

JARISCH-HERXHEIMER REACTION IN THE TREATMENT OF EARLY SYPHILIS WITH PENICILLIN AND BISMUTH-ARSPHENAMINE*

BY

ERIK A. KNUDSEN AND BENT AASTRUP

Department of Dermatology and Venereology, University of Copenhagen, Denmark

Penicillin therapy has revived interest in the complex of focal and systemic manifestations which is known as the Jarisch-Herxheimer reaction (JHR). Some of the views on the JHR from the mercury-bismuth-arsphenamine era have had to be altered. In this respect attention should be called to the investigations of Farmer (1948) on the relationship between the JHR and the dose of penicillin, which revealed that within a wide range the JHR is independent of the dose, and to the detailed description by Sheldon and Heyman (1949) of the histological reaction in the syphilitic lesions which appeared synchronously with the clinical JHR.

Many studies of the JHR are concerned with the incidence of the reaction in the various stages of early syphilitic infection. Farmer (1948) analysed 939 cases of early syphilis treated with penicillin in which a febrile JHR was equally common and equally severe in the sero-negative primary, the sero-positive primary, and the secondary stage. Blom-Ides, Polano, and Herrmann (1955) found a significantly higher incidence in the primary than in the secondary stage in a series of 394 cases of early syphilis treated with neoarsphenamine-bismuth. Putkonen and Rehtijärvi (1950) found the highest incidence in the late primary and early secondary stages in 77 cases of early syphilis treated with penicillin.

The following is a report of a study of the relationship of the time of treatment and the type of therapeutic agent with febrile JHR in early syphilis.

Material

Two groups of patients with early syphilis admitted to the University Department of Dermatology and Venereology, Rigshospitalet, Copenhagen, were studied. During the period 1951-63, penicillin was the agent of

choice, and during the period 1942-46, bismuth combined with neoarsphenamine or arsphenoxyl was the standard treatment.

Group I, 1951-63

149 consecutive cases were treated exclusively with penicillin, 300,000 to 600,000 units daily for 10 days. 105 were males and 44 females, and average age was 29 years (range 68 to 15). In 104 of the 149 cases the diagnosis was based on positive dark-field microscopy, and in the remainder on the history, clinical manifestations, and serological findings. 32 patients had primary sero-negative, seventeen primary sero-positive, and 100 secondary syphilis. 117 patients were treated with procaine penicillin retard PAM, 31 with procaine penicillin, and one with sodium penicillin. During the same period eight patients with early syphilis were treated with oxytetracycline, 250 mg. four times daily for 14 days, no other antibiotics being used.

Group II, 1942-46

184 consecutive cases of early syphilis were given bismuth-neoarsphenamine/arsphenoxyl in weekly injections of 2.0 to 3.0 ml. subsalicylate of bismuth + 600 to 750 mg. Neosalvarsan Hoechst or 40 to 60 mg. arsphenoxyl (Trepopal Leo). 85 were males and 99 females, and the average age was 25 years (range 79 to 14). In 102 of the 184 patients the diagnosis was based on positive dark-field microscopy, and in the remainder on the history, clinical manifestations, and serological findings. 23 patients had primary sero-negative, 36 primary sero-positive, and 125 secondary syphilis. 119 patients were treated with bismuth and neoarsphenamine, and 65 with bismuth and arsphenoxyl.

Method

We consider a rise in rectal temperature to 38°C. or more within the first 24 hours after starting treatment as a positive JHR. The temperature was recorded on the evening of the day before treatment, on the day of treatment, and on the morning and evening of the next day.

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Results

Table I shows that the incidence of JHR in Group I was 66.4 per cent., and in Group II 65.8 per cent. A comparison of the incidence, by stage of the disease and by therapeutic agent, also showed no difference, except in primary sero-positive syphilis, in which a positive JHR occurred in 94.1 per cent. cases of Group I and in 72.2 per cent. cases of Group II. However, the number of primary sero-negative and primary sero-positive cases in Groups I and II was too small for a statistical calculation. On the other hand, the total series (Groups I + II), which consists of 55 primary sero-negative, 53 primary sero-positive, and 225 secondary cases, permits such a calculation; this showed that the

incidence of febrile JHR, at the 5 per cent. level, was significantly higher in primary sero-positive than in secondary syphilis ($\chi^2=4.07$).

JHR appeared to be slightly more common during treatment with procaine penicillin than with procaine penicillin retard PAM, but this difference is not significant.

Three of the eight patients treated with Terramycin had a positive JHR.

The average variations in temperature for the entire series are recorded in Table II, and the average recorded maximum temperature in cases with a positive JHR in Table III (opposite). The course was almost identical in Groups I and II, independent of the stage of the disease as well as of the therapeutic agent.

TABLE I
INCIDENCE OF FEBRILE JARISCH-HERXHEIMER REACTION DURING TREATMENT OF EARLY SYPHILIS WITH PENICILLIN AND WITH BISMUTH NEOARSPHENAMINE-ARSFENOXYL

Group		I. Penicillin*			II. Neosphenamine-arsfenoxyl		
		No. Treated	Febrile reactions		No. Treated	Febrile reactions	
			No.	Per cent.		No.	Per cent.
Stage of Syphilis	Primary Sero-negative	32	20	62.5	23	15	65.2
	Primary Sero-positive	17	16	94.1	36	26	72.2
	Secondary	100	63	63.0	125	80	64.0
Therapy	Procaine Penicillin	31	23	74.9			
	Procaine Penicillin retard PAM	117	75	64.1			
	Bismuth-Neosphenamine				119	76	63.9
	Bismuth-Arsfenoxyl				65	45	69.2
Total		148	99	66.4	184	121	65.8

*One case treated with sodium penicillin has been excluded.

TABLE II
AVERAGE VARIATIONS IN TEMPERATURE DURING TREATMENT OF EARLY SYPHILIS WITH PENICILLIN (149 PATIENTS) AND BISMUTH NEOARSPHENAMINE-ARSFENOXYL (184 PATIENTS)

Temperature (°C.)—

T₁: Evening on day before treatment.

T₂: Morning on day of treatment.

T₃: Evening on day of treatment.

T₄: Morning on day after treatment.

T₅: Evening on day after treatment.

Group		I. Penicillin					II. Neosphenamine-arsfenoxyl				
		T ₁	T ₂	T ₃	T ₄	T ₅	T ₁	T ₂	T ₃	T ₄	T ₅
Stage of Syphilis	Primary Sero-negative	37.2	36.9	38.5	37.1	37.2	37.4	36.9	38.6	37.1	37.0
	Primary Sero-positive	37.4	37.1	39.5	36.9	37.0	37.4	37.0	38.7	37.0	37.5
	Secondary	37.3	37.0	38.6	37.0	37.2	37.5	37.0	38.5	37.1	37.4
Therapy	Procaine Penicillin	37.3	37.1	38.8	37.0	37.1					
	Procaine Penicillin retard PAM	37.3	37.0	38.7	37.0	37.1					
	Bismuth-Neosphenamine						37.4	37.0	38.4	37.1	37.4
	Bismuth-Arsfenoxyl						37.5	37.0	38.6	37.1	37.4
Average		37.3	37.0	38.7	37.0	37.1	37.5	37.0	38.6	37.1	37.4

TABLE III

AVERAGE MAXIMUM TEMPERATURES IN JARISCH-HERXHEIMER REACTIONS OBSERVED IN 99 PATIENTS TREATED WITH PENICILLIN AND 121 PATIENTS TREATED WITH BISMUTH NEOARSPHENAMINE-ARSFENOXYL

Group		I. Penicillin	II. Neoarsphenamine-arsfenoxy
		Maximum Temperature (°C.)	Maximum Temperature (°C.)
Stage of Syphilis	Primary Sero-negative	39·6	39·3
	Primary Sero-positive	39·5	39·1
	Secondary	39·3	38·9
Therapy	Procaine Penicillin	39·4	
	Procaine Penicillin retard PAM	39·4	
	Bismuth Neoarsphenamine		39·0
	Bismuth Arsfenoxy		39·1
Average		39·4	39·0

In 32 of the 121 patients treated with bismuth and neoarsphenamine or with bismuth and arsfoxy, a rise in temperature to 38°C. or more was recorded after the second or, in some cases, the third injection. No such "double Herxheimer" was observed during treatment with penicillin.

Discussion

The increase in the number of cases of early syphilis which occurred in Denmark about 1957 made this comparison possible. No difference was found in the incidence or course of febrile JHR. The same result was reported by Blom-Ides and others

(1955), who compared their own neoarsphenamine-bismuth series with the penicillin series of Farmer (1948). The only difference we found was that, in several cases, a "double Herxheimer" occurred after neoarsphenamine-arsfenoxy therapy. Unlike de Graciansky and Grupper (1961), we did not observe repeated febrile reactions during penicillin therapy; according to Farmer (1948), a "double Herxheimer" is seen only in patients treated with doses of 10 to 20 units/kg. body weight, and not after normal therapeutic doses of penicillin. We interpret this as one of the proofs that penicillin in the usual dosage is a more effective spirochaeticidal agent than neoarsphenamine-arsfenoxy. However, it must be borne in mind that the penicillin was administered in daily injections, whereas 5 to 7 days elapsed between the individual injections of neoarsphenamine-arsfenoxy injections.

It is well known that the JHR is more common during the primary and secondary stages than in late syphilis, but it is not generally agreed whether the incidence is influenced by the stage of the early infection at which the treatment is instituted. We found a tendency (significant at the 5 per cent. level) for the JHR to be more common in the primary sero-positive than in the secondary stage; the same tendency was seen in the series of de Graciansky and Grupper (1961) and Putkonen and Rehtijärvi (1950), and perhaps also in that of Farmer (1948) (cf. Table IV). As this difference is slight and as most of the series are small, it might be due to chance. Blom-Ides and others (1955) state that some authors require a rise in temperature to 38°C., while American workers (Farmer, 1948) set the limit at 100°F. (37·8°C.).

TABLE IV

INCIDENCE OF FEBRILE JARISCH-HERXHEIMER REACTIONS IN THE TREATMENT OF EARLY SYPHILIS IN VARIOUS SERIES

Author	Date	Stage of Syphilis								
		Primary Sero-negative			Primary Sero-positive			Secondary		
		No. Treated	Febrile Reactions		No. Treated	Febrile Reactions		No. Treated	Febrile Reactions	
			No.	Per cent.		No.	Per cent.		No.	Per cent.
Blom-Ides and Others	1955	27	8	30	47	13	28	320	41	13
*Farmer	1948	117 (117)	46 (37)	39 (32)	216 (216)	92 (78)	43 (36)	467 (467)	195 (150)	42 (32)
†Graciansky and Grupper	1961	12	7	58	35	25	71	36	19	53
Putkonen and Rehtijärvi	1950	3	1	33	14	14	100	60	30	50
Knudsen and Aastrup	1965	55	35	64	53	42	79	225	143	64

*Farmer: Figures in brackets were obtained by interpolation (see text).

†Graciansky and Grupper: The figures stated are from these authors' control group (not treated with steroid)

Some of this inaccuracy may presumably be counteracted by eliminating, by interpolation, positive reactions below 38°C. from Farmer's series and by adding these corrected values (in brackets in Table IV) to those from other series. Statistical calculation then indicates that JHR is somewhat more common in primary sero-positive than in secondary syphilis.

Unlike Putkonen and Rehtijärvi (1950), we made no attempt at grouping the secondary cases into an early and late phase, but we agree with these authors that the maximum incidence of JHR is found in the primary sero-positive and early secondary stages.

Summary

149 patients with early syphilis treated with penicillin were compared with 184 treated with bismuth and neoarsphenamine-arsfenoxy; the incidence of febrile Jarisch-Herxheimer reactions was highest in those with primary sero-positive syphilis. There was no difference in the course or incidence of the Jarisch-Herxheimer reaction, between the therapeutic agents used. The results are discussed and compared with previous reports of similar investigations.

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La réaction de Jarisch-Herxheimer dans le traitement de la syphilis précoce par pénicilline et bismuth + arsenic trivalent

RÉSUMÉ

On compare 149 patients atteints de syphilis précoce traités par la pénicilline, avec 184 patients traités par le bismuth et le néoarsphénamine/arsfenoxy. L'incidence des réactions de Jarisch-Herxheimer fut plus grande parmi ceux atteints de syphilis primaire avec réactions sérologiques positives. Il n'y eut pas de différence dans l'évolution ou l'incidence de cette réaction, quelque aient été les agents thérapeutiques utilisés.

On discute les résultats et on les compare avec des résultats précédents notés à la suite de recherches identiques.