Weil's Disease

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WEIL'S DISEASE, since its original clinical description by Adolf Weil of Heidelberg in 1886, has been diagnosed clinically in many parts of the world. Inade and Ido in 1914 discovered the pathogenic agent by inoculating the blood from a patient during the first week of the disease into a guinea-pig and found that the organism responsible was a spirochæte. Noguchi, who also studied the organism, described its typical morphology and called it the Leptospira Icterohæmorrhagica. This opened the way to more accurate diagnosis by bacteriological methods and to experimental investigation of this infection.

It was found that in the early stage of the disease, usually during the first week, the leptospira was present in the blood and that inoculation of a guinea-pig with the blood from a patient resulted in the production of leptospirosis in the experimental animal in a high percentage of cases. Later in the disease, i.e., about the third week, the organism was shown to be present in the urine, where its presence might be demonstrated by dark ground illumination of a urinary deposit or by animal inoculation. The discovery of the infecting organism by either of these methods is a difficult procedure, requiring careful co-operation between the clinician and laboratory as well as careful attention to details of technique.

A method was discovered by Schuffner of demonstrating the presence of antibodies in serum during or after the second week by means of an agglutination technique, using a young culture of the organisms. This technique has been widely applied and its specificity proven. The only drawback to this procedure is its technical difficulty and the necessity of maintaining stock cultures of strains of leptospira at a suitable growth-stage for the agglutination reaction. This latter difficulty has been somewhat overcome by the use of the formalised cultures advocated by Major Brown, which display the same specificity and sensitivity as living cultures.

Weil's disease is largely an occupational disease with a special incidence among workers employed in rat-infested premises. Thus it has been described among sewer workers (Alston and Brown, 1935; Halstead, 1935; Maxwell, 1935); fish-workers of Aberdeen (Davidson and Smith, 1935, 1939); miners (Gulland and Buchanan, 1924; Swan and McKeown, 1938; Rees, 1939; Sladden, 1939); tripe workers (Stuart, 1938). Besides this occupational incidence, sporadic cases do occur often following immersion in rat-infested streams (Robertson, 1939). In all these cases the rat is considered to be the vector of infection. In America, however, the leptospira icterohæmorrhagica of Weil's disease and the leptospira canicola, an organism which can cause 'yellows' in dogs, are considered to be identical. This raises the possibility of the dog as a possible vector of infection, and the source of infection has been traced in one case to a dog with 'yellows.' Both the patient

and the dog gave positive sero-agglutination to leptospira icterohæmorrhagica in the same titre.

Although Weil's disease has been described in many parts of Great Britain, no cases of the disease have yet been recorded from Northern Ireland, despite the fact that the disease has been suspected in this region for some years.

Two cases of suspected infectious jaundice occurred within a few weeks of one another among sewer workers in the city of Belfast, and one of these was diagnosed clinically as Weil's disease by one of us. From this case the leptospira was recovered from the urine, and has since been maintained on culture. Both cases gave a positive sero-agglutination of leptospira icterohæmorrhagica (stock strains) by Schuffner's technique in high titre.

CASE I.

Patient—Male aged 31 years; *occupation*—labourer, city sewers; *admitted*—27th August, 1939; *discharged*—22nd September, 1939.

Three weeks before the patient was admitted to hospital he took ill with a severe frontal headache, rigors, and sweatings. He was seen and treated by his own doctor with some symptomatic relief. About four days before admission his condition became worse, and he then complained of vomiting and a general feeling of nausea. The headache was still present, but had become more severe, whilst generalised pains developed throughout his body so that the slightest movement caused extreme agony. Abdominal pain was severe in character and situated mainly in the epigastrium. His throat was sore and swallowing difficult. Micturition was normal in frequency and free from pain.

On admission.—Temperature 99°; pulse 96. The patient was a well-built male subject of good nutrition, who showed slight signs of general muscular wasting. He was obviously in extreme pain, which was accentuated by any movement entailed during his physical examination. There was a generalised mild icteric tinge of the skin and conjunctivæ, but no evidence of gross anæmia or œdema. The conjunctivæ were inflamed and chemotic. The skin was dry and warm, but showed no evidence of rash or purpuric eruption. The joints could be moved passively, but the muscles were extremely tender to pressure.

The teeth were carious; the throat injected and the tongue covered with a thick white, dry fur. The abdomen was somewhat retracted, but moved slightly on deep inspiration. Abdominal tenderness was generalised with some localization in the epigastrium, right subcostal area, and both renal angles. The liver was not palpable nor the spleen enlarged. Examination of the other systems revealed no abnormality, the heart-sounds were clear and regular, murmurs absent, and the blood-pressure 100/70. The chest was clear except for an occasional moist rale.

Urinalysis.—Dark amber in colour: reaction acid: specific gravity 1018: albumen + + : bile pigment + : casts + .

Van den Bergh.—Biphasia + : indirect reaction + + .

Blood urea.—169 mgm. per cent.

Widal.—Negative.

Wassermann.—Negative.

Blood examination.—R.B.C. 3,900,000; W.B.C. 7,488; Hb. 83 per cent.
Film—nil abnormal in white or red cells.

The patient was put on alkalis, intramuscular injections of collosol calcium, and glucose drinks.

The urinary excretion was low, and the patient was still very ill on the third hospital day. The tongue was dry and covered with a brown fur. The liver was now enlarged to three finger-breadths below the right costal margin. The spleen was not palpable.

A continuous intravenous drip of glucose saline was set up on the fourth hospital day and a careful water balance kept. Despite this the patient's condition deteriorated, the blood urea rose to 278 mgm. per cent., and jaundice became deeper and vomiting recommenced.

On the seventh hospital day, when the patient's condition seemed hopeless, 100 c.c. of convalescent serum was administered intramuscularly and the continuous intravenous administration of fluids stopped owing to venous thrombosis. Two days later his clinical condition was much better and his urinary excretion improved.

The blood urea gradually returned to normal levels, and on discharge was 32 mgm. per cent. The temperature, which was intermittent, became normal, and the jaundice disappeared, although the liver enlargement persisted for some weeks.

The urinary deposit was inoculated into a guinea-pig on the twenty-fourth day of illness with negative results. A subsequent inoculation of a guinea-pig on the forty-sixth day of his illness produced typical leptospirosis. The leptospira could be seen on dark ground illumination of a mush of liver and kidney and in the heart's blood. From the blood and organs of this guinea-pig, cultures were made into Fletcher's medium and the disease transmitted to another guinea-pig by inoculation.

CASE II.

Patient—Male aged 21 years; *occupation*—labourer, Corporation sewers; *admitted*—5th September, 1939; *discharged*—16th September, 1939.

The patient stated that two days before he took ill he was working in a sewer, when a cart emptied its contents down the manhole, causing him to swallow some sewage. Two days later patient developed a severe headache and felt weak and ill. Owing to severe generalised myalgia he was unable to lie comfortably in bed, and tossed repeatedly without relief. Vomiting developed, and the patient was soon unable to retain anything in his stomach. Besides the generalised pains felt in all the muscles of the body, severe pain appeared under the left costal margin. The bowels were obstinately constipated and sleep was poor. Micturition was normal in frequency and devoid of pain.

His previous history revealed nothing of note.

On examination.—Temperature 100.2°; pulse 72. The patient was a well-nourished male of good build and nutrition. The face was markedly flushed. There was generalised mild icterus, which involved the conjunctivæ. The superficial lymph-glands were not palpable. Rash and purpuric changes were absent. The

tongue was dry and furred and the fauces inflamed. The abdomen was of normal contour and moved freely with respiration. There was no evidence of rigidity. Considerable tenderness was felt over the right and left costal margins. The liver was slightly enlarged, but the spleen was not palpable. Tenderness was marked in the R.I.F., and the cæcum could be palpated. There were no signs in any of the other systems; the lungs were clear, the pulse regular, blood-pressure 122/80, and the heart-sounds normal.

INVESTIGATIONS.

Urine.—Amber colour : neutral : specific gravity 1022 : trace of albumen : trace of blood : bile + .

Blood urea.—50 mgm. per cent.

Van den Bergh.—Biphasic reaction.

W.B.C.—10,500.

Wassermann.—Negative.

Fæces.—Occult blood present.

Urinary deposit repeatedly examined by dark ground illumination was negative for leptospira. Urine inoculated repeatedly into guinea-pigs without result.

Serum.—Schuffner's sero reaction positive in a titre of 1 in 1,000.

The temperature dropped to normal, and the patient rapidly recovered within a few days.

COMMENTARY.

Occurrence.—These two cases of Weil's disease are, we believe, the first to be recorded in Northern Ireland. Although on some occasions in the past the disease has been suspected on clinical grounds, these previous cases were without bacteriological or serological proof.

Occupation incidence.—Both of these cases occurred in sewer workers, and thus tends to confirm the high occupational incidence of the disease among these workers, which has been stressed by many authors. Both the men were employed on a rat-infested stretch of sewer, and both fell ill within a few weeks of one another. A fellow-worker was found to have been ill some weeks previously with an obscure illness and jaundice, and his serum gave a Schuffner's reaction in a titre of 1 in 10,000. He was previously also a case of Weil's disease, and it was the serum from this man which was used in the treatment of Case I.

Clinical picture.—The clinical picture was classical in both cases, in that it comprised the triad of an acute fibrile illness, jaundice, and a toxic nephritis with nitrogen retention. The clinical severity varied greatly, and while one case had what was considered a hopeless prognosis, the other was little disturbed by the disease. The more severe case had marked diminution of urinary output with evidence of extreme renal damage, and nitrogen retention which rose to 278 mgm. per cent. However, at no time during his clinical course did he show any evidence of generalised disease of the capillaries and hæmorrhages were entirely absent. Case II, on the other hand, had a little melæna and yet a much milder clinical course. Neither of the cases showed the three clinical stages which have been described for the course of the disease, and Case I was already three weeks ill

when he was first admitted to hospital, and he remained in hospital for a further four weeks before he was fit for discharge. The generalised myalgia was one of the more distressing complaints, and caused the symptoms to be greatly out of proportion to the physical signs observed. This point has been stressed in diagnosis and is of considerable importance.

While no attempt at generalisation can be made from observations on a single case, it is not without significance that a very severe case of Weil's disease showed a dramatic response to convalescent serum. The patient was in his fourth week, and showed jaundice, pyrexia, myalgia, headaches, and marked toxic nephritis. His urinary output was very low, the urine loaded with albumen and showed casts, while his blood urea had risen to 278 mgm. per cent. Clinically, his prognosis appeared to be very poor, yet within a few days of the administration of 40 c.c. intravenously and 20 c.c. intramuscularly of convalescent serum with a titre of 1 in 10,000, he had improved dramatically. He appeared better clinically, his urinary output was restored, and the nitrogen retention fell. Serum was not tried out on the other case, as his condition was so mild that it appeared unnecessary.

Commentary on the Procedure Necessary for the Diagnosis of the Disease.

The general procedure is to demonstrate the organism in the blood during the first week of the disease, in the urine during the subsequent stages, and then to confirm the diagnosis by serological means. The exact procedure will depend upon the duration of the symptoms. In the first week every effort should be made to demonstrate the leptospira in the blood, either by direct microscopic examination using a dark ground illuminator, or better, by inoculating 5 c.c. of freshly-drawn blood into the peritoneal cavity of a young guinea-pig and reproducing the disease. The cases here described were considered too far advanced for either of these procedures to be successful. The leptospira is fairly easily recognised. Its morphology can only be studied satisfactorily by dark ground illumination. It is a delicate organism about from 6 to 12 m. in length and about 0.2 m. in thickness. The coils, which are regular and closely wound, are too fine to be resolved in a stained preparation. The ends are tapering and characteristically "hooked." The growth of the organism in a fluid medium gives rise to "nests," which appear as highly refractile balls composed of many interlaced organisms.

It will probably be during the second state of the disease that a confirmation of the diagnosis will be sought in most cases. Observations indicate that the leptospira begin to appear in the urine towards the end of the second week and persist for a few weeks only, but their existence has apparently been demonstrated in some cases for several months. Direct microscopic examination of the urine is unsatisfactory, as other varieties of spirochætes may be found in normal urine. The centrifuged deposit of 60 to 80 c.c. urine in 5 c.c. of normal saline is inoculated peritoneally into a young guinea-pig. This method will only be found satisfactory if the inoculation is carried out within one hour of the urine being voided. It is necessary to administer some reagent to the patient to make his urine approxi-

mately neutral. This precaution is important, as the organism is quickly destroyed by strongly acid or alkaline urine. The successful isolation of the organism from Case I on the forty-sixth day of the disease was probably due to the adoption of this technique, as a previous inoculation was unsuccessful. Most animals will become ill, jaundiced, and die within a week. At post-mortem, the animals show generalised jaundice and there are hæmorrhages into various parts of the body, particularly the lungs, which show irregular areas of varying sizes sharply demarcated from the surrounding tissues, resembling the mottled wings of a butterfly. The spirochætes are most easily demonstrated in a suspension of the liver. It is now recognised that some animals may survive an actual infection.

A considerable amount of attention has been paid to the serological diagnosis. Specific antibodies begin to appear in the blood about the tenth day, but are not of diagnostic importance until about the fourteenth day to the eighteenth day of the disease. A definite negative reaction after the thirtieth day rules out infection.

We are indebted to Dr. R. D. Stuart of Glasgow for carrying out some preliminary tests on the agglutinating titre of the patient's serum in both of these patients. In both cases he reported a positive result. Subsequent serological examination carried out by us, using Schuffner's technique, and the strain isolated from Case I as well as strains sent to us by Dr. Stuart, confirmed this finding. In Case I a positive result was obtained in a dilution of 1/3000 on the thirty-second day of the disease. It cannot be too strongly emphasized that diagnosis of the disease is a matter of co-operation between the clinician and the bacteriologist.

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