Pathophysiology and Immunology of the Jarisch-Herxheimer-Like Reaction in Louse-Borne Relapsing Fever: Comparison of Tetracycline and Slow-Release Penicillin

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Twelve men with louse-borne relapsing fever were treated with single doses of procaine penicillin plus aluminum monostearate (PAM) intramuscularly or of tetracycline intravenously. All patients experienced a definite Jarisch-Herxheimer-like reaction. Fever and spirochetemia were significantly prolonged and peak temperature was lower and occurred later in the PAM-treated group. Peak pulmonary ventilation, metabolic rate, and arterial P02 were significantly higher in the tetracycline-treated group. Circulatory changes were similar in the two groups but were prolonged in the PAM-treated patients. Thus, tetracycline is recommended for treatment because it is more rapidly effective in eliminating Borrelia spirochetes and produces a reaction no more stressful physiologically than the one after PAM. There was no evidence of complement activation, and there was no change in immunoglobulin levels throughout the reaction. Immune complexes were detected in serum of five patients before treatment, but in fewer patients at the peak of the reaction and subsequently.

During the first half of the 1900s there were several major epidemics of louse-borne relapsing fever in Europe, the Middle East, and Africa involving at least 50 million people and resulting in more than five million deaths [1]. The principal endemic focus is now the Ethiopian high plateau, where >10,000 people may be infected each year. As long as this and other smaller foci exist another pandemic is possible. The untreated mortality ranges from 30% to 70%, but antimicrobial agents such as penicillin and tetracycline have reduced this rate to between 1% and 4%. All of the drugs that can eliminate Borrelia recurrentis spirochetes induce a severe Jarisch-Herxheimer-like reaction in most patients. Occasional deaths have been reported during this reaction, either with febrile convulsions at the fever’s peak or with subsequent acute pulmonary edema or circulatory collapse [1–5]. In one group of malnourished patients with complicating infections treated with oxophenarsine hydrochloride, the mortality due to the reaction was as high as 12% [6]. Untreated infections resolve by crisis on days 4–11 of the first episode of fever. This crisis may be as severe as the
Jarisch-Herxheimer-Like Reaction may also be fatal, and may be followed by a relapse within five days in at least 50% of cases [3, A6] (P.L.P., unpublished observation).

Attempts to prevent the reaction with acetaminophen and large doses of corticosteroids have not been successful, but peak temperature was decreased and delayed and the decrease in blood pressure during the flush phase of the Jarisch-Herxheimer-like reaction was lessened [7, 8]. Although such reactions have been regarded as all-or-none phenomena [9-11], efforts have been made to ameliorate the reaction in louse-borne relapsing fever by killing the spirochetes more gradually. Results suggested that various slow-release penicillins produce a delayed and milder reaction, but that spirochetemia is more persistent and the incidence of relapses higher in patients treated with tetracycline [1, 4, 6A, 8, 12, 13] (P.L.P., unpublished observation). None of these studies included measurements of the most important physiologic changes determining circulatory failure, which is the most dangerous development in the Jarisch-Herxheimer-like reaction. Some studies excluded severely ill patients, some were uncontrolled, and in others the two treatment groups were not studied under identical conditions.

The aim of the present study was to compare the degree of physiologic stress experienced by the patients treated with tetracycline and slow-release penicillin and to explore the immunologic mechanisms of the reaction.

Patients and Methods

Adult patients found to have *Borrelia* spirochetes in their blood were transferred from various health clinics in Addis Ababa to the U.S. Naval Medical Research Unit's ward in St. Paul's Hospital, Addis Ababa, Ethiopia (altitude, 2,535 m; barometric pressure, 550 mm Hg). Twelve men who were undergoing their first attack of louse-borne relapsing fever and consented to treatment and investigation were included in the study. They were randomly allocated for treatment with either pyrrolidino-methyl-tetracycline, 275 mg by slow iv injection, or procaine penicillin with aluminum monostearate (PAM), 600,000 units im. This dose of PAM has proved effective in louse-borne relapsing fever [12] and was reported to achieve therapeutic blood levels of penicillin for at least four days [14, 15]. Patients found to have complicating infections with *Salmonella typhi* and other pathogens were excluded. All patients received 2-3 liters of 0.9% NaCl during the first 12 hr after treatment. The clinical history and physical examination results were recorded on standard pro formas.

The methods used to measure cardiorespiratory changes have been described [7]. The electrocardiograph and rectal temperature were monitored continuously. Fine polyethylene catheters were introduced percutaneously into a brachial artery and antecubital vein. The venous catheter was advanced into the pulmonary artery. Intravascular pressures were measured by transducers and recorded with other variables on a multichannel pen and ink recorder. Before treatment, at the peak of the febrile response, and 24 hr after treatment, expired gas was collected, and simultaneously blood was sampled from pulmonary and brachial arteries for periods of 3 min. The PO2 and PCO2 of blood and gas samples and pH of blood were measured with two sets of electrodes, one maintained at 37 C and the other adjusted to the patient's core temperature so that temperature corrections could be checked. Using a computer program describing the oxyhemoglobin dissociation curve [16], oxygen saturation and content and hence cardiac output, right-to-left shunting, and dead space:tidal volume ratios were calculated. Systemic and pulmonary vascular resistances were calculated from these data.

Venous blood was sampled before treatment, at intervals of 1-3 hr during the reaction, on the next day, and on discharge from the hospital at the end of the seven-day admission. Levels of electrolytes, blood urea nitrogen, serum aspartate and alanine aminotransferases, creatine phosphokinase, plasma proteins, and bilirubin were measured by standard methods [1], as were hemoglobin levels, hematocrit, white blood cell and platelet counts, prothrombin and partial thromboplastin times, and serum fibrin/fibrinogen-related antigen levels. Bleeding time was measured by the Ivy method as described by Mielke et al. [17]. Spirochete concentrations were estimated by counting...
the average number of organisms per 10 white blood cells in thin films stained with Wright's stain and multiplying this total by the white blood cell count. The above measurements were performed in Addis Ababa.

Samples for the following measurements were stored in Addis Ababa at -70°C or below for several months. Aliquots of serum and EDTA-treated plasma were then air-freighted on dry ice to the Blood Grouping Laboratory of the Center for Blood Research in Boston, where D.H.B. determined the concentrations of complement components and other serum proteins and assayed immune complexes by Clq inhibition, and to the Centers for Disease Control in Atlanta, where S.J.M. assayed immune complexes by three other methods. Transferrin, α1-antitrypsin, haptoglobin, osmomucoid, β-lipoprotein, IgG, IgM, IgA, C3, C4, Clq, and properdin factor B were measured by the turbidometric technique (Autoanalyzer²; Technicon Instruments Corp., Tarrytown, N.Y.) as described by Ritchie [18]. Where results are expressed as a percentage of normal values, they are based on the determination of protein concentrations in 200 serum samples as compared with a pool of normal serum in which every contributor proved to be normal for all proteins. Immune complexes were assayed by the Clq inhibition radioimmunoassay [19], the modified [¹²⁵I]Clq binding test [20], staphylococcal protein A binding assay [21], and the Raji cell method [22].

The possibility of complicating infections was investigated clinically, radiographically, by culture of blood and other samples, and by detection of febrile agglutinins to S. typhi, Salmonella paratyphi, and Proteus strains OX-19 and OX-2.

**Results**

**Comparability of treatment groups.** The two groups of patients were comparable (P > 0.05) in almost all respects before treatment. All were men aged 18-38 years who were admitted to the study on days 3-6 of fever. Physical signs included jaundice, petechial hemorrhages, spontaneous bleeding (epistaxis), gallop rhythm, ronchi, tachypnea, tender hepatosplenomegaly, meningism, and muscle tenderness. Hematologic and biochemical values (table 1) showed the same pattern of abnormalities described previously [1]. Most patients had elevated levels of blood urea nitrogen and evidence of hepatocellular damage. Ivy bleeding times were prolonged in all cases. Mean ± SEM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tetracycline</th>
<th>Penicillin with aluminum monostearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.5 ± 1.2</td>
<td>22.7 ± 1.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 3</td>
<td>168 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.8 ± 2.1</td>
<td>53.8 ± 2.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36.7 ± 1.6</td>
<td>40.5 ± 1.9</td>
</tr>
<tr>
<td>White blood cells/mm³</td>
<td>7.733 ± 1.267</td>
<td>9.883 ± 1.442</td>
</tr>
<tr>
<td>Spirochetes × 10⁶/mm³</td>
<td>4.870 ± 1.313</td>
<td>3.052 ± 1.392</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>30.3 ± 2.4</td>
<td>23.5 ± 4.1</td>
</tr>
<tr>
<td>Aspartate aminotransferase (units/ml)</td>
<td>47.7 ± 4.5</td>
<td>44.3 ± 11.2</td>
</tr>
<tr>
<td>Alanine aminotransferase (units/ml)</td>
<td>32.0 ± 7.0</td>
<td>20.7 ± 4.1</td>
</tr>
<tr>
<td>Creatinine phosphokinase (units/ml)</td>
<td>6.3 ± 2.3</td>
<td>14.3 ± 6.8</td>
</tr>
<tr>
<td>Total bilirubin (mg/100 ml)</td>
<td>2.47 ± 0.52</td>
<td>1.53 ± 0.72</td>
</tr>
<tr>
<td>Total protein (g/100 ml)</td>
<td>7.45 ± 0.43</td>
<td>7.67 ± 0.42</td>
</tr>
<tr>
<td>Albumin (g/100 ml)</td>
<td>2.80 ± 0.20</td>
<td>3.05 ± 0.21</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td>31.52 ± 3.61</td>
<td>29.89 ± 11.08</td>
</tr>
<tr>
<td>Prothrombin time*</td>
<td>97.3 ± 1.7</td>
<td>96.0 ± 2.6</td>
</tr>
<tr>
<td>Partial thromboplastin time*</td>
<td>19.2 ± 4.9</td>
<td>23.3 ± 5.6</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SEM values.
* (Control value/patient value) × 100.
values for serum electrolytes and the following serum proteins were comparable in the tetracycline- and PAM-treated groups: transferrin, 189 ± 10 and 200 ± 13 mg/100 ml; α₁-antitrypsin, 294% ± 22% and 300% ± 18% of normal values; haptoglobin, 412 ± 43 and 466 ± 17 mg/100 ml; osmomucoid, 418% ± 33% and 379% ± 31% of normal values; β-lipoprotein, 141 ± 11 and 124 ± 13 mg/100 ml; IgG, 1,496 ± 186 and 1,631 ± 325 mg/100 ml; IgM, 155 ± 34 and 144 ± 15 mg/100 ml; C4, 120% ± 14% and 165% ± 18% of normal values; C1q, 271 ± 40 and 333 ± 45 μg/ml; and properdin factor B, 46.2 ± 2.7 and 55.8 ± 3.3 mg/100 ml. Pretreatment levels of C3 (169 ± 9 and 247 ± 13 mg/100 ml; \( P < 0.001 \)) and IgA (188 ± 14 and 258 ± 25 mg/100 ml; \( P < 0.05 \)) were unaccountably higher in the PAM-treated group.

Values for all physiologic variables were comparable before treatment (figures 1–4).

Reaction to treatment. All patients developed a Jarisch-Herxheimer-like reaction. About the time spirochetes disappeared from the blood, temperature, heart rate, systolic blood pressure, and respiratory frequency increased, and the patients became restless and distressed (figure 1). All patients treated with tetracycline, but only one treated with PAM, exhibited frank rigors. Peak rectal temperature was higher and was reached sooner in the tetracycline-treated group, and spirochetes were eliminated more quickly (figure 2).

Respiratory changes. Patients treated with tetracycline showed greater increases in pulmonary ventilation and metabolism (figure 3). Both groups showed evidence of disturbed pulmonary gas exchange and ventilation perfusion relationships: arterial \( P_{O_2} \) was reduced, and dead space: tidal volume ratios and right-to-left shunting were increased (figure 4). These changes were significantly more marked in the PAM-treated group. In the tetracycline-treated group all respiratory variables had returned to their pretreatment levels 2 hr after the peak of the reaction.
Circulatory changes. Circulatory changes (figure 5) were more marked in the tetracycline-treated group, but the differences did not reach statistical significance. In the tetracycline-treated group cardiac output had decreased toward normal 2 hr after the peak of the reaction. The maximum decrease in systolic blood pressure during the flush phase compared with pretreatment values was the same in both groups (25.0 ± 3.6 and 22.2 ± 5.6 mm Hg in the tetracycline- and PAM-treated groups, respectively). Hypotension (defined as a supine systolic blood pressure of <80 mm Hg) was significantly prolonged in the PAM-treated group (23.5 ± 4.2 hr) compared with the tetracycline-treated group (12.1 ± 2.1 hr). Pulmonary artery pressures and pulmonary vascular resistance were similar in the two groups: pressures decreased during the peak of the reaction by 6–12 mm Hg and then increased above pretreatment levels during the subsequent 4 hr. No patient developed signs of acute pulmonary edema, cardiac failure, or peripheral circulatory failure.

Figure 3. Changes in pulmonary ventilation and metabolic rate in 12 patients with louse-borne relapsing fever before, during, and after the Jarisch-Herxheimer-like reaction to antimicrobial treatment. The stippled area represents the normal range (mean ± SEM) in residents at an altitude of 2,460 m [23]. Six patients treated with tetracycline = (○●●●●●); six patients treated with penicillin plus aluminum monostearate = (●●●●●●); A = before antimicrobial treatment; R = at peak of reaction; P = 24 hr after treatment; BTPS = body temperature and pressure saturated (with water); and STPD = standard temperature (0 C) and pressure (760 mm Hg) dry.

Figure 4. Changes in pulmonary gas exchange in 12 patients with louse-borne relapsing fever, six treated with tetracycline (○●●●●●) and six treated with penicillin plus aluminum monostearate (●●●●●●). A = before antimicrobial treatment; R = at peak of the Jarisch-Herxheimer-like reaction; and P = 24 hr after treatment. The stippled area represents the normal range (mean ± SEM) in arterial PO2 and PCO2 in residents at an altitude of 2,460 m [23] and percentage dead space/tidal volume in residents at an altitude of 2,250 m [24].
Hematologic changes. The decrease in total white blood cell count was significantly more rapid in the tetracycline-treated group. Mean minimal counts of 2,656 ± 1,075 and 6,192 ± 1,233 white blood cells/mm³ (P < 0.1) were recorded 2.02 ± 0.44 and 4.71 ± 0.57 hr after treatment (P < 0.005) in the tetracycline- and PAM-treated groups, respectively. The respective mean decreases from pretreatment values were 5,010 ± 819 and 3,608 ± 1,219 white blood cells/mm³ (P < 0.5). The respective percentage decreases were 69% ± 8% and 35% ± 7% (P < 0.01).

Platelet counts (table 2) were similar in the two groups. They decreased to minimal levels during the first 24 hr after treatment and then increased gradually, reaching normal levels by days 5–7.

There was no difference in the levels of serum fibrin/fibrinogen-related antigen between the two groups, and no significant changes occurred during the 48 hr after treatment. Prothrombin times, which were abnormal in only two patients before treatment, became prolonged during the next 24 hr in another two patients. Partial thromboplastin times were abnormal in two patients before treatment and became prolonged in another eight patients during the next 24 hr. Clotting times were invariably normal if the patient's plasma was mixed in equal proportions with normal control plasma; this finding excluded the possibility of a circulating anticoagulant.

Biochemical changes. There was no consistent trend in changes in serum electrolyte concentrations during the reaction, but levels of blood urea nitrogen, serum aspartate and alanine aminotransferases, and creatine phosphokinase rose in almost all cases. All values returned to normal within seven days of treatment.

Immunologic changes. Levels of immunoglobulins, complement components, and other plasma proteins were in the high normal range or frankly elevated (table 3). There was no evidence of complement depletion at any stage. Values on day 1 after treatment were usually even higher than pretreatment.

Table 2. Platelet counts during treatment and recovery in men with louse-borne relapsing fever.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tetracycline</th>
<th>Penicillin with aluminum monostearate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>Before</td>
<td>38 ± 8</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27 ± 4</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>69 ± 18</td>
<td>67 ± 17</td>
</tr>
<tr>
<td>5</td>
<td>184 ± 43</td>
<td>195 ± 44</td>
</tr>
<tr>
<td>7</td>
<td>272 ± 59</td>
<td>313 ± 61</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SEM number of platelets x 10⁹/mm³.
Table 3. Changes in complement components during the Jarisch-Herxheimer-like reaction in men with louse-borne relapsing fever treated with tetracycline (TC) or penicillin plus aluminum monostearate (PAM).

<table>
<thead>
<tr>
<th>Complement component, treatment</th>
<th>Normal value</th>
<th>Pretreatment</th>
<th>Peak of reaction</th>
<th>Day 1 after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 (mg/dl)</td>
<td>100-200</td>
<td>169 ± 9</td>
<td>176 ± 10</td>
<td>214 ± 24</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td>247 ± 13</td>
<td>224 ± 13</td>
<td>193 ± 23</td>
</tr>
<tr>
<td>PAM</td>
<td></td>
<td>120 ± 14</td>
<td>106 ± 8</td>
<td>118 ± 6</td>
</tr>
<tr>
<td>C4 (mg/dl)</td>
<td>25-275</td>
<td>165 ± 18</td>
<td>163 ± 22</td>
<td>172 ± 31</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td>271 ± 40</td>
<td>272 ± 13</td>
<td>449 ± 47</td>
</tr>
<tr>
<td>PAM</td>
<td></td>
<td>333 ± 45</td>
<td>379 ± 50</td>
<td>391 ± 32</td>
</tr>
<tr>
<td>Clq (μg/ml)</td>
<td>100-200</td>
<td>46.2 ± 2.7</td>
<td>43.7 ± 3.0</td>
<td>53.7 ± 2.7</td>
</tr>
<tr>
<td>Factor B (mg/dl)</td>
<td>12-56</td>
<td>55.8 ± 3.3</td>
<td>53.8 ± 6.7</td>
<td>59.0 ± 8.7</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SEM values.

**Immune complexes.** Most serum samples proved positive for immune complexes by one or more of the four assays (table 4), but when the results were collated, there was unequivocal evidence of immune complexes in the serum of five of the 12 patients before treatment. There was a tendency for complexes to disappear during the reaction, but in two patients they were first detected at that time. Data from two patients in each group, whose serum was assayed for immune complexes throughout the reaction, are shown in figure 6.

**Penicillin levels.** Penicillin was detected in the serum of seven of nine patients at 24 hr after treatment. This group included the six patients in the study and an additional three patients with louse-borne relapsing fever treated with the same dose of PAM. The levels ranged from 0.5 to 3.7 units/ml.

All patients made an uncomplicated recovery and were well when discharged from the hospital after one week.

**Discussion**

Evidence of complement activation has been found in some patients with louse-borne relapsing fever. Bryceson [26] found low pretreatment levels of C3b and C3c in two of three patients. Galloway et al. [27] found low levels of serum hemolytic complement and properdin activity in a group of 15 patients before and 2 hr after treatment, with a subsequent increase during convalescence. Dennis et al.2 found C3 and C4 levels to be low up to 18 hr after treatment in a group of 25 patients. In the present study there was absolutely no evidence of complement depletion at any stage. Values after treatment tended to be even higher than the preceding values, suggesting an acute-phase reaction [28]. Similar results were obtained during the Jarisch-Herxheimer-like reaction of syphilis [29]. In mice infected with *Borrelia duttoni*, the Jarisch-Herxheimer-like reaction induced by ampicillin was independent of C3-9 and

required neither antibody nor cellular immunity [11], and C5-deficient mice were able to eliminate *Borrelia turicatae* from the blood as effectively as normal controls [30]. In the rabbit model of the Jarisch-Herxheimer-like reaction of early syphilis, histologic appearances of the cutaneous lesions were identical in controls and in animals depleted of complement before penicillin treatment [31]. Taken together, these findings in human and animal spirochetal infections strongly deny a role for complement activation in the pathogenesis of the Jarisch-Herxheimer-like reaction.

In the present study, immune complexes were detected for the first time in human louse-borne relapsing fever, but the specific nature of their antigen and antibody was not determined, and their significance is uncertain. Bryceson [26] considered that the absence of vascular necrotic (Arthus reaction) lesions in patients and animals examined during the Jarisch-Herxheimer-like reactions of syphilis and louse-borne relapsing fever was against a role for immune complexes in these reactions. Immune complexes were not found in glomeruli of terminally infected mice [32]. The appearance of immune complexes would be expected to activate complement, unless they were non-CF or ephemeral.

Complement activation would also be expected
if endotoxin were released by disintegrating spirochetes during the Jarisch-Herxheimer-like reaction. The evidence on this point is most confusing. Endotoxin-like activity has been demonstrated in lipopolysaccharide of *Treponema hyodysenteriae* [33]. Although no endotoxin (2-keto-3-deoxyoctonate of lipid A) was detected by gas-liquid chromatography in *B. recurrentis* spirochetes (P.L.P., unpublished observation), patients’ plasma proved pyrogenic to normal but not to endotoxin-refractory rabbits [34]. However, pyrogen tolerance in rabbits may be nonspecific, so these results do not necessarily imply a specific spirochetal endotoxin [35]. Limulus assays have occasionally proved positive in louse-borne relapsing fever and syphilis [10, 27, 29, 35], but the endotoxemia could have resulted from associated gram-negative bacterial infections or absorption of endotoxin through the wall of the bowel. Butler et al. [35] suggested that a nonendotoxic, particulate pyrogen was the cause of fever in louse-borne relapsing fever. In mice infected with *B. duttoni*, however, the limulus assay consistently becomes positive during the Jarisch-Herxheimer-like reaction induced by ampicillin, and sonicates of these borreliae can produce a generalized Shwartzman reaction [11]. We conclude that, although immune complexes were present in some of the patients with louse-borne relapsing fever, the absence of complement activation and the other evidence cited makes it most unlikely that they were involved in the pathophysiology of the Jarisch-Herxheimer-like reaction.

Compared with tetracycline, slow-release penicillin induces a Jarisch-Herxheimer-like reaction that peaks later, is less often associated with rigors, and causes a smaller increase in temperature and decrease in peripheral leukocyte count, but the fever is protracted and spirochetes are cleared from the blood more slowly [4, 12, 13]. In the present study, only one patient treated with PAM had rigors, but all showed definite if less dramatic signs of the “crisis”: increasing rate of rise in temperature, pulse rate, systolic blood pressure, and respiratory frequency associated with restlessness. Unless patients are continuously monitored, the reaction to PAM may be overlooked because it is clinically less hectic and is more likely to occur at night in patients treated during the day. This observation may explain why Salih and Mustafa [13] did not encounter the reaction in patients treated with 400,000 units of fortified procaine penicillin.

Spirochete clearance may be very slow in patients treated with PAM. In three patients in this study, spirochetes were detectable for 41–48 hr after treatment. Disappearance of spirochetes was attributed to the antibiotic, but it is clear from reports of spontaneous crises occurring in patients observed for up to 24 hr without treatment that this phenomenon could have contributed. Thus, all but two of a group of 18 patients admitted more than five days after the onset of fever suffered a spontaneous crisis during the first 24 hr after admission while treatment was withheld [3]; at St. Paul’s Hospital, five of 19 patients with clinically mild disease had spontaneous crises while under observation for 15 hr before being treated.

Cardiac output, pulse rate, systemic vascular resistance, and arterial pressure measured at the peak of the reaction were not significantly different in the two treatment groups. As in the larger group of patients studied by Knaack et al. [12], the maximum decrease in blood pressure during the flush phase after the crisis was comparable in the two groups, but hypotension was significantly prolonged in the PAM-treated group. The greater respiratory stimulation observed in tetracycline-treated patients is explained by their higher body temperatures and the muscular exercise involved in rigors. Because of their greater pulmonary ventilation, these patients were able to compensate more effectively for the marked and unexplained defects in pulmonary gas exchange seen in patients with louse-borne relapsing fever in Addis Ababa [7]. Arterial Po2 was significantly higher and dead space:tidal volume ratio was lower in the tetracycline-treated group.

Tissue-damaging effects of protracted spirochtemia and fever have been cited as possible disadvantages of PAM treatment [12]. The persistence of a pathogenic organism in large numbers in the blood would normally be regarded as undesirable, but it is difficult to measure its effect on the patient. In the present study the physiologic stress of the Jarisch-Herxheimer-like reaction, as inferred from cardiorespiratory measurements, was found to be greater in the PAM-treated group. At 2 hr after the peak of the reaction, pulmonary ventilation, metabolic rate, and cardiac output had decreased below pretreatment values in the tetracycline-treated group, at a time when
Jarisch-Herxheimer-Like Reaction

Abnormalities of hemostatic mechanism were equally severe in both treatment groups. Grossly prolonged bleeding time before treatment reflected the severe thrombocytopenia. As in previous studies, the platelet count was found to decrease during the reaction [27, 36]. Prolongation of the partial thromboplastin time during the reaction may be related to depletion of Hageman factor [27] or consumption of other intrinsic coagulation factors, but unlike in previous studies [27, 36, 37], the levels of fibrin/fibrinogen-related antigen did not increase from pretreatment levels.

Spirochetes of louse-borne and particularly tick-borne relapsing fever are known to linger in the central nervous system and other sites, where they may escape the effects of arsenical agents and the central nervous system and other sites, where tick-borne relapsing fever are known to linger. Because of the difficulty of performing follow-up studies and excluding reinfection, the risk of relapse after different treatment regimens is uncertain. Relapses have not been reported, however, in patients with louse-borne relapsing fever treated with tetracycline.

Our results indicate that the use of slow-release penicillin, although reducing the intensity of some aspects of the Jarisch-Herxheimer-like reaction, exposes the patient to prolonged physiologic stress and the potentially harmful effects of persistent spirochetemia. We consider tetracycline the agent of choice, especially in severely ill patients. This recommendation is based on tetracycline’s rapid clearance of spirochetes from the blood and on the observation that the circulatory abnormalities, which are the probable cause of most fatalities during the Jarisch-Herxheimer-like reaction, are little more severe but of significantly shorter duration than those in patients treated with PAM. Tetracycline has the advantage over penicillin that it is effective against louse-borne typhus, which often occurs with louse-borne relapsing fever in mixed epidemics. A single 100-mg dose of doxycycline proved effective in both infections [39]. It is important that typhoid and other enteric infections, which may be associated with louse-borne relapsing fever [40], are diagnosed and treated early. Erythromycin appears to act as rapidly as tetracycline [8] and should be used instead of tetracycline in children and pregnant women.

In a disease with high natural mortality, antimicrobial treatment can scarcely be withheld, particularly in view of the dangers of spontaneous crisis. At present, the Jarisch-Herxheimer-like reaction cannot be prevented, but the results of Wright’s studies with B. duttoni-infected mice suggest that naloxone and other opiate antagonists should be tested in patients [41].

Hyperpyrexia at the peak of the reaction can be controlled by cooling and by parenterally administered antipyretic agents. Most problems arise during the flush phase, when a very high cardiac output is required to maintain blood pressure in the face of intense vasodilatation. Plasma volume has been found to be approximately doubled on the day of treatment by Doberstyn et al. Despite these high values, which have also been recorded in patients with falciparum malaria [42, 43], the effective circulating volume is low because of vasodilatation. In adults, at least 2 liters of 0.9% NaCl should be infused iv during the first 12 hr of treatment. Patients should be nursed in bed for at least 24 hr to prevent postural hypotension. Vasopressor agents such as dopamine have not been properly evaluated in the treatment of this condition. Cardiogenic shock caused by myocarditis is rare: its development is signalled by rising central venous pressure and pulmonary edema. We have observed such shock in a patient admitted in spontaneous crisis before antimicrobial treatment had been given (authors’ unpublished observations). Slow iv injection of 0.5-1.0 mg of digoxin has proved effective [44], as in the myocarditis of fulminant meningococcemia [45], but conventional approaches to the treatment of pulmonary edema, such as the use of potent diuretics or venesection, could prove disastrous because of the greatly increased vascular capacitance [7].

References


17. Aronson, I. K., Soltani, K., Brickman, F. Jarisch-Herxheimer reaction in complement-depleted rabbits: histo-


