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The Epidemiology of Weil's Disease

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ABSTRACT.—Adolf Weil defined the disease as a clinical entity in 1886, and *Leptospira ictero-hæmorrhagiæ* was found to be the causative organism in 1915 by Inada *et al.* in Japan, and confirmed by Hübener and Reiter in Germany. The infection has been found in most countries, and recently there has been a great increase in the number of instances reported.

In most parts of the world rats and other small rodents harbour the organism and excrete it in the urine. This is almost always the direct or indirect source of infection of man, but natural infection of dogs and foxes takes place, and is at least a potential danger to human beings. Infection is usually related to occupation in coal-mines, fieldwork of all sorts, sewers, fish-cleaning, and to bathing in fresh water.

The organism quickly dies in an acid medium, in strong sunlight and in salt water. These facts accord with the presence of the disease in certain situations.

The route of infection of man is usually by contact of the abraded or sodden skin with infected mud or water, but it may be by inhalation of water and by bites of rats, dogs, and ferrets.

Men are much more exposed to infection than women, but in fish-cleaners the incidence is equal in the sexes. Children are sometimes infected by bathing and in houses.

The incubation time may be four to nineteen days, and is usually seven to thirteen days.

By serological methods many unjaundiced and subclinical infections can be detected among people who are often at risk, and these correct the rather high fatality rates which are derived from jaundiced cases only.

During the last three and a half years 142 authenticated instances of the disease in an obvious clinical form have been reported in the British Isles. Twenty-one occupations or circumstances were involved, and the case fatality rate was 15 per cent.

RÉSUMÉ.—Adolf Weil décrivit cette maladie comme entité clinique en 1886, et en 1915 les Japonais Inada et al. découvrirent que le *Leptospira ictero-hæmorrhagiæ* en est l'agent étiologique. Ceci fut confirmé par Hübener et Reiter en Allemagne.

La maladie a été observée dans la plupart des pays, et récemment le nombre de cas rapportés a beaucoup augmenté.

Dans la plus grande partie du monde l'organisme est porté par les rats et quelques autres petits rongeurs, et excrété avec l'urine. Celle-ci est presque toujours la source directe ou indirecte de l'infection humaine. Cependant le chien et le renard peuvent être infectés spontanément, et il est tout au moins possible qu'ils deviennent une source de danger pour l'homme.

L'infection est généralement liée au travail dans les houillères, dans les champs, dans les égouts, au nettoyage du poisson ou aux bains d'eau douce.

L'organisme meurt bientôt dans un entourage acide, au soleil brillant et dans l'eau salée. Ces faits s'accordent avec l'existence de la maladie dans certaines localités.

L'homme est d'habitude infecté par le contact de la peau écorchée ou trempée avec de l'eau ou de la boue infectée, mais peut l'être par l'inhalation d'eau ou par des morsures de chien, de rat ou de furet.

Les hommes sont plus exposés à l'infection que les femmes, mais parmi les nettoyeurs de poisson l'incidence pour les deux sexes est semblable. Les enfants sont quelquefois infectés à la suite de bains ou dans les habitations.

L'incubation peut durer de 4 à 19 jours, le plus souvent de 7 à 13 jours.

Les méthodes sérologiques permettent de déceler beaucoup d'infections sans ictère et sans signes cliniques, ce qui corrige la mortalité assez considérable obtenue par l'étude exclusive des cas présentant de la jaunisse.

Cent quarante deux cas prouvés, avec signes cliniques typiques ont été rapportés dans les Iles Britanniques pendant les derniers trois ans et demi, avec une mortalité de 15%. Vingt et unes occupations ou circonstances différentes ont été trouvées comme cause.

ZUSAMMENFASSUNG.—Adolf Weil beschrieb 1886 diesen Zustand als Krankheitsbild *sui generis*; 1915 wurde von Inada et al. in Japan *Leptospira ictero-hæmorrhagiae* als Erreger gefunden und dieser Befund wurde von Hübener und Reiter in Deutschland bestätigt. Diese Infektionskrankheit wurde in den meisten Ländern gefunden, und in der letzten Zeit hat die Zahl der mitgeteilten Fälle stark zugenommen.

Auf dem Grossteil der Erde beherbergen Ratten und einige andere kleine Nagetiere den Organismus und scheiden ihn im Harn aus. Dieser ist fast immer die unmittelbare oder mittelbare Infektionsquelle für den Menschen, doch kommen Spontaninfektionen bei Hunden und Füchsen vor und stellen zum mindesten eine mögliche Infektionsgefahr dar. Meist steht die Infektion in Zusammenhang mit Beschäftigung in Kohlenzechen, mit Feldarbeit jeglicher Art, mit Arbeiten in Sielen, Fischreinigung und mit Baden in Süsswasser.

In saurem Boden, starkem Sonnenlicht und Salzwasser stirbt der Organismus rasch ab. Diese Tatsachen stimmen mit der Beobachtung überein, dass die Erkrankung in bestimmten Bezirken vorkommt.

Die Infektion beim Menschen geschieht meist durch Berührung der abgeschürften oder durchnässten Haut mit infiziertem Wasser oder Schlamm, sie kann aber auch durch Verschlucken von Wasser oder durch Ratten-, Hunde- oder Frettchenbiss zustandekommen.

Männer sind der Infektion viel mehr ausgesetzt als Frauen, bei Fischreinigern ist indessen die Häufigkeit bei den beiden Geschlechtern die gleiche. Kinder werden gelegentlich beim Baden oder in Häusern infiziert.

Die Inkubationszeit beträgt 4-19 Tage, gewöhnlich 7-13 Tage.

Durch serologische Methoden können bei Menschen, die häufig einer Infektion ausgesetzt sind, oft ikterusfreie und symptomlos verlaufende Fälle entdeckt werden; diese Fälle stellen eine Korrektion der ziemlich hohen Mortalitätsziffer dar, die sich bei ausschliesslicher Berücksichtigung der mit Gelbsucht einhergehenden Fällen ergibt.

Während der letzten 3½ Jahre wurden in Grossbritannien 142 sichere, klinisch typisch verlaufende Fälle angezeigt. Dabei waren 21 verschiedene Berufe oder Begleitumstände beteiligt; die Mortalität betrug 15%.

IN 1886 Professor Adolf Weil, of Heidelberg, described four cases of a form of infective jaundice. Two cases had occurred in 1882 and two in 1870, and they were all so similar that he considered them to be of the same disease. In all of them there was a febrile illness with severe nervous symptoms, enlargement of the spleen and liver, jaundice and signs of renal disease, and, after a severe illness of relatively short duration, recovery was rapid. He carefully considered the differential diagnosis, and finally suggested that on clinical grounds the cases represented a new entity, although he could demonstrate neither its anatomical basis nor the infective agent.

During the next thirty years the name of Weil's disease was used in all parts of the world to describe a febrile illness with jaundice, in epidemic or endemic form, but there was doubt as to its applicability to individual cases or even as to its justification in general. Weil's belief that he had established a new entity was based on clinical judgment, and the correctness of his views was finally confirmed in 1915

when Inada and his colleagues at the Imperial University in Kyushu, Japan, demonstrated that a spirochæte which is now named *Leptospira ictero-hæmorrhagiæ*, was the cause of the disease. The illness was at that time well known in various parts of Japan as an epidemic and endemic occurrence characterized by conjunctival congestion, muscular pain, fever, jaundice, hæmorrhagic diathesis, albuminuria, and a fairly high mortality rate, and this has been the usual form of the majority of instances of the disease in all countries then and since.

This discovery was published in Japan in 1915, in U.S.A. in 1916, and in Europe it was soon made use of on the Western War Front where the infection was occurring. German workers published an independent, but not prior, discovery that Weil's disease is caused by a spirochæte which was named by Hübener and Reiter (1915, 1916) *Spirochæta nodosa*, and by Uhlenhuth and Fromme (1916) *Spirochæta icterogenes*. These names are synonymous with *Leptospira ictero-hæmorrhagiæ*, but they have not been used currently in English. The collection of all the most useful epidemiological knowledge commenced after this date, and in this review very little reference will again be made to earlier observations.

The Causative Organism

The causative organism belongs to the genus Leptospira, of which it is the type species. It has the form of a slender, cylindrical, and highly flexible filament with very tightly wound and rather shallow spirals. At each extremity it is bent over in the form of a hook. Owing to rapid rotation of these crooked ends, a figure-of-eight appearance may be produced. This spirochæte in the unstained condition is not visible under the microscope unless dark-field illumination is employed. The commonest length is between 6 and 15 μ, and the thickness is about 0·25 μ.

The Geographical Distribution of the Disease

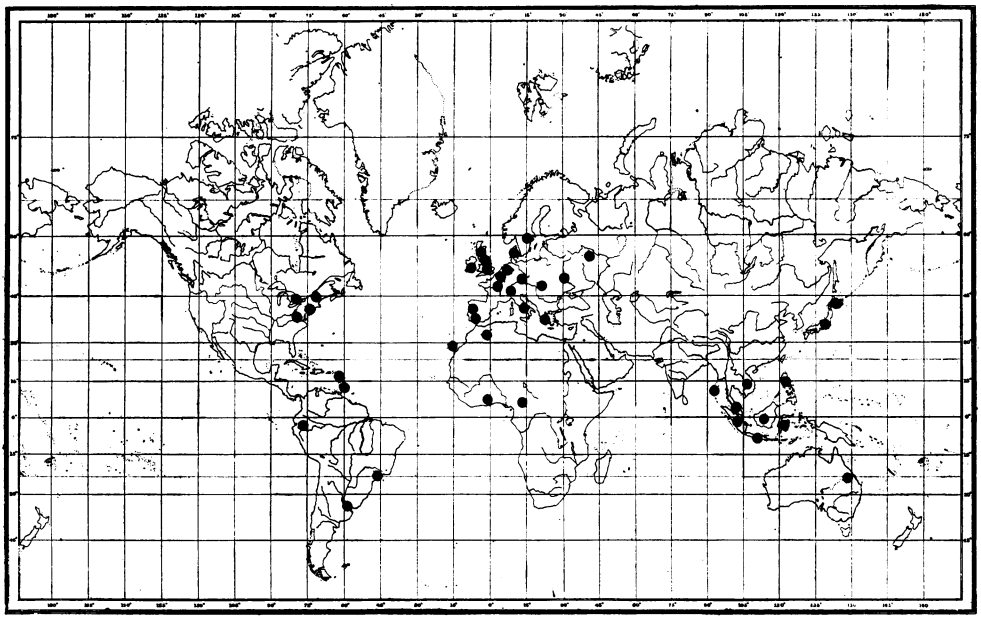
The disease is widely distributed, and there is little doubt that since methods of diagnosis, which are now easier than they were formerly, are more frequently applied, the distribution will be found to be almost universal.

The spirochætal cause of the disease was confirmed in British soldiers in Flanders by Stokes and Ryle (1916), and in French troops by Costa and Troisier (1916–17) and others. On the Italian front it was reported by Sisto (1917).

Since 1918 the disease has been recognized bacteriologically or serologically in most of the other countries or regions of the world, and reference will be made here merely to one of the more notable of the early publications on recognition of the infection, although not always the first report for each country. In Europe there are records for England (Manson-Bahr, Wenyon, and Brown, 1922), Scotland (Gulland and Buchanan, 1924), Holland (Schüffner, 1934), Denmark (Zuelzer, 1936a), Germany (Strasburger and Thill, 1929), Sweden (Malmgren, 1936), Switzerland (Gsell, 1936), Czechoslovakia (Bardos, 1936), Greece (Copanaris, 1932), Spain (Urtubey, 1929), and Portugal (Jorge, 1932). In Asia the infection has been identified in the Netherlands East Indies (Baermann, 1923), the Andaman Islands (Taylor and Goyle, 1931), French Indo-China (Bagiot and Delbove, 1934), and the Malay States (Fletcher, 1927). On the American continent the diagnosis has been established in the United States (Towler and Walker, 1927), Canada (Bates, 1926), Brazil (Piza and Gomes, 1930), Guadeloupe (Leger, 1932), Ecuador (Carbo-Neboa, 1924), and Argentina (Miyara *et al.*, 1935). In Africa the infection has been found in Morocco (Melnotte and Farjot, 1927) and the Belgian Congo (Kadaner and Corti, 1934). In Australia, Queensland has provided nearly all the cases (Drew, 1934; Cotter, 1936). These countries or regions, and a few places where the infection has been suspected, but not completely proved, are marked on Map I.

The highest incidence of the disease has been found, so far, in Holland, France, Malay States, Sumatra, and the Andaman Islands. It seems noteworthy that, as knowledge exists at present, there is an apparent absence of the disease in Egypt, Arabia, and Persia, and very scanty evidence of it in India. Outbreaks of jaundice have occurred from time to time in India, and in some (e.g. Parmanand, 1922) the diagnosis of Weil's disease has been considered probable on incomplete evidence, but, in a recent unpublished communication, Colonel Taylor states that laboratory confirmation of the diagnosis of Weil's disease has been lacking in all but a very few instances. It may be that strong sunlight in these countries is an important factor, for it is well known that bright light has a highly lethal action on the organism.

The use of adequate means of diagnosis has been rewarded by the discovery of more cases, and this is well exemplified in the history of the disease in Great Britain. In the decade after Manson-Bahr, Wenyon and Brown (1922) isolated the organism



MAP I.—Showing the countries or regions of the world where Weil's disease has been proved to be present or, in a few instances, reported without full proof.

for the first time in this country, and after Gulland and Buchanan (1924) reported the outbreak in East Lothian coal-miners, very few papers were, apparently, published relating to leptospiral jaundice in Great Britain, and most of these few dealt with mild cases which were difficult to diagnose with certainty. In July, 1934, Fairley demonstrated that the disease occurred comparatively frequently among sewer workers in London, and this caused a great deal of interest in the infection. A paper by Brown in 1935 on serological diagnosis led to sera being sent to him from all parts of the country, with the result that more than 40 cases were brought to light in seven months, and now 142 authenticated British cases which have occurred since the middle of 1933 are known to us from published and unpublished records. All these were well-marked infections showing most of the classical signs of the disease. We have no data in this country from which we can compute the proportion of jaundiced cases to the total number, but, in the British Army in Flanders, Stokes and Ryle (1916)

reported that 60% of patients did not develop jaundice, and Schüffner (1934) found the same percentage of mild, unjaundiced cases in an epidemic in Holland. It is probable, therefore, that the disease is much more prevalent than our present records testify. This is supported by the fact that Alston and Brown (1935) were able to demonstrate agglutinins and protective antibodies in the blood of nine out of 45 London sewer workers who were in good health at the time of the test, and who said that they had never had jaundice. Similar findings in the case of fish workers in Aberdeen were reported by Smith and Davidson (1936). In this way it has been revealed that as in most, or perhaps all, infectious diseases, infection may produce disease of different degrees of seriousness or no observable disturbance of health.

Five or six weeks is the usual period required for recovery from a moderately severe, non-fatal infection, and it does not appear that a second attack of the disease has been observed. This is in accordance with the findings of agglutinins in the blood twelve years after recovery from the disease (Fairley, 1934). Convalescence is in almost all cases not broken by any serious relapse, although it has been observed that the leptospira can in some instances be recovered from the urine for several weeks after the acute stage of the illness has ended. However, an infection recorded very recently by Murgatroyd (1937) shows that we must be prepared for continuance of the infection for a considerable time after the commencement of the disease. This case appears to be unique in the literature. The patient showed the usual manifestations of a moderately severe infection, but although improvement occurred at about the eleventh day of illness, there followed a period of almost four months of incomplete recovery and irregular hyperpyrexia. At the end of that time symptoms and signs of severe meningitis were found, and the specific organism was isolated from the cerebrospinal fluid twenty-five weeks after the onset of the disease. In the urine the leptospira was last found thirty-three weeks after the illness began. The patient finally recovered after eight and a half months' illness.

The Carriers of the Infective Agent

The spread of Weil's disease is almost entirely due to the fact that some species of rats and other small rodents harbour the organism and excrete it in the urine for long periods without suffering disturbance of health. The proportion of infected rats is smaller among the younger and older animals and greater in those of intermediate age, and almost the only result of the infection is that the rats' blood contains specific antibodies (Brown and Davis, 1927). Ido and his co-workers (1917) found virulent leptospira in the kidneys of 40% of *Mus decumanus* but of only 0·8% of *Mus alexandrinus*, and they quote the findings of Miyajima that the field-mouse, *Microtus montebelloi*, harbours the organism frequently. In Japan, up to 39·5% of rats caught in houses and ditches in cities were found to be infected. Since these surveys were made, twenty years ago, the presence of virulent leptospira in rats in rural and urban situations has been found in almost all parts of the world. For example, in Great Britain, various observers found that the incidence of infection in the brown rat varied up to 41%. In Australia a native species, *Rattus culmorum*, has been found to be heavily infected, in addition to other species not indigenous to the continent (Cotter, 1935). In Egypt and India, where the incidence of human infections is low, relatively few of the wild rodents harbour the organism. We have been informed, in an unpublished letter from Colonel Taylor, that in Bombay Colonel Anderson examined the kidneys of 100 rats of each of three species for leptospira. He obtained positive results from 32% of the specimens of *Rattus norvegicus*, and 7% of *Gunomys varius;* none from *Rattus rattus*. With regard to other rodents, Bessemans and Thiry (1929) found evidence of leptospiral infection in mice, and Kaneko and his co-workers (1935) found that 14·7% of 1,400 field-mice (*Apodemus speciosus speciosus*) harboured leptospira, and they considered this rodent to be one of the most important means of spread of Weil's disease and of infections due to

other, closely related, leptospira. In this country, Brown (unpublished) failed to find leptospira or evidence of antibodies to *L. ictero-hæmorrhagiæ* in 36 field-mice (*Apodemus sylvaticus*) from Oxford, and injection of macerated tissues of these mice did not cause any constitutional disturbance in guinea-pigs. In Rangoon, Taylor and Goyle (1931) found that the lesser bandicoot (*Nesokia bengalensis*) showed an infection rate of 43%. Some of the rodents are, therefore, the main source from which the infective agent may reach human beings, and the only other mammals in which infection has been clearly demonstrated in both overt and latent forms are the dog and, rarely, the fox.

The disease in dogs was first reported from France by Courmont and Durand (1917) and the subject has been thoroughly investigated by various workers especially, in Great Britain, by Okell, Dalling, and Pugh (1925). In this country the evidence, so far as it goes at present, is in favour of the type of leptospira which infects dogs being identical with the human type (Brown and Davis, 1927), but in 1931 in Holland, Schüffner (1934) isolated a strain (*L. canicola*) from the urine of a dog and found that it was serologically distinct from *L. ictero-hæmorrhagiæ*. It is now known (Schüffner, Kotter, and Schultsz, 1935) that on the continent of Europe, at least, dogs may be infected by either of these types, that there are minor differences between the diseases which they cause, and that *L. canicola* has sometimes infected human beings. These workers could not detect *L. canicola* in rats in a locality where it was common in dogs. In Sumatra, 5·7% of healthy dogs were found to harbour in the kidneys leptospira which were weakly virulent for guinea-pigs and which were considered, on that account, somewhat different from classical Weil's strains (Kouwenaar and Wolff, 1930). It has been shown, further, that in dogs, as in human beings, latent and subclinical infection occurs, and that in relation to one another, and in relation to human beings, dogs must be regarded as possible carriers of infection in some areas (Uhlenhuth and Zimmermann, 1936). It is unlikely, however, that the risk will be found to be as great as that from rats.

Dunkin and Laidlaw (1924–25) proved that a wild fox which was found sick and jaundiced in an open field near a research laboratory was infected with *L. ictero-hæmorrhagiæ*, and Dr. J. Smith has informed us in a letter that he investigated an outbreak of leptospiral jaundice in a fox farm near Aberdeen, and that three foxes died of the disease.

It is possible that pigs may sometimes be infected, for Sander (1935) has reported that a butcher developed Weil's disease eight days after he had killed a jaundiced pig.

Infection of one human being by another is very rare, but Schüffner (1934) believed that a woman had been infected in coitus, and Taylor and Goyle (1931) considered that in the Andaman Islands urination on the ground by men with slight infections had helped to spread the disease.

Viability of the Organism Outside the Animal Body

It is generally believed that the most important source of infection for the human race is the urine of rats, and the viability of the leptospira after they have been excreted on soil, into water, &c., is very important.

Zuelzer (1928) showed that the organisms are, in nature, usually found attached to other spirochætes and protozoa. Noguchi (1918) stated that in contaminated waters they were not capable of multiplying and survived less than forty-eight hours, and when added to distilled water they disappeared in seven days. They have been found in considerable numbers in the slime on the roof of a coal-mine (Buchanan, 1927), and they can readily be demonstrated in the mud in sewers (Alston *et al.*, 1935). We have found that specimens of mud from London sewers are very nearly alkaline in reaction, and that leptospira in it do not remain virulent to guinea-pigs for as long as twenty-four hours after the mud has been brought to the laboratory.

The organism is very susceptible to the action of acids and is rarely found in waters having a pH of less than 6·8. For instance, Taylor and Goyle (1931) reported that in the Andaman Islands leptospira were common in waters of pH 6·9 or over and absent in those of 6·6 or less, and Sardjito and Zuelzer (1929) have shown that they are abundant in the alkaline waters of Sumatra, where human infections are frequent, but are practically absent from the more acid waters of Java, where there are few infections.

It has long been recognized that the organisms die rapidly when they are excreted in the urine of patients suffering from the infection. It has been considered that the acid state of the urine, which is increased in the febrile condition, is responsible for this, and for purposes of cultivating the leptospira or transmitting the disease to experimental animals a practice is made of rendering the urine alkaline as soon as possible after it has been passed, or of giving the patient alkalis in order to alter the reaction of the urine *in vivo*. Recently, Davidson and Smith (1936) have brought evidence that lytic antibodies which are present in the urine in some cases may have on the leptospira an additional lethal effect, commencing as soon as the organisms reach the renal tubules.

The organism is susceptible to common salt, and it cannot live for more than three days in alkaline water containing 0·17% of sodium chloride ; it perishes rapidly in sea-water. Schüffner (1934) considers that these facts provide part of the explanation of the variations in incidence of infection by immersion in water in different parts of Holland, since there is a mixture of sea and fresh water in different proportions in different parts of the country.

The Route of Infection

Weil (1886) originally believed that infection took place through the alimentary canal. Inada (1916) was at first of the same opinion, but later he and his co-workers were satisfied that infection could take place through the shaven but macroscopically unbroken skin of a guinea-pig, and although they were able to infect animals through the mucous membrane of the alimentary canal, massive doses of infected liver tissues were used for this purpose. In studying 55 cases amongst coal miners, these observers were able to obtain only a few instances suggesting cutaneous origin, but they stated that the cutaneous route was the probable means of entry because of the following facts : (1) The incidence was greater in certain parts of the coal-mine than in others, (2) there are many cases in wet and few in dry mines, (3) the infection takes place more easily if the skin is injured, (4) coal-miners are liable to abrasions of the skin and also to skin lesions caused by working with the feet in water. Regarding the incidence of the disease in sewer workers, it may be of significance that, although both classes of these workmen are subject to abrasions of the hands and arms, the builder's labourers, who break up and handle old brick-work or concrete covered with slime, suffer more abrasions than the " flushers " who clean the walls of the sewers, and the builders were found during eighteen months' observation in London to show a case-rate about ten times as high as the flushers. Among sewer workers, several patients with Weil's disease, showed gashed or abraded wounds when they were admitted to hospital, and these wounds had been made at a time within the incubation period of the infection. Further evidence of the cutaneous route of infection is given by the incidence of the disease in the Andaman Islands (Taylor and Goyle, 1931), in fish workers in Aberdeen (Smith and Davidson, 1936), and among sugar-cane cutters in Australia (Cotter, 1936). An infection, as the result of pricking a finger with the needle of a syringe which was charged with a virulent leptospiral culture, is reported by Wadsworth (1922), and there was a well-proved instance of the disease with onset two days after the patient had trodden with an abraded foot in the blood of a rat which he had just killed (Cattaneo, 1929).

Infection by rat-bite was recognized by Ido and his co-workers (1916), who observed two patients who acquired Weil's disease seven days and from eight to nine days respectively after rat-bites. We know of three similar instances in this country in the last two years, and in two of them the illness began nine and fourteen days respectively after the bites, that is, within the incubation period.

As to whether leptospira can penetrate the unbroken skin, there is a certain amount of difference of opinion. The question is somewhat academic on account of the microscopic size of the abrasion which might well serve as portal of entrance for a leptospira, but Inada, *et al.* (1916), were of opinion that the organism could penetrate the unbroken skin, although they obtained a higher percentage of infections through an abraded surface.

Regarding the oral route of entrance, it is now well known that by sudden, accidental immersion in water, infection is more likely to occur than in the course of ordinary bathing. As Schüffner (1934) points out, this is no doubt due to the fact that an unpremeditated immersion often causes violent struggling, so that water enters the respiratory tract and, as a corollary to this, Schüffner draws attention to the danger of the " crawl " stroke in swimming in infected water.

When the organism enters by the mouth, invasion of any part of the alimentary tract by leptospira is possible as an additional or alternative means, but indisputable evidence of alimentary infection is rare. Contamination of food by rats' urine has been suspected, and Jorge (1932) described an outbreak in Lisbon with 126 cases in a month, which he attributed to drinking water from a certain fountain that had been fouled by rats. Although the organism was not isolated from any of these cases and guinea-pigs were injected but did not become infected, the serum of several patients was found to agglutinate both the London and the Lisbon strains of *L. ictero-hæmorrhagiæ*. It is a pity that the cause of this outbreak was not conclusively proved because, if it were indeed an epidemic of Weil's disease, it could provide some interesting epidemiological evidence.

Mechanical transmission of the infection sometimes occurs. We detected the disease by agglutination in a patient who had been bitten by a dog which had just previously killed a rat (Wigmore and Denning, 1936) and another case is reported (Brown and Cleveland, 1932) in which infection followed a bite by a ferret which had immediately before been bitten on the lip by a rat. In these cases it is only natural to assume that the teeth of the dog and of the ferret were contaminated by contact with the infected viscera of the rats. We know another example of ferret-bite in which the same mechanical transmission of infection is probable, since we could not demonstrate agglutinins in the ferret's blood. In these three cases the intervals between the bite and the onset of the illness were five, seven, and ten days, respectively which agree with the ordinary incubation period and resemble that in those infections developing after rat-bite, which have been mentioned.

During the early investigations of the disease it was suspected that insects might provide a means of transmission of the infection, either mechanically or as intermediary hosts of the leptospira, but this has not been confirmed in any form. Noguchi reported in 1918 that the larvæ and adults of the Culex mosquito, the larvæ of the house-fly and the bluebottle fly, wood-ticks (*Dermacentor andersonii*) and leeches failed to become carriers of the leptospira when fed on infected guinea-pigs or their organs, and that therefore they cannot be shown to play the part of an intermediary host of *L. ictero-hæmorrhagiæ*. Gay and Sellards (1927) found that virulent strains of leptospira survived in *Aedes ægypti* for as long as three weeks in certain instances, but they failed to transmit infection by bites of these infected insects. Bonne (1924) found survival for at least forty-eight hours in the bed-bug, but there is no evidence that this insect plays a part in transmitting the disease. Even in the tropics well-considered opinion is against insect transmission, as is stated, for example, by Taylor and Goyle (1931) with regard to the disease in the Andaman Islands.

Incidence as Regards Sex and Age

In most circumstances in which Weil's disease has occurred, males are much more exposed to the risk than females. Of the last 47 infections which Brown has examined from all parts of the British Isles, all were in males. Domestic and laboratory infections have shown that women are certainly susceptible, but the best opportunity of comparing the relative susceptibility of the sexes has been found in fish workers in Aberdeen (Smith and Davidson, 1936), where illness occurred in both men and women, and latent or slight infection was detected in 24% of men and 24·3% of women.

As regards age, it is only by bathing and in the uncommon instances of domestic infection that children are at risk, but a case of this kind in a boy aged 10 years has been reported (Kerr, 1936) and the occurrence of leptospiral meningitis in children has been emphasized by French writers (Marie and Gabriel, 1936).

Seasonal Incidence

Seasonal variation of incidence has been noticed chiefly in the case of field workers. In Japan it was found that in coal mines, infection occurred at all times of the year, but in other circumstances the disease was seen most in the seasons of moderate temperature and least during the hottest and coldest parts of the year. In the Andaman Islands the great majority of infections occurred in field workers during the wet season (Taylor and Goyle, 1931), and in Europe there is an increase of infections in the summer and autumn, due to bathing in fresh water.

Incubation Time

The incubation period has been most accurately recorded by Schüffner, who found that in 37 cases due to falling into infected water it varied from four to nineteen days, and that in 31 (84%) of them it was from seven to thirteen days. This agrees with the estimate made in other circumstances which very often do not admit of accuracy in every instance. In the case of the laboratory infection reported by Wadsworth (1922) the period was eight days. A very short incubation time is not very uncommon—an example of two days has been recorded by Cattaneo (1929).

Fatality Rates

In view of what is known of mild and symptomless infections, it is evident that case-fatality rates for different groups will depend on the extent to which the less severe infections are taken into account. It is this which gives rise, in a very large measure, to the differences in case-fatality rates of from 5% to 50%. In the future, when the total incidence of the disease will probably be more fully determined, it will be possible to discern more accurately whether some strains of leptospira are more virulent than others, whether some groups of people are more susceptible to the same strains, or whether some circumstances of infection increase the severity of the disease. At present the part played by such factors cannot be clearly defined, and an average fatality rate of 15 to 50% among patients who have been treated in hospital indicates only the risk of a fatal issue in any case with observable jaundice. The table on page 56 shows that of 142 patients in the British Isles since July 1933, 22 died—a case-fatality rate of 15%.

In some circumstances an estimate of the chance of serious infection can be made with regard to a group of people who are constantly exposed to the risk. For instance, in London there are about 1,000 sewer workers in regular employment, and during the last two and a half years, four fatal and 14 non-fatal infections were treated in hospitals. This provided a case-incidence rate of 0·7% per annum and a total fatality rate of 0·16% per annum.

The Relation of Occupation, &c., to Weil's Disease

The epidemiological factors which have been discussed explain the relation of the disease to certain occupations. The major factors concerned are excretion of the leptospira by rats, the wetness of the general surroundings, and abrasions of the skin.

The 142 cases which have been discovered in Great Britain since July 1933 are drawn from most of the occupations which have been associated with infection in other parts of the world and, for their interest to clinicians in this country, they have been tabulated (as under). These were all incapacitating illnesses—subclinical infections are not included. Laboratory investigation of the majority has been

Table Showing Occupation, &c., and Number of Deaths among Cases known in the British Isles from July, 1933 to February, 1937

Occupation, etc.	No. of cases	No. of deaths	Locality *
(1) Fish worker	46	3	Aberdeen [45], Isle of Man
(2) Coal-miner	34	6	Northumberland and Durham [29], Swansea, Fifeshire [3], and Edinburgh
(3) Sewer-worker	19	5	London
(4) Bathing	15	2	Glasgow, Yorks, Preston, Lincs, Leicestershire, Birmingham, Bucks [4], Winchester, Aldershot [3], and Sussex
(5) Bathing and living in rat-infested house	1	0	Glasgow
(6) Canal worker	1	0	Herts
(7) Gravel pit worker	1	0	Herts
(8) Ship's traveller	1	1	London
(9) Farm worker, &c.	4	1	Edinburgh, Lancashire, Worcester, and Torquay
(10) Zoo-keeper	1	0	Edinburgh
(11) Gardener	3	1	Edinburgh, Newcastle [2]
(12) Labourer	5	2	Aberdeen, Edinburgh, Bristol [3]
(13) Mason	1	0	London
(14) Slaughter-house worker	1	0	Carlisle
(15) Rag worker	1	0	Stonehaven
(16) Laboratory worker	1	0	London
(17) Medical student	1	0	Edinburgh
(18) Boy scout in contact with rats	1	0	Glasgow
(19) Rat-bite	3	1	Dublin, Northants, Norwich
(20) Ferret-bite	1	0	Barnstaple
(21) Dog-bite	1	0	Aldershot
Total	142	22	

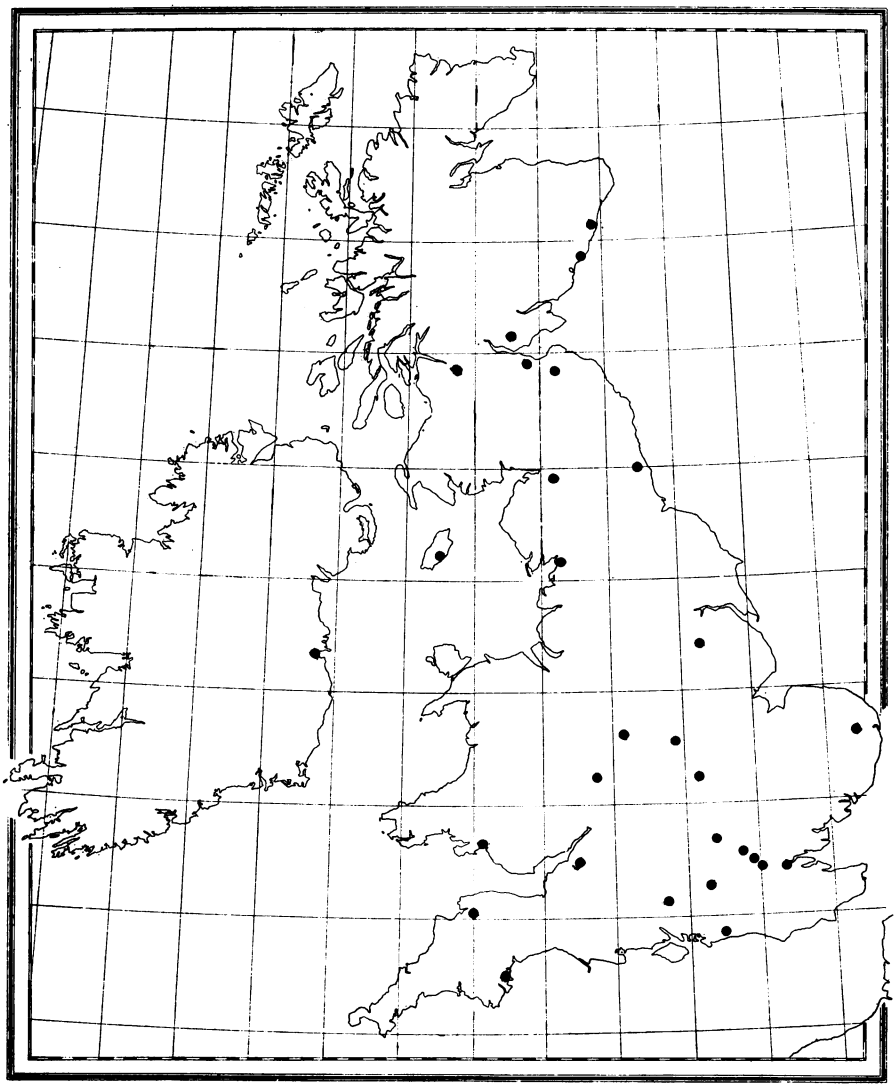
* Where more than one case has been found in a locality the number is given in brackets.

made by Brown in London, and of most of the others by Smith in Aberdeen. Those which have been reported already are from the publications of Alston *et al.* (1935), Coles (1936), Davidson and Smith (1936), Fairley (1934), Halsted (1935), Kerr (1936), Lendrum (1936), Maxwell (1935), Murgatroyd (1937), Neale (1935), Swan and McKeon (1935), Watson *et al.* (1935), Wigmore and Denning (1936), and Wolstencroft (1935). Unpublished cases are included by permission of Drs. S. P. Bedson, S. Faulds, and J. Smith. The cases are recorded in the table, and the localities in which they occurred are marked on Map II. In a world-wide review, the occupations and circumstances in which the risk of infection is greatest are coal-mining, field-work of various sorts, fish-cleaning, sewer work, and immersion in fresh water. The same causes are at work with slightly differing importance in all these situations.

Coal-mining

The disease has been studied most fully in this occupation in Japan and Great Britain, and in all areas where several instances have occurred it has been found that there were many patients from wet mines and few from dry ones. The Japanese considered that in a particular part of a mine in which they made some of their early

studies, pumping out the accumulated water stopped the disease. The wetness may increase the number of rats in the mine by providing them with water to drink, and it will protect leptospira from desiccation after they have been excreted in the rats' urine. Also, the miners' skin is made sodden and more permeable by the wet



MAP II.—Showing the localities in the British Isles where Weil's disease has been proved to be present.

conditions, and it is also frequently abraded by the rough walls and floor of the galleries.

FIELD-WORK

Numerous examples of the relationship of field-work to the disease have been found in Japan, the East Indies, and the Andaman Islands. Most of these have

been in workers in the rice-fields, and in the Andamans the seasonal increase of the disease coincided with the flooding of the ground during the south-west monsoon from May to October. In 1933 it was first revealed in Queensland that sugar-cane workers were exposed to the infection (Cotter, 1936). An unusual number of wet days with very high rainfall occurred in 1933 in the district affected and much surface water was present. There is heavy rat infestation in and around the cane-fields, and the hands, wrists and forearms of the cane-cutters are continually abraded by the lower leaves and ends of the cane, and contamination by the soil is unavoidable. All the conditions of infection by leptospira are clearly present.

During the Great War the disease was usually contracted in the open, for the patients were almost invariably attacked in the trenches or immediately after leaving them (Dawson, Hume, and Bedson, 1917).

Fish-cleaning

It is in Aberdeen that this source of infection has been studied. The chief factor in this situation is lack of cleanliness in many of the fish-curing premises. Fish remnants are left lying at the end of the day and rats are thereby attracted in large numbers. Leptospira are excreted and can actually be detected in washings from the tables and floor. The cleaning of the premises before each day's work is often imperfect. Abrasions of the hands and continual wetting of them are features of the work. Prevention has been planned and, in such indoor, circumscribed conditions, should be comparatively easy.

Sewer Workers

Several of the conditions which cause infection among sewer workers have been mentioned. The incidence is much greater among the builders' labourers who handle the broken brick-work covered with mud from the bottom of the sewer (figs. 1 and 2) than among the " flushers " who clean the sewer walls. The rats live in the ground or in houses near the sewer, and reach it by disused or broken drain-pipes opening into it. They come to the sewer for water mainly at night when there is no one to disturb them, and their footprints can often be seen in the mud at the side of the stream (fig. 3). Continuous efforts are being made to block the access of rats to the sewers, and to protect the workmen by cleaning and dressing any cuts which they receive when at work.

Immersion in Water

The most illuminating work on this type of the infection has been done in Holland, and several references have already been made to it. The table shows that 15 out of 142 infections in the British Isles appear to have been caused by bathing in rivers and canals, and this is the fourth largest group in the series. Wounds, especially on the feet or legs, often seem to be associated with infection, and in such cases it may be from mud below the water or on the banks that the leptospira enter the body. In other cases, the danger may arise in the entry of infected water into the respiratory tract, as occurs during struggling to prevent drowning, or in the " crawl " stroke in swimming.

Serological Differentiation of Leptospira

We have referred already to *L. canicola*, which Schüffner has distinguished from *L. ictero-hæmorrhagiæ*. In addition, many other types of leptospira have been recognized on account of serological differences, relationship to various human diseases, and pathogenicity to animals. Those which cause infections other than Weil's disease concern us very little, but among them *L. hebdomadis*, the cause of

FIG. 1.—Showing builder's labourers breaking the floor of a sewer and removing by hand pieces of slime-covered concrete.

FIG. 2.—Showing men handling the broken concrete beside the new brick-work by which it is being replaced.

seven-day fever in Japan, and *L. grippo-typhosa* of swamp-fever in Eastern Europe, may be mentioned. Another fever in Japan is known as akiyami and is due to *L. autumnalis* (Koshina *et al.*, 1925). These observers differentiated two types of this organism, Akiyami A and Akiyami B. The A type they found to be highly virulent for guinea-pigs, and in their opinion it was serologically distinct from *L. ictero-hæmorrhagiæ* and *L. hebdomadis*. The B type was less virulent for guinea-pigs and was serologically identical with *L. hebdomadis*. According to Stéfanopoulo and Hosoya (1928), however, Akiyami A type is closely allied to *L. ictero-hæmorrhagiæ*.

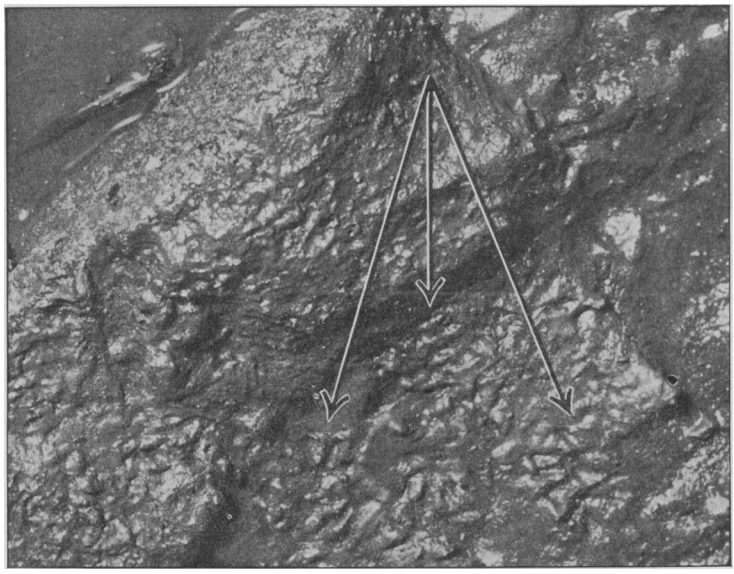


FIG. 3.—Showing rats' footmarks in the mud at the side of a sewer stream.

Fletcher (1927) was able to divide the leptospira with which he worked in the Malay States into six distinct serological groups, which he named *Ictero-hæmorrhagiæ*, *Akiyami A*, *Akiyami B*, *Pyrogenes*, *Nallathamby*, and *Eruthyan*. Schüffner (1934) reported eight types in the Netherlands East Indies.

In the Andaman Islands, Taylor and Goyle (1931) found that most of their strains formed a group serologically distinct from any others with which they could compare them, and the remainder were similar to strains found in Malay and Sumatra. In the British Isles all the strains which have been found so far in human infections have been of one serological type.

The Relationship of Saprophytic to Pathogenic Strains

One of the most controversial subjects regarding leptospirosis is the question whether the saprophytic leptospira, *L. biflexa*, can ever become pathogenic. This spirochæte was described by Wolbach and Binger in 1914 before *L. ictero-hæmorrhagiæ* was known and, morphologically, the two organisms are identical. *L. biflexa* has been found very widely in natural fresh waters and in all manner of damp places, and it has been regarded by most workers as not capable of infecting the higher animals. Contrary views have, however, been maintained by some. Uhlenhuth and Zuelzer (1921) grew a water leptospira for a year in a medium of serum-water and found that it was then pathogenic for guinea-pigs. Uhlenhuth and Hermann

(1927) " blocked " the reticulo-endothelial system of young wild rats, inoculated them with the water strain and afterwards isolated pathogenic leptospira from the animals. Baermann and Zuelzer (1928) also were of the opinion that on prolonged cultivation water strains became pathogenic to human beings. In a recent communication, Zuelzer (1936b) stated that, as judged by agglutination and lysis, there are certain gradual transitions from the pathogenic strains to the free-living leptospira, and that *L. grippo-typhosa*, which is the cause of swamp-fever, is related to the other pathogenic strains. On the contrary, many workers have not been able to confirm these findings, and the majority of observers (such as van Thiel, 1933) do not consider that the saprophytic water strains can ever become pathogenic. Taylor and Goyle (1931) suggested that there is always the possibility that Uhlenhuth and his colleagues were working with water strains obtained from sources in which pathogenic strains might also have been present, and Brown and Davis (1927) found that strains of *L. ictero-hæmorrhagiæ* and of *L. biflexa* were serologically distinct. In addition, during the procedure of isolation and maintenance of virulent strains from patients suffering from Weil's disease, we have constantly been able to demonstrate that cultures of pathogenic leptospira lose their pathogenicity for guinea-pigs after subculture for about four months. Therefore, if the pathogenic strains lose virulence in this way it is difficult to see how the non-pathogenic strains acquire it in the course of the same procedure.

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