# THE CLINICAL ASPECTS OF SPIROCHÆTOSIS ICTERO-HÆMORRHAGICA OR WEIL'S DISEASE.

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## *Stages of the Disease.*

Fiedler[1] has divided the progress of Weil's disease into three stages. According to him, the first 2 or 3 days constitute the initial period. The second stage commences variously from the 3rd to the 6th day following the onset of the disease, and is characterized by icterus, edema of the liver, tumor of the spleen, albuminuria, hemorrhagic diathesis, etc. He classes a defervescent period from the 7th to the 8th day as the third stage, and adds also a stage of convalescence. We believe, however, that a different division of the disease into three periods, *i.e.*, first or febrile stage, second or icteric stage, and a third or convalescent stage, has better justification. As will be explained in detail, each stage has its characteristic features with respect to the behavior of the spirochetes in the blood, the antibodies, the excretion of the organisms with the urine, and their distribution in the organs. According to our view, the first and second stages continue each for about a week; and the convalescent stage begins with the 3rd week of illness, although the boundaries of the different stages are not sharply demarcated. Icterus, the main symptom of the second stage, has its beginning in the middle of the first and reaches its climax in the second period.

*Febrile Stage.*—This stage continues from the onset of the disease to the 6th or 7th day. The main symptoms, which are initiated with chills or high fever, are intestinal disturbances, headache, cramp-

[1] Fiedler, A., Weitere Mittheilungen über die Weil'sche Krankheit, *Deutsch. Arch. klin. Med.*, 1892, l, 232.

ing muscular pains, marked hyperemia of the conjunctiva bulbi, albuminuria, etc. Death occurs rarely in this stage. The period is characterized by free circulation of the spirochetes in the peripheral blood, although their number may not be great. Blood taken during this period and injected intraperitoneally into guinea pigs produces a typical reaction. The infectivity of the blood decreases gradually, as shown by the 69 infection experiments cited in Table I.

TABLE I.

*Infection Experiments with Blood from Weil's Disease. April, 1912, to December, 1915.*

| Day of illness. | No. of animals injected. | Positive. | Per cent positive. |
|---|---|---|---|
| 2 | 4 | 4 | 100.0 |
| 3 | 10 | 10 | 100.0 |
| 4 | 13 | 13 | 100.0 |
| 5 | 12 | 11 | 91.6 |
| 6 | 14 | 12 | 85.7 |
| 7 | 8 | 4 | 50.0 |
| 8 | 4 | 0 | 0 |
| 9 | 1 | 1 | 100.0 |
| 12 | 1 | 0 | 0 |
| 18 | 1 | 0 | 0 |
| 19 | 1 | 0 | 0 |
| Total..... | 69 | | |

As shown in the table, guinea pigs were in all cases infected in a typical manner when they received intraperitoneally blood drawn from patients during the first 4 days of illness. By the 5th day, the infectivity of the blood is already diminished, one case only out of the 12 proving negative (positive 91.6 per cent). With blood taken on the 6th day the results showed 85.7 per cent positive, and on the 7th day 50 per cent. These findings seem to indicate that with the progress of the disease, the spirochetes disappear gradually from the blood stream, owing to the spirochetolytic and spirocheticidal action upon them of antibodies developed in the blood. We are led to believe that antibodies, though few in number, are present as early as the 5th day, but their number is not sufficient for demonstration by Pfeiffer's method.

No difference is observed in this stage of Weil's disease in the peritoneal fluid obtained after the use of serum of patients and that of healthy persons. The guinea pigs under experimentation die of typical symptoms on the same day as the control animals, or a day later or earlier. Hence the inference of a slight development of antibodies can be made only indirectly from results achieved with the infection experiments.

Spirochetes are excreted with the urine during this stage, and the injection of the urinary sediment produces in guinea pigs a typical infection. It is not as a rule possible, however, to demonstrate the organisms in the urine by dark-field illumination. The distribution of spirochetes in the organs resembles that found in the experimental animals. Numerous spirochetes are seen in the liver.[2]

*Second or Icteric Stage.*—This stage continues from the 7th or 8th to the 12th or 13th day of illness. Generally it covers a little less than a week. As a rule, the symptoms of the first stage decrease in intensity, and in their place appear icterus, hemorrhagic diathesis, marked general weakness, nervous symptoms, and cardiac weakness. But all these symptoms have their onset during the middle or toward the end of the febrile period, and reach their greatest intensity during the second stage. Death is most prevalent during this period. Of eighteen fatal cases, in sixteen death occurred between the 8th and the 16th day from the onset of the disease.

This stage is characterized by the fact that it is rarely possible to infect guinea pigs by the intraperitoneal injection of patients' blood, only one out of six experiments proving positive. It is evident that the spirochetes have already disappeared from the peripheral blood. Moreover, it is possible to demonstrate antibodies in the blood by Pfeiffer's method. The finding of spirochetes in the peritoneal fluid of the experimental animals by Pfeiffer's method shows that a different condition exists in them from that observed in the control animals. Spirochetolysis is present, and the experimental animals die in a typical manner 4 or 5 days later than the control animals. When on the other hand, the injected human serum contains

[2] Kaneko, R., and Okuda, K., The distribution in the human body of *Spirochæta icterohæmorrhagiæ*, *J. Exp. Med.*, 1917, xxvi, 325.

no antibodies, the experimental animals die on the same day as the control animals, or at the utmost 1 or 2 days earlier or later. A difference of 3 days is rare. Hence we conclude that when the experimental animals die 4 or more days later than the control animals, the serum must contain a certain number of antibodies. Their degree of development at this stage is incomplete, for with complete development of antibodies, the experimental animals would recover from the infection.

In our experiments we employed 1 cc. of serum and 1 cc. of pure culture of the spirochetes, or a liver emulsion containing the organisms; ten spirochetes to an optical field by dark-field illumination (Leitz oc. 3, obj. $\frac{1}{12}$ oil immersion). Injections were made intraperitoneally. The gradual increase in the number of antibodies can be observed by testing, according to Pfeiffer's method, serum obtained during various stages of the disease. The duration of life of the experimental animals lengthens in the course of the disease, and finally with complete development of antibodies, the animals do not become ill at all. Occasionally the antibodies are fully developed as early as the 8th day. We observed two cases of this kind.

In the second stage, the spirochetes are easily demonstrated in the urine by dark-field illumination. On the 10th day of illness it was possible to show them in 17.4 per cent of the cases, with a gradually growing percentage up to 52.2.

Corresponding to the development of the antibodies, the spirochetes disappear first from the blood, and then from the liver. Hence their distribution in the second stage differs from that of the febrile stage.

*Third or Convalescent Stage.*—This period begins on the 13th or 14th day. The intensity of the icterus characteristic of the second stage then subsides gradually, and anemia and marked emaciation become apparent. This period is characterized by complete development of the antibodies in the blood, the disappearance of spirochetes from the blood, their abundant excretion with the urine, frequent high fever (called relapsing fever by Weil, and after fever by us), and later on, by the excretion of antibodies with the urine. The distribution of the spirochetes in the organs is noteworthy. No organisms are found in the liver and other organs except the kidneys,

where they are always present. They are occasionally found in cardiac muscle.

The percentages of spirochetes excreted with the urine gradually increase and reach their maximum on the 15th or 16th, up to the 23rd or 24th day of illness. By the 19th or 20th day practically all cases show spirochetes in the urine. After the 25th day, the percentages decrease. It was found that twenty-two out of twenty-four patients had ceased to excrete spirochetes after 40 days. One patient excreted them on the 42nd day, and another on the 63rd. The duration of most abundant excretion covers from 3 to 6 days. Comparing the onset of the period of abundant excretion of the spirochetes in the urine with the appearance of the complete antibodies in the blood, we find that the first phenomenon precedes the latter by from 2 to 5 days, though occasionally the conditions may be reversed.

Histologically, the spirochetes are found on the 17th or 18th day only in the kidneys, having disappeared from the other organs with complete development of antibodies in the blood.

### *Incubation Period.*

The period of incubation, according to our computations, varies from 5 to 7 days with skin infection; it is seldom as long as 13 days. In the epidemic of Weil's disease which occurred in Hildesheim, Germany, Hecker and Otto estimated the time of incubation as covering at least a week. Our observations in Japan entirely coincide with this finding, and our conclusions concerning the incubation period are based on the histories of patients following our study of the portal of entry of the *Spirochæta icterohæmorrhagiæ in animals.*

### *Pathology of the After Fever.*

The behavior of the fever during the first stage coincides with that observed in cases of Weil's disease in Europe. During the period of convalescence, frequently there is a recurrence of rather high, remittent fever, which Weil and Fiedler have termed relapsing fever. According to Fiedler, in Europe it occurs in 40 per cent of the cases. In Japan we have observed it in 28.2 per cent of our

patients. So far as the character of this fever is concerned, our interpretation differs from that of Weil and Fiedler, and we have employed the term after fever for the following reasons.

The fever has its onset on the 14th or 15th day, sometimes on the 13th, rarely on the 12th or 16th day. There may be an afebrile interval of from 2 to 10 days following the fever of the first stage. The fever covers a period of from 4 to 20 days. It usually reaches a height of 38–40°C., and the temperature is frequently above that of the first stage. The fever is markedly remittent in character, particularly at its maximum. The temperature rises gradually, remains from 3 to 4 days at its greatest height, and then begins gradually to decline. In fatal cases, there is no after fever.

As indicated above, we cannot agree with the view of Weil and Fiedler that this fever is to be regarded as relapsing in character, on the following grounds.

(*a*) We have never observed a recurrence of the main symptoms; *i.e.*, hyperemia of the conjunctiva bulbi, exacerbation of the icterus, hemorrhagic diathesis, edema of the lymph glands, etc. Notwithstanding the presence of the fever at this time, only the symptoms which usually accompany a rise in temperature are found, such as headache, general weakness, etc.; and although the temperature is high, life is not endangered. The fever of the first stage is accompanied by marked leukocytosis, while this condition is not constant in the later fever.

(*b*) Secondly, all the infection experiments conducted on guinea pigs during this period were negative. With the exception of the kidneys, no spirochetes, or very few, are found in the organs.

(*c*) In the third place, the spirochetolytic and spirocheticidal antibodies are fully developed in the blood at this period. If, on the other hand, spirochetes were to reappear in the blood, we should be justified in regarding this fever as relapsing.

We believe, therefore, that the fever of the third stage is different in character from that of the first.

The pathogenesis of the after fever is not clear. Clinically, no particular changes are observed in the organs, and there are no complications or suppurations. The blood of eight patients which was subjected to careful bacteriological examination was found to be

sterile. Hence we are unable to trace the origin of the fever to a secondary infection. It appears that the after fever coincides with the presence of the antibodies in the blood and the abundant excretion of spirochetes in the urine. Furthermore, the curve of the serum-treated guinea pigs which survived resembled closely the fever curve of patients in the third stage of illness.

It is our belief that this fever is to be regarded as a reaction on the part of the immune organism to the subsequent resorption of spirochetic toxins. Spirochetolysis continues for the whole period of the disease, but only with the appearance of complete immunity does the organism react in the form of fever. The toxins arise from the disintegration of the spirochetes within the organs, above all, the kidneys, where probably a proliferation of spirochetes takes place during the convalescent stage, when numerous specimens can be observed. On the other hand, it must be remembered that the after fever occurs in only 28.2 per cent of the cases, while the phenomena of antibody formation and excretion of spirochetes occur with constancy. It appears that the pathogenesis of the after fever requires still further investigation.