

FEBRILE HERXHEIMER REACTION IN DIFFERENT PHASES OF PRIMARY AND SECONDARY SYPHILIS*

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Putkonen and Rehtijärvi (1950) published the results of a study on the Herxheimer reaction in early infectious syphilis. It was found that the febrile Herxheimer reaction occurs with different frequency and intensity at different stages of early syphilis and is practically absent at the latent stage of the disease. Because the number of cases of primary syphilis was rather small, the collection of data was continued. The accumulation of patients was slow until 1963 when early syphilis began to increase in Finland. This increase has made it possible for us to report on the results of a larger series of cases of primary and secondary syphilis.

Material and Methods

This study concerns a series of 251 previously untreated patients, 109 with primary and 142 with secondary syphilis; there were 139 men and 112 women. The seventeen patients with primary and sixty patients with secondary syphilis studied by Putkonen and Rehtijärvi (1950) are included in this series. All patients diagnosed as having primary syphilis were darkfield-positive. Darkfield examination was also positive in 91 of the 142 patients with secondary syphilis, when performed on samples from genital papules, condylomata, inguinal lymph nodes, or cantharidin blisters made on syphilitic eruptions. All patients diagnosed as having secondary syphilis had typical clinical signs and positive serological tests; these were: old-type crude Wassermann reaction, both with and without sensitization with

cholesterol, Kahn standard, VDRL slide flocculation, and *Treponema pallidum* immobilization test (TPI).

In all patients the Herxheimer test was performed by injecting 100,000 units of aqueous penicillin G intramuscularly. Axillary temperatures were recorded immediately before injection and thereafter at hourly intervals for 24 hours, during which the patients were confined to bed. A rise in the axillary temperature to at least 37.6°C. was regarded as a significant reaction.

Results

Primary Syphilis

This group comprised 93 males and sixteen females. The patients were grouped according to the results of the serological tests. The sensitivity of the tests increased in this order: Wassermann, cholesterol Wassermann, Kahn, VDRL. Patients with a negative Wassermann and cholesterol Wassermann but positive Kahn and/or VDRL tests were regarded as partially sero-positive, and patients with positive results in all four tests as sero-positive. When the Herxheimer test was performed 35 patients were sero-negative, 31 partially sero-positive, and 43 sero-positive.

The mean temperature among the 35 patients with sero-negative primary syphilis rose to 37.6°C. A significant febrile reaction occurred in only nineteen cases (Table I). Seven of the sero-negative patients later became partially sero-positive or sero-positive; five of them belonged to the group with a significant febrile reaction.

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TABLE I

HERXHEIMER REACTION IN PRIMARY SYPHILIS
RELATION OF MAXIMUM TEMPERATURE TO PATIENTS' SEROLOGICAL REACTIVITY

Serological Reactivity	No. of Cases	Maximum Temperature (°C.)					Mean
		36.6-37.5	37.6-38.5	38.6-39.5	39.6-40.5	40.6	
Negative	35	16	10	6	3	0	37.6
Partially positive	31	7	4	13	6	1	38.4
Positive	43	2	9	15	16	1	39.2
Total	109	25	23	34	25	2	38.6

The mean temperature in the 31 patients with partially sero-positive primary syphilis rose to 38.4°C. In this group a significant reaction was recorded in 24 cases. In the group with sero-positive primary syphilis the mean temperature rose to 39.2°C. and only two of the 43 patients did not have a significant temperature rise.

The individual differences in the course of syphilitic infection are well demonstrated by the cases of primary syphilis in two sailors, 27 and 25 years of age. They were both infected by the same woman during the same night. A genital ulcer was noticed after 28 days and 33 days respectively. At examination 41 days after the infection, both were darkfield-positive. The former patient was sero-negative and the latter partially sero-positive. The temperature in the Herxheimer test rose to 38.0°C. and 39.0°C. respectively.

Secondary Syphilis

Of the 142 patients with secondary syphilis, 46 were men and 96 were women. Darkfield examination was positive in 32 males and 59 females. In addition to the reagin tests, the TPI test was performed in 53 cases. In four of them the TPI test was non-reactive and in 49 reactive. All patients with non-reactive TPI tests were darkfield-positive when the Herxheimer test was performed.

The febrile response to penicillin in patients with secondary syphilis is presented in Table II. A significant Herxheimer reaction was observed in about 60 per cent. of all patients with secondary syphilis. In general, those with early manifestations of secondary syphilis reacted to penicillin with higher temperatures than those with late manifestations. In patients with roseola the relatively low mean rise in temperature is explained when they are

further subdivided according to other simultaneous signs of syphilis. Seventeen of the patients with roseola had a still unhealed primary ulcer. In sixteen of these a significant febrile reaction was recorded. On the other hand, of the 21 patients with roseola combined with late secondary manifestations (palmar and/or plantar syphilides, condylomata, alopecia), only twelve showed a significant febrile reaction. The mean maximal temperature in patients with early and late roseola rose to 38.8°C. and 37.8°C. respectively.

The Febrile Herxheimer Reaction as an Indication of the Date of Syphilitic Infection

In 71 patients the date of infection was known with reasonable accuracy. The Figure (opposite) shows the maximal rise in temperature as a function of the time between infection and the Herxheimer test. The patients are divided according to the stage of the disease and patients with primary syphilis also according to the results of the serological tests.

A significant febrile reaction was not observed in any of the five patients tested within one month of infection. Four out of eight patients tested between 31 and 40 days after infection exhibited a significant febrile reaction. Thereafter, the relative number of febrile Herxheimer reactions rose steeply, and between 61 and 100 days after infection all patients reacted with a significant rise in temperature. Later on the reaction began to weaken, so that only two out of seven patients with syphilis of more than 100 days' duration had a significant febrile Herxheimer reaction.

Discussion

The results of this extended study corroborate the findings of Putkonen and Rehtijärvi (1950) on the

TABLE II
HERXHEIMER REACTION IN SECONDARY SYPHILIS
RELATION OF MAXIMUM TEMPERATURE TO PATIENTS' CLINICAL SIGNS

Clinical Sign	No. of Cases	Maximum Temperature (°C.)					Mean
		36.6-37.5	37.6-38.5	38.6-39.5	39.6-40.5	40.6	
Roseola	61	15	21	15	8	2	38.4
Skin papules	28	5	9	7	7	—	38.6
Genital papules	44	13	20	6	5	—	38.1
Palmar and/or plantar syphilides	39	20	13	2	4	—	37.8
Alopecia	25	15	8	—	2	—	37.7
Oral mucous patches	17	12	3	2	—	—	37.5
Condylomata lata	41	28	10	2	1	—	37.5
Total	142	58	43	21	18	2	38.1

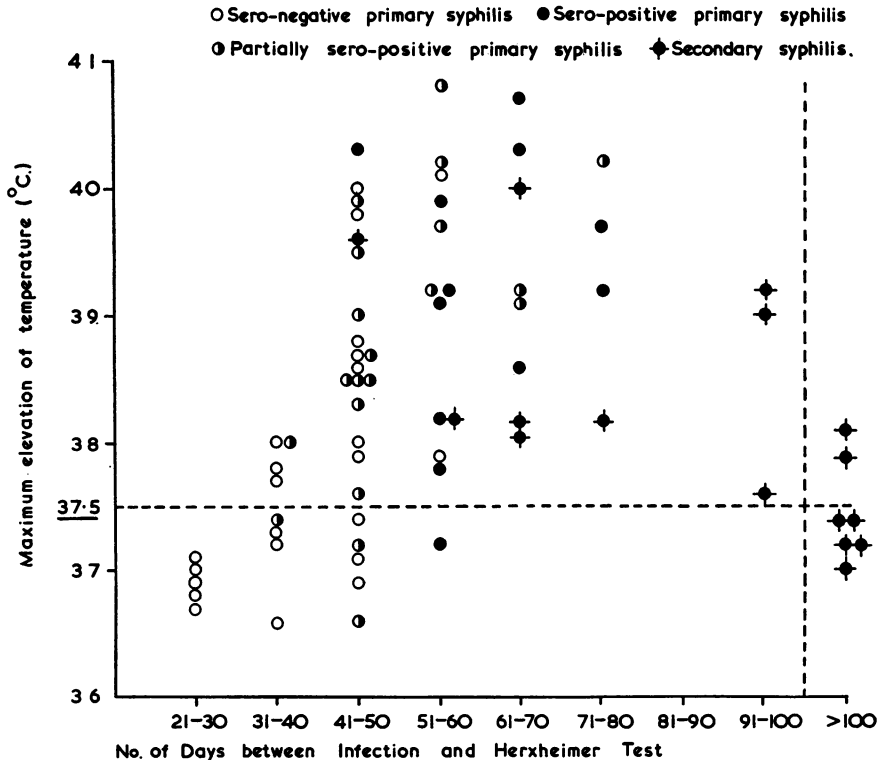


FIGURE.—Maximal rise in temperature in relation to days elapsing between syphilitic infection and Herxheimer test.

frequency and intensity of a febrile Herxheimer reaction in different phases of early syphilis.

It has been claimed by Farmer (1948) and Hochleitner (1965) that a febrile Herxheimer reaction occurs with equal frequency in sero-negative and sero-positive primary syphilis. In the present series, however, a significant reaction occurred in 95 per cent. of sero-positive, 75 per cent. of partially sero-positive, and only 55 per cent. of sero-negative patients with primary syphilis. The last percentage is further reduced if the seven patients who later became sero-positive are excluded.

All ten patients with sero-positive primary syphilis reported in 1950, showed a febrile Herxheimer reaction. Such a reaction was not observed in two out of 33 later cases. According to Farmer (1948), very small amounts of penicillin are sufficient to inhibit a patient's reaction to a repeated dose of this drug. Many other antibiotics have the same effect. It is possible that the two patients mentioned above had already received some antibiotics even though they did not remember it. One of them was a sailor, and it is known that mates on ships often distribute antibiotics for many and various reasons.

The reported frequency of the febrile Herxheimer reaction in secondary syphilis varies from 76 per cent. (Hochleitner, 1965) to 45 per cent. (Garnier, 1961). If secondary syphilis is taken as one group, our result lies midway between these figures and corresponds with that of Knudsen and Aastrup (1965). Naturally, the frequency of the febrile Herxheimer reaction is greater, the lower the level of temperature used as a criterion of a significant reaction. On the other hand, the frequency of the febrile reaction in a given series also depends on the relative number of patients with early or late manifestations of secondary syphilis. In our series patients having early roseola with still unhealed primary lesions displayed high temperature peaks, whereas a febrile reaction was seldom observed in patients with late secondary manifestations, such as palmar or plantar syphilides, condylomata, or alopecia.

In contact tracing, it is important to know the duration of the patient's syphilitic infection which is usually estimated on basis of the triad: history, clinical signs, and results of serological tests. In untreated patients, the Herxheimer reaction can also

be of considerable value in this estimation. In our clinic the "Herxheimer test" is, indeed, performed as a routine procedure in all cases of syphilis and serves as a good control of both history and clinical examination.

Summary

The febrile Herxheimer reaction was studied with a test dose of 100,000 units aqueous penicillin G in 251 untreated patients, 109 of them with primary and 142 with secondary syphilis. A rise of the axillary temperature to 37.6°C. or higher was observed in 95 per cent. of the patients with sero-positive primary syphilis, but in only 55 per cent. of those with sero-negative primary syphilis. The mean maximal temperatures were 39.2°C. and 37.6°C. respectively.

The interval between infection and the Herxheimer test was known in 55 of the 109 cases with primary syphilis. None of the five patients with an interval of less than 30 days gave a significant febrile reaction. On the other hand, a definite febrile response was observed in four out of eight patients after an interval of 31 to 40 days, and in all patients after an interval of 61 to 100 days since infection. The occurrence of significant Herxheimer reactions in early secondary syphilis did not differ from that in sero-positive primary syphilis. The reactivity of the patients, however, decreased with increasing duration of the disease, so that a fever of 37.6°C. or more developed in only 32 per cent. of patients with condylomata lata, in which group the mean maximum temperature was 37.5°C. Only two of the seven patients with an infection of more than 100 days' duration showed a significant reaction.

The authors emphasize that, in untreated cases of early syphilis, the Herxheimer test serves as a control of the case history and even of the clinical examination of the patient.

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La réaction fébrile de Herxheimer dans les différentes phases de la syphilis primaire et secondaire

RÉSUMÉ

La réaction fébrile de Herxheimer a été étudiée avec une dose de 100,000 unités de pénicilline aqueuse G chez 251 patients non-traités, 109 souffrant de syphilis primaire et 142 de syphilis secondaire. Une hausse de température axillaire jusqu'à 37,6° C. ou plus a été observée dans 95 pour cent des malades souffrant de syphilis primaire avec réaction séro-positif mais chez seulement 55 pour cent des patients souffrant de syphilis primaire avec réaction séro-négative. La moyenne des températures était de 39,2° C. et 37,6° C. respectivement. L'intervalle entre l'infection et le test Herxheimer était connu dans 55 des 109 cas de syphilis primaire. Aucun des cinq malades où l'intervalle était de moins de 30 jours a donné une réaction fébrile notable. Une réaction fébrile marquée, d'autre part, a été observée chez quatre des huit malades après un intervalle de 31 à 40 jours et chez tous les patients après un intervalle de 61 à 100 jours depuis l'infection. L'apparition des réactions notables de Herxheimer dans la syphilis secondaire précoce n'était pas différente de celle des cas de syphilis primaire à réaction séro-positif. La réaction des malades, cependant, a diminué avec la durée croissante de la maladie, ainsi par exemple une température de 37,6° C. ou plus s'est montrée dans seulement 32 pour cent des malades avec des condylomata lata. Dans ce groupe la température moyenne maximum était 37,5° C. Seulement deux des sept malades souffrant d'une infection datant de plus de 100 jours ont montré une réaction significative.

Les auteurs font ressortir que dans les cas non-traités de syphilis précoce, le test Herxheimer sert de contrôle à historique du cas et même à l'examen clinique du patient.