INTRODUCTION

Louse-borne relapsing fever is a life-threatening illness of pandemic potential caused by the spirochaete *Borrelia recurrentis*. The case fatality rate, which may reach 40% during an epidemic, is usually 5% or less in antibiotic treated patients (Chung and Chang, 1939; Robinson, 1942; Wolman, 1944; Greaves et al., 1945; Stuart, 1945; Ingraham and Lapenta, 1946; Garnham et al., 1947; Heisch, 1950; Bryceson et al., 1970). However, treatment with an antimicrobial agent is usually accompanied by a violent Jarisch-Herxheimer-like reaction which, in itself, is a cause of morbidity and perhaps the mortality in the disease (Parry et al., 1967; Bryceson et al., 1970; Parry et al., 1970; Warrell et al., 1970). Attempts to moderate this reaction by decreasing initial antibiotic dosage or by administration of corticosteroids have proven unsuccessful (Bryceson et al., 1970). Because one of the authors (JJP) had the impression that louse-borne relapsing fever patients treated with repository penicillins suffered a relatively mild reaction, a study comparing the Jarisch-Herxheimer-like reaction in penicillin and tetracycline treated patients was undertaken.

PATIENTS AND METHODS

Subjects for the study were selected from the outpatient population of St. Paul's Hospital, Addis Ababa, Ethiopia. Twenty-seven febrile patients who were found to have a positive blood film for *Borrelia recurrentis* and who were not seriously jaundiced, hypotensive or in frank heart failure, were admitted for study between March and September of 1970. Two of these patients were subsequently excluded from the study when they were found to have a concomitant gram-negative bacteraemia. The patients were all indigent. They varied in age from 12 to 40, and all but one were males.

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The patients were treated within 24 hours of admission after baseline clinical and laboratory observations had been made. Twelve patients whose hospital numbers ended with an even digit were given a single injection of 600,000 units of penicillin aluminium monostearate intramuscularly; thirteen patients with hospital numbers ending in an odd digit were given a single injection of 250 mg. of tetracycline hydrochloride intravenously. Haemoglobin, haematocrit, erythrocyte sedimentation rate, platelet count, urinalysis, chest x-ray, a 12-lead electrocardiogram and serum creatinine, alkaline phosphatase, bilirubin and glutamic oxaloacetic transaminase (SGOT) were obtained on all patients on the first or second hospital day.

The patients had rectal temperature (utilizing a telethermometer), blood pressure, pulse rate, respiratory rate, cardiac auscultation, white blood cell count, while blood cell differential count, and spirochaete density (as described by Bryceson et al., 1970) performed half hourly until the reaction began. Thereafter observations were made quarter-hourly until spirochaetes were no longer found in the blood and the blood cell count had risen above 5,000 per c.mm.

During the course of the study, it became apparent that the onset of the Jarisch-Herxheimer-like-reaction was delayed and its duration prolonged in the penicillin treated patients. Thereafter, the interval between observations was lengthened in these patients; the rectal temperature, pulse rate and respiratory rate were noted hourly until the spirochaetes had disappeared from the blood. Cardiac auscultation was performed hourly beginning with the eighth post treatment hour. Their white blood cell counts, differential counts, and spirochaete densities were determined every two hours until the eighth post treatment hour and hourly thereafter until clearance of the spirochaetes.

The change in temperature ($\Delta T$) was measured as the difference between the peak temperature after treatment and the temperature on admission. The fever index was determined by plotting the fever curve from the time treatment began until the temperature fell below 38 °C and measuring the area below the curve in square inches. One-by-one cm. standard graph paper was utilized. The scale was 1 cm. for every hour and for every half degree centigrade. The area under the curve was measured with a compensating polar planimeter (Gelman No. 39Z31). The rate-pressure product was determined by multiplying the systolic blood pressure by the pulse rate at the time when the peak pulse rate was noted in each patient. This was then divided by 100 to obtain a more manageable number.

CHARACTERIZATION OF JARISCH-HERXHEIMER-LIKE REACTION

The Jarisch-Herxheimer-like-reaction that follows tetracycline treatment of louse-borne relapsing fever has been well characterized by Parry and his co-workers (Parry, 1967; Schofield, 1968; Bryceson, 1970). The important features include:

1. A chill phase. This begins about one hour after administration of the antimicrobial agent and terminates 10 to 30 minutes later at the time the spirochaetes disappear from the blood. It is manifest clinically by rigor, tachypnoea, tachycardia, arterial hypertension and an abrupt rise in body temperature. Physiologically, there is

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RESULTS

Comparability

On admission, the white blood cell count and erythrocyte sedimentation rate were higher than were normal in all patients. The liver function tests were abnormal in three of the serum samples.

Severity of Reaction

Table 2 characterizes the Jarisch-Herxheimer-like-reaction after treatment with tetracycline. A similar rise began about one hour after the treatment. The peak temperature was noted 10 to 30 minutes later. The $\Delta T$ was 0.4 °C. It started 24 hours after the treatment. The table shows a comparison of patients treated with the two different drugs.
an increase in cardiac output, an increase in total peripheral vascular resistance, and a decrease in the leucocyte count. The leukopenia is due primarily to a fall in the number of polymorphonuclear cells and is thought to reflect leucocyte sequestration.

2. A flush phase. This begins with the disappearance of the spirochaetes, lasts for several hours, and usually terminates with the full recovery of the patient. At the start of this phase, the patient becomes flushed, diaphoretic and hypotensive. The arterial pressure drops quickly, reaching its lowest point two to nine hours after the rigor. The body temperature continues to rise for a few minutes, peaks, and gradually falls to normal, leaving the patient comfortable, but exhausted. Physiologically, the cardiac output is maintained at high levels. The total peripheral vascular resistance falls at the beginning of the flush and may persist at low levels well into recovery. The leucocyte count returns to normal.

3. Aggravation of myocardial lesions. Electrocardiographic and clinical evidence of disturbed myocardial function is often seen in patients with louse-borne relapsing fever. These abnormalities include: prolonged QTc interval, arrhythmia, elevated central venous pressure, gallop sounds and pulmonary oedema. They often appear or become more marked during the reaction.

RESULTS

Comparability of the Tetracycline and Penicillin Groups (Table 1)

On admission to the hospital, no significant clinical differences were found between the two treatment groups. Similarly, the haemoglobin, haematocrit, and erythrocyte sedimentation rate were the same for the two groups. The initial mean blood spirochaete density of the penicillin treated group was higher than that in the tetracycline treated group. Likewise, admission liver function tests, serum creatinine values and platelet counts were more abnormal in the penicillin treatment group. However, with the exception of the serum creatinine, none of the differences was significant.

Severity of the Jarisch-Herxheimer-like-reaction

Table 2 compares the clinical observations made during the Jarisch-Herxheimer-like-reaction of two treatment groups. A clinical “crisis” characterized by the sudden onset of severe rigors, abrupt temperature rise, tachycardia, tachypnoea and anxiety was observed in all 13 patients treated with tetracycline. The “crisis” began 30-75 minutes (mean 60) after the tetracycline injection and was extremely distressing to the patient. A similar “crisis” occurred in only one patient treated with penicillin. It started 2½ hours after the intramuscular injection.

The $\Delta T$ was greater in the tetracycline patients, due in part to a higher mean peak temperature in this group as compared to the penicillin treated patients (41.3°C vs. 40.8°C). In contrast, both the fever index and the duration of fever were greater in patients treated with penicillin.

A gallop rhythm was heard more frequently during the reaction in patients treated with tetracycline (9/13) than in penicillin treated patients (3/12). The gалlops appeared at the peak of the febrile response and usually did
not persist beyond the period of the reaction. Peak systolic blood pressures and pulse rates were higher in the tetracycline group. This is perhaps best demonstrated by a comparison of the mean rate-pressure products of the two groups. The hypotensive phase that accompanied the return of the temperature toward normal was of equal severity and duration in the tetracycline and penicillin treated groups. One patient developed a supraventricular tachycardia (ventricular rate 240) eight hours after treatment with tetracycline. He was easily converted to normal sinus rhythm by carotid massage. No other arrhythmias were noted.

Table 3 shows the striking fall in the polymorphonucleocyte counts that occurred during the reaction. This fall was more marked in the tetracycline group. Spirochaetes disappeared from the peripheral blood very rapidly in patients treated with tetracycline and shortly after the onset of the clinical crisis (mean disappearance 1½ hours after the start of therapy). Spirochaetes were detected for a much longer period of time (mean 17.3 hours) in patients treated with penicillin.

Relapse

Patients were kept under observation from 8-51 days (mean 13½ days) and no blood smear positive relapses were observed in either treatment group. However, 5 patients, 2 treated with tetracycline and 3 with penicillin, developed fever following treatment for relapsing fever. One patient had an infiltrate on chest x-ray and large numbers of Ascaris lumbricoides eggs in his stool; both the fever and the infiltrate in the chest resolved spontaneously in a few days. A second patient with prolonged fever developed a pleural friction rub with a white blood cell count of 18,000 per c.mm. This resolved without treatment. A third patient developed fever and was treated with chloramphenicol with a decrease in fever. After three days of treatment, the fever recurred while chloramphenicol was still being given. Chloramphenicol was discontinued and the fever disappeared in four days without further therapy.

The fourth patient with prolonged fever received chloramphenicol with a prompt response in his fever after 24 hours. The last patient had a low-grade fever for five days that disappeared without treatment. All 5 patients had several sterile blood cultures, normal white blood cell counts (except no. 2, as noted), several negative blood films for haemoparasites, non-diagnostic acute and convalescent febrile agglutinins, and four had a negative chest x-ray.

DISCUSSION

The treatment of louse-borne relapsing fever with antimicrobial agents has not been entirely satisfactory because of the occurrence of a Jarisch-Herxheimer-like-reaction. This has been noted following treatment with arsenicals (Chung and Chang, 1939), rapidly absorbed penicillin (Taft and Pike, 1945), streptomycin (Narain and Kalra, 1950) and tetracycline (Parry et al., 1967). The mechanism of this reaction is not yet understood. Various investigators have suggested that endogenous pyrogen (Schofield et al., 1968) or endotoxin (Bryceson et al., 1971) released during phagocytosis or destruction of the spirochaetes might account for the reaction. Whatever the mechanism, it is clear that not only is the onset of the reaction temporally related to the disappearance of the spirochaetes from the peripheral bl

Presently, tetracycline is being considered an agent for the treat

Sanford, 1969; Brown et al. (1970), however, noted that the mode of administration was of great importance in determining the speed with which a patient developed a Jarisch-Herxheimer-like reaction. Presently, tetracycline is being considered an agent for the treat...
the peripheral blood, but that the severity of the reaction depends upon the speed with which they disappear (Stuart, 1945).

Presently, tetracycline is the most frequently recommended antimicrobial agent for the treatment of relapsing fever (Harries, 1969; Southern and Sanford, 1969; Bryceson et al., 1970; Parry and Petersdorf, 1970). Bryceson et al. (1970), however, were unable to find a dose of tetracycline or a mode of administration which altered the severity of the reaction or the speed with which the spirochaetes were cleared from the blood. Schuhardt (1952), in a series of in vitro tests, demonstrated that the tetracyclines were rapidly borreliacidal in moderate concentrations. By contrast, penicillin was found to be a slow, but potent, borreliacidal agent. Rykels (1970) noted that patients with louse-borne relapsing fever treated with procaine penicillin had a less severe Jarisch-Herxheimer-like reaction and cleared their peripheral blood of spirochaetes more slowly than a similar group of patients treated with oral tetracycline.

This study provided evidence that the Jarisch-Herxheimer-like reaction can be moderated by using penicillin aluminium monostearate which slowly eliminates spirochaetes from the bloodstream. The clinical crisis was observed in every patient treated with tetracycline. It occurred in only one patient treated with penicillin. This may have been due to rapid drug absorption; variation in rate of absorption is quite high with this preparation (Weinstein, 1965).

It should be emphasized that the marked reactions seen in the tetracycline group followed the intravenous administration of this agent and conceivably might have been less severe if the oral route had been used. Considering our own experience with oral tetracycline in this disease and that of Bryceson et al. (1970), this seems unlikely. There are two major objections to the use of penicillin aluminium monostearate in the treatment of relapsing fever. First, spirochaetes are killed slowly. The spirochaetaemia is thus prolonged as is the total duration of fever. Objective measurements of the possible tissue damaging effects of prolonged fever have not been done, but none of the patients treated with penicillin developed cardiac, renal, or hepatic dysfunction. This possibility needs closer scrutiny and studies are under way utilizing serial electrocardiograms, creatine phosphokinase and isocitrate dehydrogenase, as well as routine liver and renal function tests.

The second objection to the use of penicillin in the treatment of this disease is the reported failure of penicillin in preventing relapses (Heisch, 1950; Taft and Pike, 1945; Muwazi, 1946; Tucker, 1946; Darwish, 1959; Merskey, 1947; Krakowsky and Edelstein, 1949; Kaul, 1949 and Yeo, 1950). It is important to note, however, that all of the above reports deal with tick-borne relapsing fever. A review of the literature, (Greaves et al., 1945; Ingraham and Lapenta, 1946; Ling, 1947; Shaul and Saferstein, 1947; Harrison and Whittington, 1951) in respect to relapse after penicillin in louse-borne disease, reveals only a few instances of prolonged spirochaetaemia and one of recrudescence within three days of treatment with procaine penicillin (Harrison and Whittington, 1951).

Our own experience documents the effectiveness of penicillin aluminium monostearate in the treatment of louse-borne relapsing fever. We watched our patients for an average of two weeks in the hospital and no blood-film-
positive relapse occurred. None of the patients returned at a later date with relapsing fever. It seems to us that the possibility of relapse after penicillin is not a significant argument against its use in the louse-borne disease.

SUMMARY
Twenty-five patients with louse-borne relapsing fever were treated with either a single parenteral injection of tetracycline hydrochloride or penicillin aluminum monostearate. The Jarisch-Herxheimer like reaction accompanying therapy was less severe in the penicillin treated patients. There were no deaths and no relapses noted in either treatment group. Penicillin aluminium monostearate is recommended for the treatment of this disease.

TABLE 1
Pretreatment laboratory values

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAM</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>SGOT (sigma units)</td>
<td>110</td>
<td>47</td>
</tr>
<tr>
<td>Alkaline phosphatase (sigma units)</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Bilirubin (mg.%)</td>
<td>4.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Creatinine (mg.%)</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Platelet Count (per c. mm.)</td>
<td>37,100</td>
<td>50,800</td>
</tr>
<tr>
<td>Spirochaete density (per c. mm.)</td>
<td>57,000</td>
<td>11,000</td>
</tr>
</tbody>
</table>

TABLE 2
Clinical observations during the reaction

<table>
<thead>
<tr>
<th>Observation</th>
<th>Treatment Group</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAM</td>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>P. Value</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Clinical crisis</td>
<td>1/12</td>
<td>13/13</td>
</tr>
<tr>
<td>Temperature change (ºC)</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Fever index (sq. in.)</td>
<td>9.37</td>
<td>3.95</td>
</tr>
<tr>
<td>Duration of fever (hours)</td>
<td>17.2</td>
<td>8.5</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>3/12</td>
<td>9/13</td>
</tr>
<tr>
<td>Pulse x systolic BP 100</td>
<td>118</td>
<td>153</td>
</tr>
</tbody>
</table>

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Ling, C. C. (19
Merskey, C. (19 reference to
TABLE 3
Laboratory observations during the reaction

<table>
<thead>
<tr>
<th>Laboratory observation</th>
<th>PAM Treatment Group</th>
<th>Tetracycline Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial PMN Count (per c. mm.)</td>
<td>6850</td>
<td>6170</td>
</tr>
<tr>
<td>Decrease in PMN Count (per c. mm.)</td>
<td>3060</td>
<td>4560</td>
</tr>
<tr>
<td>Percent PMN Fall (%)</td>
<td>45</td>
<td>74</td>
</tr>
<tr>
<td>Spirochaete disappearance time (hours)</td>
<td>17.3</td>
<td>5</td>
</tr>
</tbody>
</table>

P. Value

>.80
>.40
<.01
<.001

REFERENCES


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**CASE REPORT**

A 16 year old emergency. Fi.

On examination with no palpable uniformly and tenderness. Th was demonstr. A rectal exa.

*Requests for Pathology, F: Addis Ababa.*