respectively a flavivirus and a phlebovirus. Schüffner 9 reports in cautious and reserved words that lepto-
spires were found in cases of black water fever, but perhaps leptospirosis and black water fever were confused.

Infection sources and transmission

The discovery of lepto-
spires as the causative agents of leptospirosis paved the way for the investigation of transmission routes. Through the emerging science of microbiology evidence was gathered that lepto-
spires occurred in water, wet soil and mud and even in tap water. The difference between harmless lepto-
spires, belonging to the biflexa-complex, later named Leptospira biflexa, now named L. biflexa sensu lato and pathogens belonging to the interrogans-complex, now Leptospira interrogans sensu lato, was not immediately clear. On epidemiological grounds it was clear that infections could be contracted in water. It is interesting to mention here that for a time some investigators held the view that harmless free-living lepto-
spires could change into pathogenic lepto-
spires. 10 This transformation claim seemed initially to be supported by experiments indicating that by culture procedures and animal passage non-
pathogenic lepto-
spires could adopt pathogenic qualities. Numerous later experiments by other researchers trying to replicate these experiments consistently failed, so the idea that harmless saprophytes could turn into pathogens was abandoned. 5,7,11,12 Remarkably, those who held the wrong view, that harmless lepto-
spires could become pathogenic, held the modern view, that there is only a single disease called leptospirosis with various manifestations, be it that we know now that lepto-
spires come in many different but antigenically stable variants.

At the time of discovery of lepto-
spires as disease agents, there was already a suspicion that rats played a causative role in the chain of events leading to disease. It was observed that Weil’s disease was associated with the occurrence of rats, notably in the trenches during the First World War. However, association does not necessarily mean a causal relationship. Not everybody was convinced that rats were infection sources as it was observed that humans got leptospirosis without any rat in sight. Actually, the seeming absence of rats gave support to those who held the concept of a miasma. In the miasmatic view, the isolation of lepto-
spires from patients could be considered to be of secondary significance. A modern, compared to the miasmatic theory, but nevertheless wrong view was that there were pathogenic lepto-
spires living free in water. It could well be that humans were infected by these harmful lepto-
spires living free in the water. One should admit that it was puzzling that leptospirosis occurred with no visible sign of the presence of rats and, the other way around, that rats occurred without a single human case of Weil’s disease. 6,8,4

The puzzle was only solved when it was found out that lepto-
spires can survive in the environment under favourable conditions (neutral pH or slightly alkaline water), long after the excreting rat has disappeared and that they rapidly perish after excretion in an unsuitable environment (acid water). 5,3

Gradually, with the isolation of lepto-
spires from many other rodents and other animals and backed by epidemiological evidence the notion was accepted that rats and other carrier animals, are usually the infection sources and transmitters of leptospirosis.

Vector-born leptospirosis?

The apparent role of rats did not exclude the possibility that vector animals could transmit the disease. Research on possible vectors was vigorously pursued. Kuenen 4 and Mochtar 6 report on theories on vectors that were current at the time: leeches, stinging flies, bedbugs and mosquitoes were considered possible culprits. Just like in yellow fever, in Weil’s disease person-to-person transmission was thought not to occur, although we now know it does, be it seldom: intra-
uterine transmission, transmission by mother’s milk, by sexual intercourse and by close contact with patients and patient’s urine have been reported. 5,13

As yellow fever was known to be transmitted by
mosquitoes, the search focussed on them as possible transmitters of leptospires. However, extensive experiments showed that mosquitoes did not transmit leptospirosis as leptospires rapidly deteriorate in the mosquito stomach.\textsuperscript{5,7,8} Moreover, on epidemiological grounds a role for mosquitoes was considered unlikely as Weil’s disease did occur in the absence of mosquitoes.

Occasionally, investigators using the animals mentioned above succeeded under experimental conditions in transmitting leptospires but van Thiel\textsuperscript{4} explains this as a mechanical transfer of leptospires in the blood meal of the would-be vectors.

Due to the finding of leptospires in rat kidneys, backed by epidemiological observations, the notion took root that rats were reservoirs and spread leptospires with urine in the environment, where the micro organisms under favourable conditions can survive for a long time. Gradually, the notion grew that leptospires as a rule invade humans through mucous membranes or the broken skin and perhaps the thoroughly soaked skin; and that man usually is infected by direct or indirect contact with the urine of rats.

\textbf{Leptospirosis in various forms}

With the discovery of the causal relationship between leptospires and Weil’s disease, the problems with the distinction between leptospirosis and other diseases were far from over.\textsuperscript{1} Actually, the situation became more complex. Many diseases resembling Weil’s disease were discovered, that were caused by leptospires and were antigenically dissimilar from the leptospires that caused Weil’s disease. They had names that referred to local epidemiological conditions, for instance mud fever, harvest fever, swineherd’s disease, autumnal fever, cane cutter’s disease, to mention a few.

In Sumatra a dengue-like disease, sprochaetosis febrilis, caused by leptospires was discovered.\textsuperscript{5,8} It was caused by a leptospira serovar that at that time was called \textit{Leptospira pyrogenes}. It was soon suspected and later confirmed that other serovars could cause the same or a similar disease. Mud fever only distantly resembled Weil’s disease. It was discovered to be caused by \textit{Leptospira grippotyphosa}, today serovar Grippotyphosa. Once the cause was identified it appeared that various other diseases with other names, for instance harvest fever, were found to be caused by the same serovar.

Gradually it became clear that there were many variants of leptospires causing a range of disease manifestations.\textsuperscript{5,14} By this time the term leptospirosis was used in its plural form. Diseases were named after the causative leptospira variant; hence, the names \textit{Leptospirosis pyrogenes}, \textit{Leptospirosis grippotyphosa}, etc. Indeed, some serovars tend to affect predominantly certain organ systems such as the liver (leading for instance to jaundice), the kidney (causing anuria), the brain (causing meningitis) or lungs (pulmonary bleeding) causing a loosely defined range of signs and symptoms. However, there is too much variation in clinical manifestations to justify a strict tying of a serovar to a form of disease: the more observations were made worldwide the more it became clear that serovars may cause severe disease with all the characteristics of Weil’s disease, but also mild disease or other symptoms. Therefore, naming a form of leptospirosis after the causative serovar proved untenable in the long run and the tendency has been abandoned to connect a certain serovar with a certain syndrome. Although certain serovars tend to give a certain type of disease, the present day tendency is to regard leptospirosis as a single disease with a wide variety of manifestations and caused by one of many different serovars. According to this view, the term Weil’s syndrome is preferred rather than Weil’s disease.

\textbf{Leptospirosis in India}

After the description of Weil’s disease and with the discovery of many different leptospira variants, leptospirosis was found to occur almost worldwide and to be particularly prevalent in the humid tropics. Leptospirosis could occur as a relatively mild disease but in some areas, notably in China, a severe form of leptospirosis with pulmonary haemorrhage proved to be an important public health problem. By the end of the last century severe leptospirosis with pulmonary haemorrhage as a prominent symptom was reported not only from China but also from more places in the world than originally thought. In India, where leptospirosis was known to occur since many decades on the Andamans,\textsuperscript{15} this severe type of disease thought to be a haemorrhagic fever, was rediscovered over a decade ago on these islands as a form of leptospirosis and with renewed interest and vigour the disease is studied there.\textsuperscript{16} In India, alert clinicians\textsuperscript{17-19} who were aware of the disease, stimulated leptospirosis research in the second half of the last century up to today. They have a keen eye for an old problem that is still very much alive, namely of confusing clinical pictures by diseases resembling leptospirosis: recently Hantavirus infection.\textsuperscript{20} The number of investigators has further increased and leptospirosis is a subject of interest in the community of microbiologists and other experts in the field of infectious diseases.

\textit{The same old problems}

Leptospires were found in many animal species and the relation between leptospires and their animal hosts has essentially been clarified.\textsuperscript{13} Schematically speaking, a differentiation can be made between an animal host species that is carrier and natural maintenance host for a certain serovar, that transmits its infection to its offspring and that suffers no or little harm and on the other hand accidental hosts, that are accidentally infected, are a dead end for transmission and usually develop overt disease. Transitional situations occur with leptospires adapting to new hosts.
Our knowledge of leptospirosis has increased hugely during the past century. Leptospirosis was observed to occur practically worldwide. In many parts of the world the disease is endemic but it can achieve epidemic proportions when transmission conditions are favourable such as during periods of high rainfall and flooding. Leptospirosis is increasingly perceived as a disaster-related disease. The term emerging-disease is often used today. Whether leptospirosis is really emergent or re-emergent is a question of limited interest, but what is important is a renewed interest in a disease that may or may not have been around but was and is often overlooked. It is hard, if not impossible, to compare the leptospirosis situation worldwide now with the situation a century ago. Since then much more has come to our knowledge on the distribution of leptospirosis, but even now there is still a lot of uncertainty about the disease in various regions of the world. Since a hundred years, much has changed: the human population has increased, humans have encroached upon areas that used to be pristine jungle and unknown serovars lurking in the remaining jungle are waiting to be discovered. Unknown serovars may infect humans when they enter the habitat of the maintenance-host, known serovars may adapt to new hosts and start to spread. This phenomenon has been seen with serovar hardjo type Hardjoprajitno that we saw spreading around under our very noses, so to speak, affecting cattle and farmers.  

The taxonomy of leptospires has become very complicated. The number of newly detected serovars has become large and complicated to a degree that identification has become cumbersome. Fortunately DNA analysis brought an enormous added value to serological analysis and is in many respects complementary, for instance because it can sometimes distinguish in an epidemiologically important way between antigenically similar but genetically different types. However, the introduction of new analytical methods has confirmed that the taxonomy of leptospires is highly complex. A consolation should be that a precise identification of serovars with modern technology might help tracking down animal reservoirs and designing control measures.  

*Lessons from the past*

What strikes me when I dig into old scientific literature up to a century ago, is that our predecessors approached problems rationally, apart from the pre-scientific miasma concept and thought along lines of research that we are using today. Plausible hypotheses were proposed, some right, some wrong and while successful scientific breakthroughs were achieved on one hand, just like now, on the other hand costly time and energy was spent in exploring dead end roads, just like now. Mistakes were made by mixing up strains and exercising insufficient care in isolating and culturing leptospires. It all sounds too familiar. Contamination with saprophytes plays havoc with leptospirosis research even today. Saprophytic leptospires are everywhere. They can be found in surface and tap water and in damp places. Think of serovar Andamana strain CH11, that was originally isolated from a moderately severe case of jaundice, but now the reference strain is not pathogenic, displaying the characteristics of a saprophyte. Sometime in the past, contamination of the original isolate or mixing-up of strains may have occurred. The contamination and mixing-up problem has not lost its urgency. Today it is as important, as it was during the past hundred years, to prepare culture medium with meticulous care using sterile equipment and ingredients to avoid growth of contaminants. Sub-culturing should be performed with scrupulous discipline to avoid mixing up of strains. Culture samples should be collected aseptically to avoid false positive results by isolating a contaminating saprophyte.  

What strikes me as a very constructive attitude in our predecessors is the extensive reporting of negative results, sometimes with clear expression of feelings of both, necessity and reluctance. Of course, in research it is almost inevitable that we devise now and then wrong hypotheses and explore unrewarding dead end research routes for too long. The reporting of negative results is a useful clue to stop pursuing wrong goals and to reveal false hypotheses. It seems to me that today we are too reluctant to publish negative results. Of course, we all like to come forward with beautiful new and positive results, but, as research is often grooping around in the dark with trial and error being part of the creative scientific process, reporting negative results teaches your fellow-researchers where not to search and may prevent wasting precious time, energy and money.  

Leptospirosis is as elusive as it was since it was first recognized. The clinical diagnosis is still difficult and leptospirosis is easily confused with other febrile diseases displaying a variety of symptoms that are also found in leptospirosis. An accurate and rapid diagnosis is important in the interest of the individual patient in need of treatment and in the interest of public health. Similarly, quick and reliable typing of isolates is important to gain insight in epidemiology and to design effective control measures. In the course of a century and more, enormous progress has been made in diagnosis and typing. Still, there is plenty of room for improvement. The need still stands for quick, simple, robust, reliable and affordable diagnostic tests and to amply introduce and implement these tests, paying special attention to areas with limited health care facilities and to outbreaks. Finally, our knowledge of leptospirosis has hugely increased during the last hundred years or so and the professionals working in the fields of human and veterinary health as well as the general population, especially the risk groups, deserve to be kept aware and informed about leptospirosis.  

**References**


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