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PHYSIOLOGIC CHANGES DURING THE JARISCH-HERXHEIMER REACTION IN EARLY SYPHILIS
A Comparison with Louse-Borne Relapsing Fever

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13. ABSTRACT

In twelve of fifteen patients with early syphilis body temperature increased by more than 0.5°C after treatment with penicillin. In all cases the blood leukocyte count increased; the lymphocyte count fell in seven of eight patients, but neutropenia was never observed. In four of the patients detailed cardio-respiratory measurements were made. During the Jarisch-Herxheimer reaction (J-HR) metabolic rate increased, but pulmonary ventilation and cardiac output exceeded metabolic requirements. There was evidence of impaired pulmonary oxygen uptake, and systemic arterial blood pressure fell due to decreased vascular resistance.

The role of leukocyte pyrogen in the Jarisch-Herxheimer reactions of secondary syphilis and louse-borne relapsing fever (LBRF) is discussed, and possible reasons are suggested for the differences in timing and intensity of the reactions in the two diseases and for the absence of an early neutropenia in syphilis.

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Physiologic Changes During the Jarisch-Herxheimer Reaction in Early Syphilis

A Comparison with Louse-Borne Relapsing Fever

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In twelve of fifteen patients with early syphilis body temperature increased by more than 0.8°C after treatment with penicillin. In all cases the blood leukocyte count increased; the lymphocyte count fell in seven of eight patients, but neutropenia was never observed. In four of the patients detailed cardiorespiratory measurements were made. During the Jarisch-Herxheimer reaction (J-HR) metabolic rate increased, but pulmonary ventilation and cardiac output exceeded metabolic requirements. There was evidence of impaired pulmonary oxygen uptake, and systemic arterial blood pressure fell due to decreased vascular resistance.

The role of leukocyte pyrogen in the Jarisch-Herxheimer reactions of secondary syphilis and louse-borne relapsing fever (LBRF) is discussed, and possible reasons are suggested for the differences in timing and intensity of the reactions in the two diseases and for the absence of an early neutropenia in syphilis.

A dramatic reaction, resembling the Jarisch-Herxheimer reaction, follows the treatment of louse-borne relapsing fever (LBRF) with penicillin or tetracycline [1,2]. The phases of the endotoxin reaction [3] can be recognized in this response [4]. After a prodomal period of about one hour following intravenous injection of tetracycline there is a chill phase lasting from ten to thirty minutes during which body temperature, arterial pressure, and pulse and respiratory rates increase. The leukocyte count falls precipitously at about this time, and spirochetes disappear from the peripheral blood, arterial pressure falls during the ensuing flush phase, and during the phase of defervescence the physiologic variables return towards normal.

Little information is available about physiologic changes associated with the Jarisch-Herxheimer reaction of syphilis. In the present study clinical and physiologic observations were made in patients with early syphilis treated with penicillin, and the changes were compared with those already described in LBRF.

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METHODS

Fifteen patients with early syphilis confirmed by dark field examination were admitted to Princess Tsehai Memorial Hospital, Addis Abeba (altitude 7,500 feet, average barometric pressure 582 mm Hg). They consented to treatment and investigation.

In eleven of the patients (Cases 5–15, Table I) respiratory and cardiac rates, arterial and central venous pressures, body temperature and total and differential leukocyte counts were measured at thirty minute intervals for eight to fourteen hours using methods described previously [2]. When steady base line values had been obtained, 1 mega unit of benzyl penicillin was given intravenously and 1.4 mega units of procaine penicillin were given intramuscularly.

In the other four patients (Cases 1, 2, 3 and 4, Table I) a more detailed study of the cardiorespiratory changes was made using methods which have been described previously [4]. After clinical assessment, forced expired volume in the first second (FEV_1), vital capacity (VC) and peak expiratory flow (PEF) were measured with a McDermott bellows spirometer and Wright peak flow meter while the patients sat upright. During the remainder of the study the patients lay supine in bed. Electrocardiogram leads were attached and rectal, forehead and forearm skin temperatures were measured continuously with an electric thermometer.

A polyethylene catheter (PE 60) 22 cm long was inserted into a brachial artery using the Seldinger percutaneous technic [5], and an OPP 160 polyethylene catheter 90 cm long was introduced into the right side of the heart through a left antecubital vein using the same technic. These catheters were flushed with heparin-saline solution and were connected to saline manometers. Brachial and pulmonary arterial mean pressures ($\bar{P}_{BA}$, $\bar{P}_{PA}$) were measured using the sternal angle (assumed to be 5 mm Hg above zero pressure) as reference point.

At intervals during the study expired gas and arterial and mixed venous blood were sampled simultaneously for three minute periods. The arterial and mixed venous blood samples were analyzed immediately for blood gas tensions (P_{O_2}, P_{CO_2}); also measured were pH using Radiometer electrodes, oxygen saturation using a Kipp hemoreflector, oxygen content using the method of Linden, Ledsome and Norman [6] and bicarbonate concentration using a Natelson micromanometric apparatus. The accuracies of these determinations have been given [4]. Arterial glucose, lactate and pyruvate concentrations were estimated by enzymatic methods (Sigma Chemical Co.). Expired gas volume and composition were measured.

The first expired gas collection was made before treatment. Two mega units of benzyl penicillin were then injected intravenously, followed by 0.5 mega unit of benzyl penicillin and 1.5 mega units of procaine penicillin intramuscularly. A further collection was made at the peak of the reaction, which was signaled by rigors in one patient and by a sharp rise in rectal temperature to a peak in the other three patients. In two patients collections were made two hours later and on the next day twenty hours after treatment, and finally, 100 per cent oxygen was breathed for forty-five minutes to allow calculation of residual (anatomical) right to left shunt.

Blood gas tensions and pH were measured at an electrode temperature of 37°C. They were corrected to mean rectal temperature during the sampling period

TABLE I Symptoms and Changes in Body Temperature and Blood Leukocyte Count in Fifteen Patients with Early Syphilis During the Jarisch-Herxheimer Reaction Following Penicillin Treatment

Case No.	Age (yr) and Sex	Exacerbation of Local Lesions	Rigors	Body Temperature °C			Leukocyte Count		
				Initial	Peak	Time of Peak*	Initial	Peak	Time of Peak*
1	30, M	+	+	37.0	39.2	6.5	11,380	13,630	3.75
2	26, M	+	−	37.5	39.3	6.5	9,850	13,880	4.75
3	38, M	+	−	37.2	39.0	6.75	11,830	14,500	5.5
4	35, F	+	−	37.9	39.5	6.5	10,880	16,400	5.5
5	19, F	−	−	35.8	37.8	6.5	7,180	8,680	3.5
6	19, F	+	+	36.8	38.3	5.5	7,430	11,850	6
7	25, M	++	+	37.1	38.1	7.75	7,390	11,980	7.75
8	32, M	−	−	36.3	36.7	7	5,990	7,920	8
9	27, M	−	−	37.1	38.0	7	10,750	13,700	6
10	25, M	−	−	36.7	36.9	4.5	13,550	20,780	6.75
11	26, M	+	+	37.3	39.5	6.25	7,510	10,150	6.75
12	32, M	++	+	36.5	38.5	7.25	8,540	15,500	6.25
13	30, M	+	−	37.1	38.7	6.5	5,510	7,730	7
14	22, M	−	−	36.8	37.6	10	4,750	9,650	9
15	17, M	+	++	36.9	39.6	6	8,250	11,250	6
Mean				36.9	38.4	6.7	8,719	12,507	6.2
± 1 SD				±0.5	0.9	1.1	2,466	3,420	1.4

* Time in hours following administration of penicillin.

Figure 1. Case 4. Patient with early syphilis showing numerous condylomatous and ulcerative skin lesions.

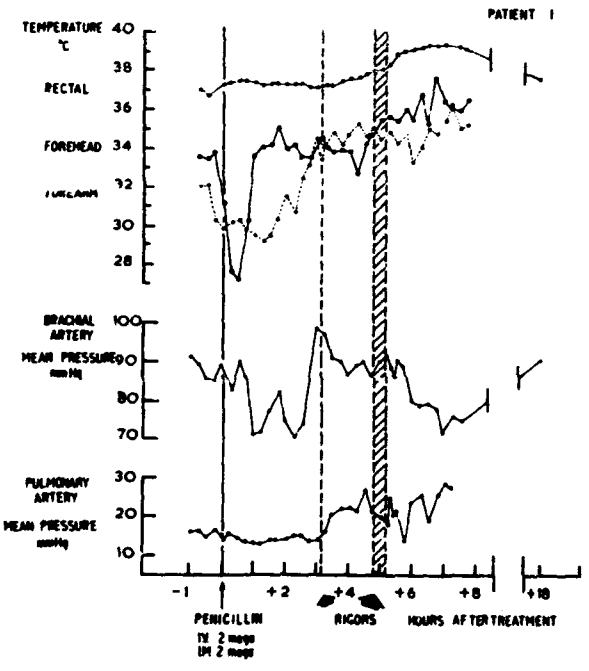

Figure 2. Case 1. Serial changes in body temperatures and brachial and pulmonary arterial pressures in a representative patient with early syphilis.

using factors derived by in vitro tonometry studies [7] for P_{O_2} and P_{CO_2}, and Figure 6 of Kelman and Nunn's paper [8] for pH.

Calculations. Physiologic dead space:tidal volume ratio ($V_D:V_T$) was calculated by the Bohr equation and "ideal" alveolar P_{O_2} by the alveolar air equation [9]. Pulmonary venous admixture as a percentage of cardiac output ($\dot{Q}_{va}:\dot{Q}_t$) was derived by the shunt equation using a procedure which has been described [4]. Cardiac output was calculated by the Fick equation.

RESULTS

The twelve male and three female patients were young adults (seventeen to thirty-eight years) who had been exposed to infection from four to sixteen weeks before admission. Their genital primary chancres had appeared from three to eight weeks before admission. Fourteen of the patients had numerous mucocutaneous condylomatous and ulcerative lesions in the genital and perianal regions and elsewhere (Figure 1). In three of these there was also a roseolar rash. One patient had a roseolar rash alone.

Clinical and physiologic data obtained in the fifteen patients are presented in Table I.

The Reaction. After treatment eight of the patients became distressed and complained of various aches and pains. Five of them felt burning

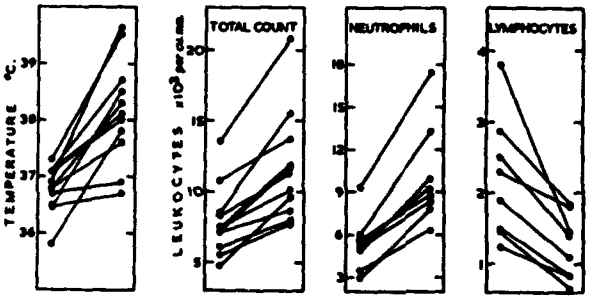

Figure 3. Maximal changes in body temperature and total and differential blood leukocyte count in eleven patients (Cases 5 through 15) with early syphilis.

TABLE II Anthropometic Data from Four Patients (Cases 1 through 4) with Early Syphilis Before Treatment

Case No.	Height (cm)	Weight (kg)	FEV_1 (L)	VC (L)	FEV_1:VC (%)	PEF (L/min)
1	164	49	3.5	3.9	90	445
2	158	55	3.4	3.95	87	430
3	174	53	2.8	4.1	63	435
4	160	54	3.3	4.0	83	500

NOTE: FEV_1 = forced expired volume in first second; VC = vital capacity; PEF = peak expiratory flow.

discomfort in their skin lesions. Six of the patients had rigors. Chest roentgenograms were normal before and after treatment in the four patients (Cases 1 through 4) in whom they were taken. In one patient (Case 2) the QT interval corrected for heart rate (QT_c) was prolonged on the day after treatment, and the P wave increased in voltage during the reaction. Flattening of T waves or S-T segment abnormalities were seen in all four patients studied in detail.

Body temperature increased after treatment in all cases (Table I). The mean rise was 1.5°C (range 0.2 to 2.7°C). In three patients it did not exceed 0.8°C, which is the limit of diurnal variation in health [10]. Serial changes in rectal and skin temperatures during the reaction in a representative patient (Case 1) are illustrated in Figure 2. In this patient rectal temperature fluctuated between 36.8° and 37.5°C until 3.9 hours after penicillin injection, when it began to rise. There was a transient rigor at 3.2 hours, and there were prolonged rigors lasting about twenty minutes 5.1 hour after treatment. Rectal temperature reached its peak of 39.2°C 6.6 hours after treatment, ninety minutes after the second episode of rigors had begun. At 2.25 hours it had fallen to 39.0°C. In the group as a whole peak temperature ranged from 36.7° to 39.5°C which was reached 4.5 to 7.75 hours after treatment (Table I). Skin

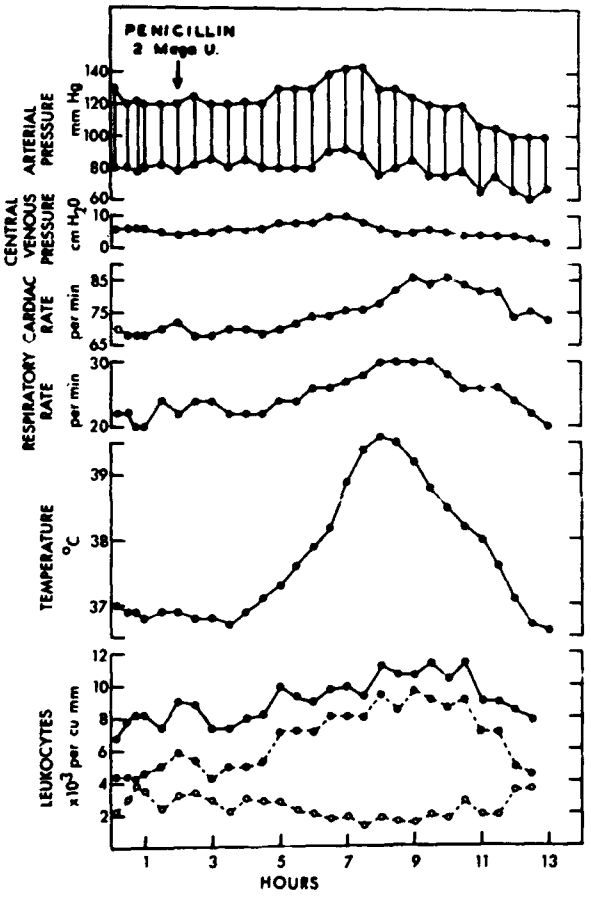

Figure 4. Case 15. Serial observations from a patient with early syphilis illustrating the time relationship between cardiorespiratory, temperature and blood leukocyte changes during the Jarisch-Herxheimer reaction.

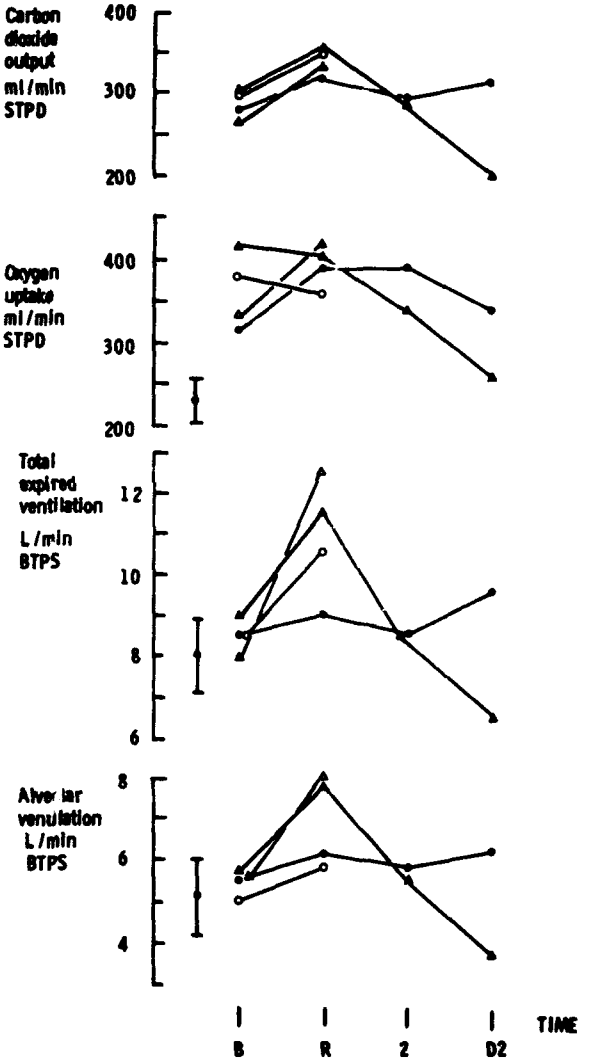

Figure 5. Over-all gas exchange and pulmonary ventilation in four patients (Cases 1 through 4) with early syphilis during the Jarisch-Herxheimer reaction. Key: ● = Case 1, ▲ = Case 2, ○ = Case 3, △ = Case 4. Time axis indicates expired gas collections before treatment (B), at the peak of the reaction (R), two hours later (2) and on the day after treatment (D2). Normal values for the altitude of 7,500 feet are given at the left (mean ± 1 SD). Source of normal data: Chiodi [31].

temperatures were variable. In some patients there was a fall, suggesting cutaneous vasoconstriction during the first hour after penicillin injection (Figure 2).

Total leukocyte count (Table I, Figure 3) increased during the reaction in each patient and there was an absolute neutrophil leukocytosis. The absolute lymphocyte count fell in seven of the eight patients in whom it was measured. Serial changes in total and differential leukocyte count in relation to other physiologic variables are illustrated for a representative patient (Case 15) in Figure 4.

Cardiorespiratory Studies. The four patients (Cases 1 through 4) in whom more detailed cardiorespiratory measurements were made are described in Tables I and II. Ventilatory capacity (FEV_1, VC and PEF, Table II) was virtually normal before treatment. In respect to over-all gas exchange (Figure 5), carbon dioxide output ranged between 265 and 305 ml/minute and oxygen uptake between 315 and 415 ml/minute before treatment, indicating mildly increased metabolic rate. At the peak of the reaction carbon dioxide output had increased in all cases, but oxygen uptake increased in only two cases (by 75 and 85 ml/minute). Total expired ventilation and respiratory frequency were virtually normal before treatment: they had increased at the peak of the reaction, together with alveolar ventilation but V_D:V_T

TABLE III Results of Physiologic Measurements in Four Patients with Early Syphilis*

Variable (normal range)	Case No.	Times of Observations B	R	2	D2
Rectal temperature (°C)	1	37.0	39.0	39.0	37.0
	2	37.5	39.2	38.4	36.7
	3	37.2	39.0	...	...
	4	37.9	39.5	...	...
Respiratory frequency (17.9 ± 3.6 breaths/min)	1	19	20	16	20
	2	19	23	19	18
	3	15	23	...	...
	4	17	30	...	...
Respiratory exchange ratio (0.83 ± 0.03)	1	0.89	0.82	0.75	0.94
	2	0.74	0.87	0.85	0.78
	3	0.79	0.96	...	...
	4	0.80	0.80	...	...
Dead space:tidal volume ratio (0.24 ± 0.04)	1	0.23	0.21	0.20	0.23
	2	0.24	0.21	0.24	0.22
	3	0.30	0.25	...	...
	4	0.18	0.23	...	...
Arterial bicarbonate concentration (21.5 ± 1.0 mM/L)	1	23.1	22.7	22.1	22.8
	2	22.2	22.5	19.5	22.7
	3	...	...	...	...
	4	20.0	...	...	...
Arterial pH (7.39 ± 0.05)	1	7.44	7.51	7.45	7.44
	2	7.42	7.47	7.38	7.44
	3	...	...	...	...
	4	7.42	...	...	...
Arterial O_2 content (18.6 ± 0.9 ml STP/100 ml)	1	15.5	15.5	15	17.5
	2	17.5	15.5	16	16
	3	15	14.5	...	...
	4	13	13.5	...	...
Mixed venous O_2 content (ml STP/100 ml)	1	11.5	11	10.5	13.5
	2	13	12.5	11.5	11.5
	3	12.5	11.5	...	...
	4	10	11.5	...	...
Arteriovenous O_2 content difference (ml STP/100 ml)	1	4	4.5	4	4
	2	4.5	3	4.5	.5
	3	2.5	3	...	..
	4	3	2	...	...
Hemoglobin concentration (14.9 ± 0.7 gm/100 ml)	1	14.2	13.9	13.6	13.9
	2	14.5	13.9	13.9	14.2
	3	14.8	14.7	...	...
	4	12.7	12.6	..	...
Hematocrit (48.8 ± 2.5%)	1	44	44	43	44
	2	45	41	43	33
	3	44	41.5	...	...
	4	38.5	38	...	...
O_2 binding capacity/gm hemoglobin (1.33 ± 0.12 ml STP)	1	1.23	1.26	1.20	1.37
	2	1.39	1.26	1.25	1.22
	3	1.20	1.10	...	...
	4	1.16	1.26	...	...
Pulmonary arterial mean pressure (15.4 ± 2.9 mm Hg)	1	16.2	22.9	12.1	12.5
	2	...	17.7	14.0	...
	3	21.1	17.3	...	...
	4	...	...	...	...
Pulmonary vascular inflow resistance (3.3 ± 1.1 mm Hg/L/min)	1	2.7	2.6	1.4	1.5
	2	...	1.3	1.7	...
	3	1.7	1.3	...	...
	4	...	...	...	...
Arterial lactate concentration (mM/L)	1	0.58	0.58	1.73	0.96
	2	0.58	0.58	0.67	0.48
	3	0.58	0.53	...	...
	4	0.39	0.48	...	...
Artertial pyruvate concentration (mM/L)	1	0.03	0.05	0.18	0.06
	2	0.03	0.06	0.08	0.06
	3	0.06	0.05	...	...
	4	0.06	0.06	...	...
Arterial glucose concentration (mg/100 ml)	1	88	92	85	100
	2	65	85	100	100
	3	81	85	...	...
	4	78	85	...	...

* Normal values for 7,500 feet (mean ± 1 SD) from Warrell and Pope [11], are given in brackets. Observations were made before penicillin treatment (B) at the peak of the Jarisch-Herxheimer reaction (R), two hours later (2) and on the next day (D2) twenty hours after treatment.

(Table III) remained normal throughout the reaction (Figure 5). Arterial P_{CO_2} (Figure 6) was low before treatment in three patients, and it decreased at the peak of the reaction. Arterial bicarbonate concentration (Table III) was normal throughout. The three patients in whom arterial pH (Table III) was measured were mildly alkalemic (pH 7.42 to 7.44) before treatment, and pH rose further during the reaction.

Hemoglobin concentration was low at 12.7 gm/100 ml in the female patient (Table III, Case 4). It fell by 0.3 gm/100 ml during the study in two patients (Cases 1 and 2). Oxygen binding capacity of hemoglobin was somewhat below the values obtained by the same methods in healthy residents of Addis Ababa [11]. In three cases arterial P_{O_2} (Figure 6) ranged between 56.5 and 67 mm Hg before treatment and was below the normal range for this altitude. It increased slightly during the reaction. "Ideal" alveolar to arterial P_{O_2} difference ranged between 5 and 11 mm Hg before treatment and decreased during the reaction. Arterial oxygen saturation (Figure 6) was below the normal range before treatment. In the two patients in whom measurements were repeated after the reaction, saturation had increased to within the normal range. Arterial oxygen content (Table III) was below the normal range in three cases, and since mixed venous oxygen content was relatively high, the arteriovenous difference was small. $\dot{Q}_{va}:\dot{Q}_t$ (Figure 6) was extremely high in all cases. It ranged between 22 and 27 per cent before treatment. In one patient (Case 4) it increased to 42 per cent at the peak of the reaction, in the others it decreased or did not change. On the day after treatment $\dot{Q}_{va}:\dot{Q}_t$ was still high at 35 and 15 per cent in two patients (Cases 1 and 2); the degree of anatomic shunting (breathing 100 per cent oxygen) was negligible (Figure 6).

Cardiac output (Figure 7) was high (range 8 to

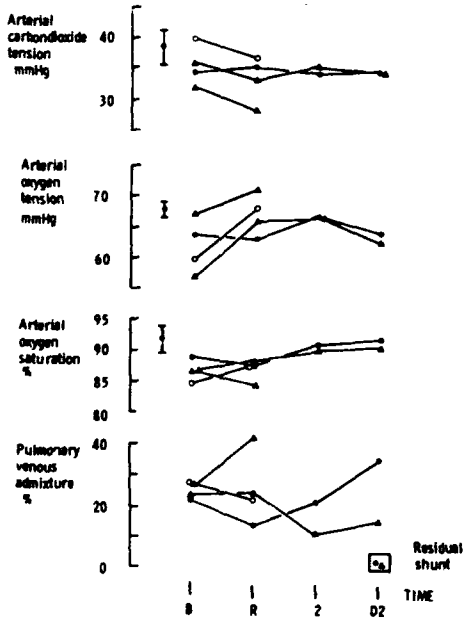

Figure 6. Arterial blood gases and calculated pulmonary venous admixture (as a percentage of cardiac output) in four patients (Cases 1 through 4) with early syphilis during the Jarisch-Herxheimer reaction. Key: As in Figure 5. Sources of normal data: Chiodi [31] and Warrell and Pope [11].

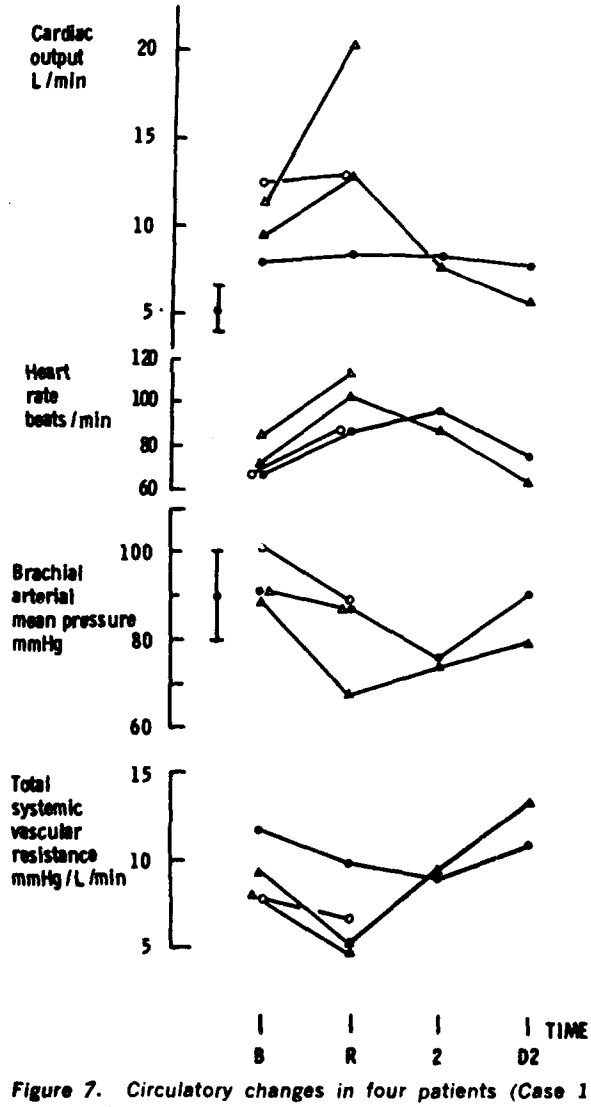

Figure 7. Circulatory changes in four patients (Case 1 through 4) with early syphilis during the Jarisch-Herxheimer reaction. Key: As in Figure 5. Source of normal data: De Micheli et al. [32].

12.5 L/minute) before treatment and increased by 0.5 to 9 L/minute by the peak of the reaction whereas heart rate increased by 15 to 32 beats/minute. Brachial arterial mean pressure ($\bar{P}_{BA}$) Figure 7) decreased gradually after penicillin injection but increased transiently as the patients became apprehensive at the time rectal temperature began to increase. $\bar{P}_{BA}$ fell as rectal temperature reached its peak and then returned to normal by the next morning. In one patient (Case 1) $\bar{P}_{BA}$ rose abruptly before the first episode of rigors and fell after the second episode had ended. Serial changes of $\bar{P}_{BA}$ in this patient are illustrated in Figure 2. Mean levels of $\bar{P}_{BA}$ during the expired gas collections are given in Figure 7. Total systemic vascular resistance was low before treatment (range 7.9 to 11.6 mm Hg/L/minute and fell during the reaction (Figure 7).

Pulmonary arterial mean pressure ($\bar{P}_{PA}$) was measured in three patients (Cases 1, 2 and 3). In two of these (Cases 1, Figure 2, and 3) $\bar{P}_{PA}$ increased during the reaction by 14.5 and 10 mm Hg, respectively (maximum changes from pretreatment levels) but in the remaining one (Case 3) there was a 6.5 mm Hg fall in $\bar{P}_{PA}$. Mean levels of $\bar{P}_{PA}$ during the expired gas collections are given in Table III. Pulmonary vascular inflow resistance (Table III) remained or fell below normal levels during the reaction.

TABLE IV Comparison of Jarisch-Herxheimer Reaction in Syphilis and Relapsing Fever

Reaction Characteristic	Relapsing Fever	Syphilis
Systemic effects	Always, severe	Not always, variable severity
Onset following treatment	Within 1 hour	Within 2 hours
Peak of crisis	Second hour following treatment	4 to 8 hours following treatment
Temperature response	Rapid, constant, little variation	Slow, inconstant, wide variation
Mean temperature rise	1.4°C (1.1°–1.9°C)	1.5°C (0.2°–2.7°C)
Leukocyte count	Falls at the height of reaction with subsequen rise	Rises at the height of reaction with subsequent fall
Neutrophils	Fall	Rise
Lymphocytes	Fall	Fall
Leukocyte degranulation and vacuolation	Observed	Not observed
Site of spirochaetes	Mainly blood	Mainly tissues

Slight increases in arterial glucose, lactate and pyruvate concentrations were detected during the reaction in some of the patients (Table III).

COMMENTS

We have used the term "Jarisch-Herxheimer reaction" (J-HR) in its original sense [12,13]: aggravation of the local lesions and fever associated with systemic symptoms which are provoked by the treatment of early syphilis. Histologically, local lesions show an acute transient inflammatory reaction with congested capillaries and veins. Neutrophils and mononuclear cells appear and migrate through the swollen vascular endothelium into the edematous tissue [14,15].

A neutrophil leukocytosis accompanied, or preceded by up to three hours, the rise in body temperature. This confirms the observations of McDowell [16] and Skog and Gudjonsson [15]. In contrast to Skog and Gudjonsson [15], however, we have seen leukocytosis in the absence of a significant rise of temperature (Cases 8 and 10), and unlike these investigators and Joulia, Pautrizel, Texier and Seabra [17] we did not detect eosinopenia six to nine hours after penicillin injection.

The febrile reaction following treatment of louse borne relapsing fever (LBRF) may also be regarded as a J-HR [2,18], and it is compared with the reaction in syphilis in Table IV and Figure 8. It differs from the J-HR of syphilis in developing faster, in being more severe in its clinical and physiologic manifestations [4], and in the fact that it is accompanied by a striking leukopenia followed by leukocytosis [2,19]. These differences need not imply that the pathogenesis of the reaction is different, but rather they may result from the different distribution of spirochetes in the two diseases. In early syphilis spirochetes are found predominantly in the skin and other tissues whereas in LBRF they are predominantly in the blood stream. In both diseases phagocytosis of spirochetes which have been exposed to antibiotic probably initiates the reaction. In LBRF the antibiotic affects the spirochetes almost instantaneously. Schofield, Talbot, Bryceson and Parry [2] have suggested that the resulting phagocytosis causes a sudden release of leukocyte (endogenous) pyrogen and thus the features of the reaction. There is also evidence [20] that fever in LBRF is associated with an endotoxin. Sudden release of endotoxin could also account for these features. In early syphilis, death and phagocytosis of the organisms must follow diffusion of antibiotic and

migration of leukocytes into the tissues with the result that the reaction will be slower to develop. The first polymorph leukocytes to enter the tissues would, as a result of phagocytosis, be expected to release leukocyte pyrogen [21] which, by its local inflammatory action [22], would gradually speed up the immigration of leukocytes and so accelerate pyrogen production, resulting in a reaction which starts slowly and gathers speed.

A patient with syphilis whose temperature rises 3°C during the J-HR has a milder reaction than a patient with relapsing fever whose temperature rises only 1°C. This suggests that the severity of the reaction is determined by the rate of endotoxin release and/or pyrogen production, whereas the temperature rise depends on the quantity of pyrogen released and the speed of its destruction. In syphilis the rate at which leukocyte pyrogen is destroyed might balance the slower rate at which it is produced, which would account for patients showing leukocytosis without fever.

Experimentally, intravascular injection of dead organisms [23] or of endotoxin [24,25] results in sequestration of leukocytes in the capillaries, particularly in the lungs. This is probably the cause of the transient leukopenia in the reaction in LBRF [2]. Death and phagocytosis of organisms and the release of leukocyte pyrogen [26] all stimulate leukocytosis. In syphilis, intravascular phagocytosis and sequestration will be unimportant, and the relatively slow development of events makes it likely that neutrophil leukocytosis keeps pace with or exceeds neutrophil migration into the tissues. Lymphopenia, which is a feature of the reactions in both syphilis and relapsing fever, could be explained either by simple passive exudation of lymphocytes into the inflamed lesions without a compensating stimulus to lymphopoiesis, or to the migration of a specifically sensitized population of lymphocytes to antigen newly released from disintegrating spirochetes [18].

The cardiorespiratory and biochemical changes during the J-HR in syphilis do not appear to have been studied previously. In the four patients in the present study rectal temperature was lower than in the patients with LBRF recorded by Warrell and associates [4]. Before treatment the mean rectal temperature was 37.4°C compared to 40.3°C, and at the peak of fever after treatment it ranged between 39.0° and 39.5°C compared to 41.1° to 42.6°C. The peak was not reached in patients with syphilis until between 6.5 and 7.5 hours after treatment compared to 90 to 195 minutes in the patients with LBRF. Metabolic rate increased much less during the reaction in syphilis than in LBRF. This difference was explained by the higher body temperatures in LBRF and the prolonged energetic rigors, which were less intense or absent in syphilis. Total expired ventilation increased less in syphilis than in LBRF (to 9 to 12.5 L/minute compared to a mean 28.9 L/minute). Alveolar ventilation was in excess of metabolic demands as shown by the low arterial P_{CO_2} (28 to 36.5 mm Hg) at the peak of the reaction. Unlike the patients with LBRF there was little fall in arterial bicarbonate concentration during the reaction whereas changes in arterial lactate and pyruvate levels were unimpressive except in one patient (Case 1) whose lactate level rose to 1.73 mM/L two hours after the peak of the reaction. The most striking respiratory abnormality in these patients, as in those with LBRF, was impaired pulmonary oxygen uptake. Arterial P_{O_2} and oxygen saturation were below the normal range for an altitude of 7,500 feet, and pulmonary venous admixture was high during the reaction. The observation that breathing 100 per cent oxygen virtually eliminated venous admixture excludes anatomic shunting. Impaired pulmonary uptake might have resulted from ventilation-perfusion inequality or inadequate oxygen diffusion.

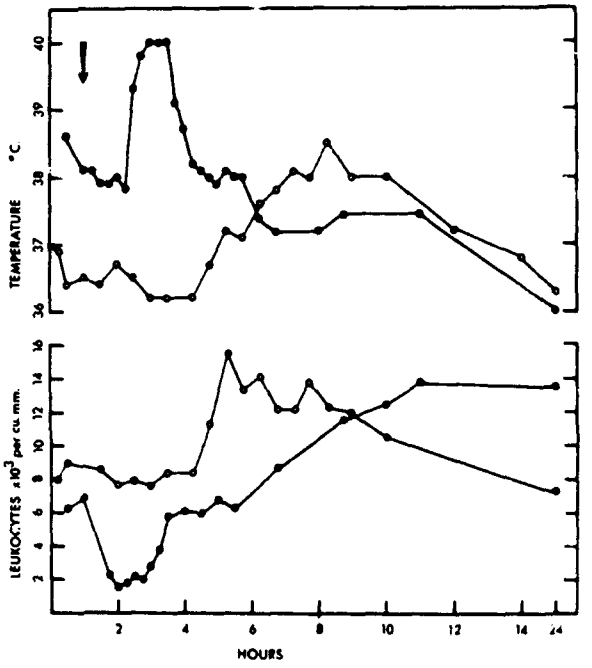

Figure 8. Comparison of changes in body temperature and blood leukocyte count in patients with early syphilis (○) and louse-borne relapsing fever (●) during the Jarisch-Herxheimer reaction.

Against the former was the normal physiologic dead space and normal roentgenographic appearances. Abnormal hemoglobin was implied by the low oxygen binding capacity per gram hemoglobin (Table III), as in the patients with LBRF.

Circulatory changes were generally more marked than ventilatory changes in the patients with syphilis. Cardiac output and heart rate increased during the reaction, and systemic arterial mean pressure had fallen at the peak of fever, implying a decrease in total systemic vascular resistance. Pulmonary arterial mean pressure and vascular resistance followed a similar pattern of change.

The respiratory and circulatory changes were qualitatively similar in the two diseases, but all were more marked in LBRF. Variation of responses within the group of patients was greater in syphilis than in LBRF but, since the phases of the reaction were less well defined in syphilis, the timing of measurements may have been less comparable.

There is evidence that in the reaction in LBRF the magnitude of cardiorespiratory changes is not simply related to body temperature [4]. The physiologic features of this reaction can be reproduced in an afebrile patient by reinjection of blood sampled during the original reaction. High levels of endotoxin have been demonstrated in this blood [20]. These observations suggest that the physiologic manifestations of the febrile reaction of LBRF, and by analogy those in the J-HR of syphilis, result from actions of endotoxin which may be separable from the effect on body temperature. The "all or nothing" character of the reactions in syphilis [27] and LBRF [20] is consistent with known properties of the endotoxin-leukocyte pyrogen system [18,28]. Corticosteroids may modify the J-HR of syphilis [29,30], but in LBRF large doses given by continuous infusion failed to prevent the reaction although temperature was suppressed initially [4]. This may be explained by the differences in the quantity of endotoxin present before and during the reactions in the two diseases.

We conclude that the reactions following treatment in syphilis and relapsing fever are essentially similar in their pathogenesis and physiologic effects. The differences in pathology of the diseases probably explain why the reaction in LBRF is more severe and develops more rapidly than the J-HR of syphilis and is accompanied by leukopenia rather than leukocytosis. Our observations indicate the degree of physiologic stress associated with the J-HR reaction in early syphilis. Metabolic rate is increased, but breathing and circulation are stimulated beyond metabolic requirements. Vasodilatation leads to a fall in blood pressure despite the high cardiac output. Since the heart is not directly involved in early syphilis the great increases in cardiac output demanded during the J-HR reaction should not prove dangerous, but the tendency to hypotension makes it necessary for the patient to stay in bed for at least twenty-four hours after treatment. In late syphilis, however, narrowing of the coronary ostia and the abnormalities of oxygen transport already discussed may jeopardize cardiac output and result in cardiac failure and circulatory inadequacy during the reaction.

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