A STUDY OF REACTIVE ARTHRITIS AND ITS RELATIONSHIP TO HUMAN IMMUNODEFICIENCY VIRUS INFECTION

BY:

DR ZACHARIAH KASONGO, BSc(HB), MB,ChB (UNZA)

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DISSERTATION FOR THE DEGREE OF MASTER OF MEDICINE (SURGERY) OF THE UNIVERSITY OF ZAMBIA
STATEDMENT

I hereby certify that this study is entirely the result of my individual effort. The sources that I am indebted to, I have acknowledged in the text and in the references.
DEDICATION

To my wife Catherine, and to my children Brian, Ngandwe, Mwape and Malita for their patience and understanding.
DECLARATION

I hereby declare that the work presented in this study for the Master of Medicine Degree (Surgery) has not been presented wholly or in part for any other degree and is not currently being submitted for any other degree.
ACKNOWLEDGEMENTS

I am deeply indebted to the Zambia Army for the financial support. Special gratitude to my supervisor for this project, Professor John Jellis for his valuable suggestions for the methods of data collection and for access to patients under his care.

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LIST OF CONTENTS

A. DEFINITIONS
B. LITERATURE REVIEW
C. INTRODUCTION
D. PATIENTS AND METHODS
E. INVESTIGATIONS
F. TREATMENT PROTOCOL
G. RESULTS
   (i) Clinical features
   (ii) Pathological features
   (iii) Biochemical features
   (iv) Radiological features
   (v) Synovial biopsy
   (vi) Synovial fluid aspirate
   (vii) Excreta
   (viii) Results of treatment
   (ix) Final outcome
H. DISCUSSION
I. CONCLUSIONS
J. REFERENCES
K. TABLES
DEFINITIONS

1. REACTIVE ARTHRITIS describes a non-purulent joint disease developing after infection elsewhere in the body\(^{1}\). It is commonly associated with infections of the urogenital or gastrointestinal tracts\(^{2,3,4}\).

2. THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) is a retrovirus implicated in the causation of the acquired immuno-deficiency syndrome (AIDS) as defined by the World Health Organisation and the Centre for Disease Control (WHO/CDC)\(^{8}\).

3. PERSISTENT GENERALISED LYMPHADENOPATHY (PGL) refers to palpably enlarged lymph nodes of two or more extrainguinal groups, which are not contiguous and for which there is no other cause other than primary HIV infection\(^{32}\).

4. JOINT INVOLVEMENT was considered to be present if there was a history of pain in that joint and pain on passive movement of the joint, with or without joint swelling, tenderness or effusion.
5. **RHEUMATOID ARTHRITIS** was considered present in a joint if there was chronic pain and swelling due to synovial hypertrophy with or without detectable effusion, in a patient with the typical pattern of polyarthritis of medium and peripheral joints typical of this disease.
LITERATURE REVIEW

Reactive arthritis is a relatively new concept. The term was first used by Ahvonen and co-workers in 1969\(^1\) to describe a non-purulent joint disease developing after infection elsewhere in the body, but only more recently has it come into common usage. The examples in humans are the clear associations of infection in the urogenital tract with Reiter's Syndrome and in the bowel with ankylosing spondylitis\(^2\), but reactive arthritis has been observed following Yersinia, Chlamydia, Salmonella, Shigella, Campylobacter and Brucella infections\(^3,4\).

The Association of reactive arthritis with human immuno-deficiency virus (HIV) infection is an interesting recent development. Non-specific arthritis has been reported regularly from this region of Africa, but true rheumatoid arthritis has been uncommon. In 1969, Gelfand\(^5\) reported upon 115 patients admitted with primary joint disorders and found that non-specific arthritis accounted for 63 cases. Turner (1962) and Hall (1966), quoted by Gelfand\(^5\), reported a high incidence of arthritis of an uncertain kind which affected several, mainly large joints with pronounced effusions. The condition ran a fairly typical course, starting in one joint, such as the knee
or ankle, and spreading to two or more other joints. From the University Teaching Hospital (UTH), Lusaka, Zambia in 1978 Jellis\(^{(6)}\) reported non-specific arthritis in 35 of 67 patients who underwent synovial biopsies for suspected tuberculous arthritis over seven years.

In 1992, Jellis\(^{(7)}\) reported an analysis of 147 HIV-positive patients seen in the Orthopaedic Clinic during an eleven-month prospective study to July 1991. Thirty-seven of these patients presented with reactive arthritis.

Rowe and co-workers\(^{(24)}\) investigated 123 patients with HIV infection for musculoskeletal symptoms. Thirty-four patients presented with acute peripheral non-erosive arthritis with an average of four joints affected in each. The knee was involved in 23 of these patients. Various infections were associated with the onset of arthritis and two patients, with a recent history of diarrhoea, had serological evidence of Yersinia infection. No micro-organisms were identified within the joints, except for HIV itself. At the onset of the arthritis, four of these patients had AIDS, but 11 were not suspected of being HIV-positive until tested, following referral for their arthritis.
Rosenberg and colleagues\(^{(25)}\), from an examination of 24 HIV positive patients with arthritis, found reactive arthritis in seven. Kaye\(^{(26)}\) reviewing the literature from 1981 to 1988 for the various rheumatological manifestations of HIV disease noted that Reiter's Syndrome and reactive arthritis were the commonest arthritides seen in HIV-positive patients. Lastly, Jeandel\(^{(27)}\), reviewing rheumatological manifestations during the course of HIV infection, noted that, in tropical Africa, there has been an increase in reactive arthritis of Reiter's type. He went on to postulate that HIV might have a direct arthritic effect.

Bacteria and their products have been linked with many forms of inflammatory reactive arthropathy and rheumatoid arthritis-like disease. Schwab and his colleagues\(^{(14)}\) were able to induce a chronic polyarthritis resembling rheumatoid arthritis by injecting susceptible rats with preparations of bacterial cell walls. Wilder\(^{(15)}\) induced a similar polyarthritis in rats by intraperitoneal injection of dead, sonicated, Group A streptococci and, later, he was able to produce a similar disease with preparations from bacteria that constitute the normal bowel flora of humans.

There are many possible ways in which infection could lead to polyarthritis. One hypothesis is that bacteria at a remote site could induce an antigen-antibody reaction and the antibodies produced could be carried to the synovial membranes of joints, which are part of the sinusoidal tissues of the body.
There the antibodies could cross react with a component of synovial membrane, especially if the bacterial antibodies share similar antigen receptor sites (epitopes) with articular tissue. This molecular mimicry (16) is exemplified in rheumatic heart disease and the arthropathy developing after a streptococcal sore throat.

An alternative hypothesis suggests that bacteria, or their cell walls, may be carried to a synovial joint and lodge in the microvascular endothelial cells of the synovium, which are mononuclear phagocytes of the sinusoidal system. The result would be endothelial cell activation and synovitis (17).

A third hypothesis for the cause of reactive or rheumatoid arthritis is that bacterial cell wall fragments, by their peptidoglycan-polysaccharide moiety, can directly activate the alternative pathway of the complement system. This, in turn, activates local macrophages and T-lymphocytes to produce inflammatory mediators such as interleukin 1, tumour necrosis factor, prostaglandins and superoxide anion. It is suggested that this is the mechanism that induces arthritis in the experiments in susceptible rats (17).
Such experimental reactive arthritis may be perpetuated by the repeated injection of smaller doses of bacterial cell wall preparations. Even preparations from other species of bacteria may then produce the same response.

The molecular size of the cell wall components is important in determining the clinical type of the arthritis. Small cell wall fragments with molecular weights of less than $5 \times 10^6$ induce a fast, but fleeting, response that is apparent within 24 hours. Larger fragments of molecular weight greater than $500 \times 10^6$ produce a slowly evolving persistent chronic arthritis that develops over a period of months. The enterobacteriaceae, which include Shigella and Salmonella, have cell wall components with molecular weights of around $1 \times 10^6$ (18), and consequently are associated with acute arthritis.

Resistance of the cell wall to biodegradation is also a critical determinant in the expression of cell wall induced arthritis in rats (17). Cell walls of Group A streptococci are resistant to mammalian lysozyme. Consequently, phagocytes cannot degrade them, and they will persist in synovium to stimulate chronic inflammatory arthritis. In contrast, cell walls from staphylococci are rapidly degraded by phagocytes and, therefore, these cell walls are poor inducers of chronic arthritis.
As noted above, bacteria may share antigenic epitopes with host tissues. One of these, heat shock protein (65kd protein) is found in both mycobacterial and streptococcal cell walls and has been implicated in arthritis\(^{(17)}\), probably by the same mechanism of molecular mimicry.

A neuronal peptide hormone, substance P (SP), appears to contribute to the severity of experimental arthritis in rats\(^{(19)}\). SP was shown to induce the release of prostaglandin E2 from synoviocytes and to induce their proliferation. SP can also modulate such activities as inflammation, phagocytosis, and T-lymphocyte proliferation, presumably after release from the nerve fibres that innervate joints. It also activates and causes proliferation of the CD4 helper-inducer lymphocytes. Release of SP can be triggered by the microbe or by its cell walls once sequestered in the joint.

Evidence for an infective aetiology for reactive arthritis, rheumatoid arthritis and ankylosing spondylitis in humans has been provided by Ebringer and colleagues\(^{(20)}\). Rheumatoid arthritis has been observed after repeated episodes of Proteus mirabilis infection, especially in people positive for HLA-DR4 antigen, and ankylosing spondylitis after infection with Klebsiella pneumoniae in people carrying HLA B-27 antigen.
The incidence of the HLA B-27 antigen is thought to be low in Sub-Saharan African. In a recent study from Zimbabwe\(^{(21)}\) in which an association was shown between HIV infection and rheumatoid-like seronegative arthritis in 13 individuals, no patient was B-27 positive. This finding is consistent with the work of Woodrow\(^{(22)}\), who has pointed out the virtual absence of the B-27 marker in African blacks. The presence of HLA-DR4 antigen has, however, recently been confirmed in South African Zulus\(^{(9)}\).

Rheumatoid-like arthritis has also been observed in people infected with the spirochete Borrelia burgdorferi, which causes Lyme disease\(^{(3)}\).

A viral aetiology for rheumatoid arthritis has also been considered by some investigators although such a hypothesis would be difficult to prove. Epstein-Barr virus, parvovirus and retroviruses have all been suggested at one time as causative agents, but there is little hard evidence for a direct viral aetiology.
INTRODUCTION

In Lusaka, a rising incidence of both reactive arthritis and HIV disease has been noted (7), and one of the prime objectives of the study was to investigate the relationship of these two diseases. There are no figures from previous years for the incidence of reactive arthritis but it seems to have been uncommon (6).

In view of the sharp rise in reported cases of reactive arthritis and the apparent association of reactive arthritis with HIV infection, it was decided to study the disease in detail.

The main objectives were to determine the clinical and pathological characteristics of reactive arthritis and to elucidate whether the disease in HIV-positive patients was a distinct clinical entity.

A secondary objective was to study the effects of non-steroidal anti-inflammatory analgesic drugs (NSAIDS) on the course of reactive arthritis.

This prospective study covered the period from March 1991 to September 1992.
PATIENTS AND METHODS

In total, 215 patients entered the study. Most were referrals from the medical and surgical out-patient clinics of UTH, but some were from peripheral provincial or district hospitals. The patients admitted to the study were adults (aged 14 to 60 years) with arthritis in which trauma, tuberculosis, gout and joint sepsis had been excluded as aetiological factors. Rheumatoid arthritis and rheumatoid-like arthritis were included because the clinical distinction between reactive and rheumatoid arthritis is not clear cut.

A special out-patient clinic was opened for patients with reactive arthritis. They were briefed individually on the objectives of the study and told in confidence that among other tests HIV serology would be done to see if the virus was implicated in the aetiology or changed the response to treatment. They were further informed that a questionnaire would be opened and updated at subsequent visits and that they would be followed, initially fortnightly, then at longer intervals if symptoms improved, for a total of six months. They were all to start on acetylsalicylic acid (Aspirin) irrespective of whether they had been on this drug previously, before switching over to indome-thacin (Indocid). This would provide a baseline for the study and assist in interpreting the subjective and objective response to treatment. Antibiotics and steroids were to be used rarely, and only as a last resort for resistant cases.
Of the 215 patients seen, 119 completed the study. There were three main reasons for the large drop out.

Fifty-four (60%) of these 96 patients, objected to the repetition of Aspirin or Indocid with which they had already been treated by the referring doctor at irregular intervals, but without any effect. In other words, they expected a better and stronger drug with an antibiotic dispensed concurrently. Although the questionnaire was opened and clinical data entered, this group had no laboratory tests done and did not return for follow up.

Twenty-seven patients (30%), tried both Aspirin and Indocid for a total of two months without response. Their final comment was "What next, Doctor?", and they quietly disappeared from the scene. These had had some laboratory tests done.

Very few patients left the study because they objected to HIV testing. Many indirectly volunteered to have the test at the first visit by requesting for, "even the most embarrassing blood test of this century", so that, "this thing eating me slowly inside can be detected and rooted out permanently".

Distance of residence from the hospital should not have influenced the drop-out rate, because the intervals between
reviews were long enough to allow an individual or his relations to organise transport to hospital.

Those who completed the study came to appreciate the polite and sympathetic reception from the nursing staff at the clinic and the individual attention given to each patient, attention which they claimed had not been accorded at the referring clinics. Adequate stocks of Aspirin and Indocid ensured that patients never ran out of medicines and this too was an incentive for them to return for review.

For each patient, a standard questionnaire was completed which comprised the following data:

(a) **PERSONAL IDENTITY**

Name, Age, Sex, marital status, occupation, best contact address, file number and orthopaedic study number.

(b) **HISTORY**

Note was made of duration of illness, date of presentation at clinic, date and mode of onset. In the systematic
review, a record was made of joints affected and the
order of involvement, and any history of weight loss,
fever, sweats, diarrhoea, dysuria and urethral discharge for one
or more months, as well as of previous admissions.

(c) **PHYSICAL EXAMINATION**

A general examination record was made of habitus (normal/
thin/ectoectic); lymphadenopathy (symmetry/size/site of
largest node); recent skin rash, genital ulcer or infection
and any oral pathology. The patient was examined for joint
swelling, tenderness, effusion, range of movement and wasting
of adjacent muscles in addition to other systems.

On completion of the examination, each patient was
categorised as having reactive arthritis or not and
his/her clinical HIV stage and performance scale were recorded
according to the WHO/CDC criteria\(^{(8)}\). This performance scale
is as follows:

Scale 1: Patient asymptomatic, normal activity.

Scale 2: Symptomatic, normal activity.

Scale 3: Bedridden less than 50% of the day during
last month.

Scale 4: Patient bedridden more than 50% of the day
during last month.
(d) INVESTIGATIONS

Investigations included in the protocol and done at first visit were:

Haemoglobin

Total white cell and differential counts,

Erythrocyte sedimentation rate (ESR, Westergren),

Uric acid,

Serology for HIV,

VDRL,

Anti-streptolysin 'O' titre (ASOT), and

Rheumatoid factor (Rh factor).
Haematological tests were done on the Cobas Argos 5 diff. haematology analyser (Roche); uric acid was estimated by an enzymatic calorimetric method with uricase and 4-aminophenazone (uric acid PAP-Roche). ASOT and rheumatoid factor were determined by a simple particle agglutination test and were not quantified. Antibodies to HIV were detected by a competitive enzyme-linked immunosorbent assay (ELISA) (Wellcome recombinant ELISA, new generation) and non-competitive ELISA (Wellcome HIV1 and 2).

Aspiration of joints was performed at the first visit to the clinic by the investigator using aseptic technique. The overlying skin was cleaned with 70% methylated spirit. A 19-gauge needle and a 10ml syringe were used for aspirating the joints. Specimens were put into sterile bottles and immediately taken to the laboratory.

Stool or rectal swabs were collected in the laboratory by the technician assigned to the project.

The aspirates, stool or rectal swabs were examined by a microbiologist by microscopy, and culture and antibiotic sensitivity tests were performed using standard techniques for both aerobic and anaerobic bacteria (29). Stool was further processed (28) for the isolation of Salmonella, Shigella, Yersinia and other enteropathic bacteria.
Radiology of the chest and affected joints, and synovial biopsies, were deemed desirable investigations, but it was not considered feasible or ethical to do these tests on all patients. They were only done on a few selected patients, notably those with unrelenting disease.

(e) TREATMENT PROTOCOL (Fig 1)

All patients were given Aspirin for the first two weeks. The dose was 600mg four times a day (qid) for patients weighing 50kg or less and 900mg qid for patients weighing more than 50kg.

To minimise the side effects (eg abdominal pain and gastro-intestinal bleeding) sometimes associated with such a high dosage, patients were advised to take the Aspirin with food or milk.

Response to medication was assessed subjectively by subsidence of joint swellings and effusions and improved range of movement of affected joints. In the patients who responded to Aspirin, treatment was stopped at four weeks, but they were still followed up at the clinic.

Patients who failed to respond to the initial Aspirin course or relapsed after initial response, were switched to Indocid, which was also taken with milk or food. They were started on 25mg three times a day (tds) for two
weeks and medication was stopped after four weeks if there was a good response. If the response was poor after two weeks, the dose of Indocid was increased to 50mg tds and continued for a further four weeks if there was good response. Otherwise, medication was stopped at two weeks if there was a poor response. The treatment schedule is shown as a flow chart in figure 1.

On both regimes, patients were given supportive therapy, which included rest of the affected joints during exacerbation of symptoms, and they were taught simple active mobilising exercises when they became pain free. If the pain and joint swellings were severe and incapacitating the patient was admitted to the ward, but most patients were managed and followed up as out-patients.

Tense effusions were aspirated and any diarrhoea or urinary tract infections were treated. If repeated cultures of synovial effusions and excreta proved negative and the patient remained symptomatic in spite of the full treatment regime, an intra-articular injection of methylprednisolone (Depomedrol) and an oral antibiotic (eg tetracycline) was prescribed and the effect assessed.
After six months, the data was analysed. The patients were divided into two main groups:

Group 1  HIV-positive, and

Group 2  HIV-negative

The HIV-negative patients with reactive arthritis were used as controls to see whether their disease and their response to treatment was different from that of the HIV-positive patients.
RESULTS

1 CLINICAL FEATURES

A total of 215 patients were examined. Although some were excluded from subsequent analysis because they did not complete the trial, their clinical disease and the joints affected were recorded. The pattern was found to be similar to the remaining 119 patients (85 males and 34 females) who were further investigated. Of these, 65 patients (54.6%) were HIV-positive (44 males and 21 females) (Group 1) and 54 (45.4%) were HIV-negative (41 males and 13 females) (Group 2). The mean age of patients in Group 1 was 30 years (range 16-48 years) and the mean age of the patients in Group 2 was 32 years (range 14-52 years).

In Group 1, the relationship of the onset of arthritis to the stage of HIV disease was noted. Of the 65 HIV-positive patients, 20 had no clinical signs of HIV disease (Stage 0). Eleven patients had generalised Lymphadenopathy alone (HIV clinical stage 1), and 15 had lymphadenopathy and weight loss of less than 10% of body weight (HIV clinical stage 2). Nine patients were found to have generalised lymphadenopathy, persistent diarrhoea, febrile episodes and weight loss of more than 10% (HIV clinical stage 3), and 10 had frank AIDS.
In Group 2 (HIV-negative patients), 38 patients also had clinical signs that could be related to HIV infection. Sixteen patients had no such clinical sign (Stage 0), while four were placed in HIV clinical stage 1, 23 in stage 2, 5 in stage 3 and 6 had AIDS.

Thus 16 patients, 10 in Group 1 and 6 in Group 2, on clinical examination had AIDS, as defined by the criteria of the World Health Organisation and Centre for Disease Control (WHO/CDC)\(^8\) at the time that they presented at the Orthopaedic Clinic.

In Group 1, the mode of onset was spontaneous in 77% and followed an attack of dysentery in 23%. In Group 2, these figures were 67% and 33% respectively. No patient had reactive arthritis associated with urethritis, despite the fact that many patients were young and gave a history of previous sexually transmitted disease.

The joints affected by reactive arthritis were typically diffusely and moderately swollen and warm. A few patients, however, had cool but swollen joints. Swollen joints were tender and there was moderate pain on movement which, together with swelling and effusion, limited the range of movement for that particular joint. Wasting of adjacent muscles was noted only in long-standing cases of reactive arthritis. The effusion fluid was either clear and straw-coloured or slightly turbid.
In Group 1, the pattern of joint disease (Fig 2) was oligo-articular (one to five joints affected) in 54 (83%) patients, or polyarticular (more than five joints affected) in 11 (17%). In Group 2, the disease was oligo-articular in 52 (96%) and polyarticular in only 2 patients (4%). Although there was a higher proportion of HIV-positive patients with polyarthritis this did not reach statistical significance. Joints involved (Fig 3 and 4) were mainly the knee (Fig 5), ankle, wrist and elbow with hip, interphalangeal and shoulder joints involved in a small number of cases. In those with polyarthritis, there was a typical rheumatoid pattern of involvement of the hands (Fig 9).

When patients were asked to indicate one joint as being the worst, the knee had an even greater predominance (Fig 5, 6). In most patients, the most severely affected joint was affected bilaterally (Fig 7), but where only one side was affected it was more commonly the right side in both Group 1 and Group 2 patients. The knees, ankles and wrists were similarly the main joints involved in the 96 patients that were clinically examined, but excluded from further study because they defaulted before their HIV status was known.

The duration of symptoms from onset to presentation at the clinic in both HIV-positive and HIV-negative patients was between one and three months.
<table>
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<tr>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Variable</th>
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<tr>
<td>HIV-NEGATIVE (n=54) AND HIV-NEGATIVE (n=59) PATIENTS</td>
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TABLE 1: COMPARISON OF HEMATOLOGICAL DATA BETWEEN HIV-POSITIVE AND HIV-NEGATIVE PATIENTS

The hematological features are summarized in Table 1.
Although the mean values for haemoglobin, total white cell count and absolute lymphocyte count were lower in Group 1 patients, the difference was not statistically significant. The mean ESR was higher in Group 1 patients and this reached statistical significance (P=0.004). The difference was more marked in the AIDS patients.

3. SEROLOGICAL AND BIOCHEMICAL VARIABLES

A rheumatoid factor test was performed in 26 HIV-positive patients (4 positive, 22 negative) and in 24 HIV-negative patients (5 positive, 19 negative).

A VDRL test was performed in 38 HIV-positive patients (1 positive, 37 negative) and 36 HIV-negative patients (2 positive, 34 negative).

An ASOT was performed in 25 HIV-positive patients (6 positive, 19 negative) and 25 HIV-negative patients (5 positive, 20 negative).

A uric acid estimation was done in 16 HIV-positive patients, mean 0.34mmol/l (range 0.13-0.4) and in 15 HIV-negative patients, mean 0.35mmol/l (range 0.12-0.58). Normal range Uric acid 0.12-0.42mmol/l.

There were no statistically significant differences in the values between the two groups.
4. **RADIOLOGICAL FEATURES**

Twenty joint radiographs and 31 chest radiographs were done. Radiographs of affected joints were normal in 18 patients (12 HIV-positive and 6 HIV-negative). In two others there were early osteoarthritic changes in the knees. One chest radiograph showed evidence of healed tuberculosis and the rest were normal.

5. **SYNOVIAL BIOPSY**

Histological study of open knee joint synovial biopsies from eight selected patients with marked joint swelling (five HIV-positive and three HIV-negative) revealed chronic inflammatory infiltrate mainly lymphocytes and polymorphonuclear leucocytes with non-specific changes (Fig 10).

6. **SYNOVIAL FLUID**

Straw-coloured or slightly turbid synovial fluid was aspirated in 32 patients (22 HIV-positive and 10 HIV-negative). The fluid contained many cells. These were mainly lymphocytes and polymorphonuclear leucocytes, with either predominating, and occasional plasma cells were present.

For 10 patients (6 HIV-positive and 4 HIV-negative), a cell count was performed on the aspirated synovial fluid. In each case there were over 100 cells per high-power field, predominantly lymphocytes. All showed no growth on attempted culture.
7. **EXCRETA**

Forty-four unselected patients (24 HIV-positive and 20 HIV-negative) had stool cultured and in only one patient was a chloramphenicol-sensitive Salmonella species grown. The patient was seronegative and had presented with diarrhoea predating his arthritis. His diarrhoea and arthritis completely resolved on treatment with chloramphenicol.

Two seropositive patients had Ascaris lumbricoides ova in their stool and were treated with pyrantel pamoate (Combantrin), but this did not influence the course of their arthritis.
8. RESULTS OF TREATMENT

TABLE II  RESPONSE TO TREATMENT IN GROUP 1 (HIV-POSITIVE)
(n=65) AND GROUP 2 (HIV-NEGATIVE) (n=54) PATIENTS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HIV SEROLOGY</th>
<th>NOT TRIED</th>
<th>PATIENT GOT WORSE</th>
<th>NO CHANGE</th>
<th>IMPROVED</th>
<th>TOTAL</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
<td>HIV +ve</td>
<td>1</td>
<td>17</td>
<td>28</td>
<td>19</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>HIV -ve</td>
<td>1</td>
<td>15</td>
<td>23</td>
<td>20</td>
<td>54</td>
</tr>
<tr>
<td>Indocid</td>
<td>HIV +ve</td>
<td>18</td>
<td>1</td>
<td>19</td>
<td>11</td>
<td>49</td>
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<td>(normal dose)</td>
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<tr>
<td></td>
<td>HIV -ve</td>
<td>15</td>
<td>2</td>
<td>16</td>
<td>15</td>
<td>48</td>
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<tr>
<td>Indocid</td>
<td>HIV +ve</td>
<td>43</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>49</td>
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<td>(high dose)</td>
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<tr>
<td></td>
<td>HIV -ve</td>
<td>44</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>48</td>
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</table>

Two patients gave a definite history of peptic ulcer disease and were, therefore, not given Aspirin, but commenced on Indocid which they tolerated well. The nine patients (six HIV-positive and three HIV-negative) who failed to respond to high-dose indomethacin were given a combined course of indomethacin, tetracycline and methylprednisolone.

9. FINAL OUTCOME

The outcome of both groups at 6 months is shown in figure 8. It is of note that only 3 (4%) of the HIV-positive group returned to normal while 12 (22.9%) of the HIV-negative group had done so.
DISCUSSION

Reactive arthritis describes a non-purulent joint disease developing after infection elsewhere in the body\(^1\). Well recognised examples are the clear association of urethral infection with Reiter's Syndrome and of bowel infection with ankylosing spondylitis\(^2\). Reactive arthritis has also been observed following Yersinia, Chlamydia, Salmonella, Shigella, Campylobacter and Brucella infections.\(^3,4\)

Reactive arthritis is now thought to be at one end of a spectrum of disease that has true rheumatoid arthritis at the other extreme. Indeed, it may well be that they share a common aetiology and that differences are a matter of degree of chronicity and immune response. The association of HIV disease with reactive arthritis is a further recent development that this investigation was designed to study.

Non-specific arthritis has regularly been reported from this region of Africa\(^5\), but until recently, true rheumatoid arthritis has been uncommon. Now the incidence of rheumatoid arthritis is increasing and the Uganda experience is typical\(^9\). There have been progressively larger series of patients with rheumatoid arthritis reported from Mulago Hospital, culminating in a series of 404 patients with classical rheumatoid arthritis, the largest series from Africa so far. In earlier
reports, rheumatoid arthritis appeared as a mild disorder with few extra-articular features, low morbidity and a low rate of seropositivity for the rheumatoid factor. Only during the last decade, have reports included many cases of severe disease, a high rate of rheumatoid seropositivity and much disability. Reports from Kenya (10), Central Africa (11) and Southern Africa (12) have mirrored the Ugandan experience.

In Lusaka, a rising incidence of both reactive arthritis and HIV disease has been noted (7) and one of the prime objectives of this study was to investigate the relationship of these two diseases. There are no figures from previous years for the incidence of reactive arthritis, but it seems to have been uncommon (6).

During a period of six months in 1992, Kehoe and Jellis (13) investigated the HIV status of 100 adults (15 to 55 years) admitted to the University Teaching Hospital with fractures. Thirty-two percent of these patients proved to be HIV-positive. The authors suggested that this figure can be taken to illustrate the incidence of HIV disease in the adult population, because it represents a random group of adult patients whose only criterion for admission was that of trauma. All 32 patients had very early HIV disease clinically.

In this study of reactive arthritis, 55% of patients were HIV-
seropositive, suggesting a strong association of the two diseases. Most of the seropositive patients had clinical signs of HIV disease and, in fact, many of the seronegative patients also had signs of HIV disease, an observation which will be discussed later.

Gelfand, Hall and Turner (5) investigated patients with primary joint disorders and found non-specific arthritis which affected large joints especially the knees and ankles with pronounced effusions. The condition started in one joint and spread to other joints. Jellis (7), Rowe and co-workers (24) investigated patients with reactive arthritis and noted a similar pattern of joint involvement.

In the present study, few differences were found in the character of the reactive arthritis between the patients in Group I (HIV-positive) and Group II (HIV-negative). The numbers of joints involved, the location of the involved joints, the extent of joint swelling and tenderness, the duration of symptoms and signs and the response to treatment were all very similar. It is likely, therefore, that we are dealing with the same disease in the two groups of patients and that the HIV is not directly responsible for reactive arthritis.
There were slight differences, however, in the mode of onset of reactive arthritis between the two groups of patients. More of the sero-positive patients had an apparently spontaneous onset of arthritis, while in the HIV-negative patients there was more often a history of diarrhoea predating their arthritis. It is well known that HIV-positive patients experience frequent bacteraemias(3) and it is possible that the recurrent bacteraemias are responsible for the increased incidence of reactive arthritis in this group.

Among the sero-negative patients, some had clinical signs and symptoms of HIV disease. During the study period there was a considerable outbreak of diarrhoeal diseases in Lusaka.(33) Many of these patients presented with symptoms and signs (fever, diarrhoea, weight loss and lymphadenopathy) common in HIV infection and they were therefore clinically categorised as HIV-positive. These signs could, however, have been due to debility from their chronic diarrhoea.

Six HIV-negative patients were clinically diagnosed as having AIDS. The possibility exists that these were patients with pre-terminal HIV disease who had lost their ability to form antibody and therefore tested HIV-negative(32).
Among the investigations done, radiographs, synovial biopsies and microbiological studies did not help to elucidate the problem. The negative stool cultures probably reflected the fact that the causative organism had been eradicated by previous antibiotic therapy. All synovial aspirates proved sterile on attempted culture. This was also the experience of Rowe and Foster\(^{(24,31)}\) in their study of rheumatological lesions in individuals with HIV infection.

The haematological values were not significantly different between the two groups, except for the sedimentation rates which were higher in the HIV-positive patients. Although the ESR is, by itself, a non-specific finding in most disorders, many HIV-positive patients have a high ESR even without having reactive arthritis. The high ESR observed may be an expression of HIV disease rather than of reactive arthritis in this group, or a summation of both factors.

Although there were many low values for haemoglobin, total white cell counts and absolute lymphocyte counts, the mean values fell within normal limits for both groups of patients. This probably explains how these patients managed to mount such good resistance to their infections. The two patients who died during the course of treatment already had frank AIDS when referred to the Orthopaedic Clinic.
Few patients had polyarticular disease, but the involvement of the large joints of the limbs, particularly the knees, ankles and elbows, makes reactive arthritis a particularly disabling disease.

Nonsteroidal anti-inflammatory analgesic drugs (NSAIDS) were used in treatment because of their anti-prostaglandin effect \(^{30}\). Although beneficial in the relief of symptoms in both groups of patients, their use was not associated with significant regression of the arthritis, particularly in the patients who developed AIDS.

There were fewer patients who got worse while taking Indocid than on Aspirin, so that Indocid might be considered the more effective drug. There were, however, more patients who actually improved on Aspirin in both groups, but this may have been simply because more patients were kept on Aspirin. High-dose indomethacin was given only to a very few patients, because it was considered that most were faring well on the lower dosage. Using the Chi-squared test, there was no significant difference between the responses in Groups I and II.

Steroids, antibiotics and high dose indomethacin did not offer extra benefit in the nine patients whose response to high dose indomethacin was poor. Since these drugs are relatively more expensive and may be attended by more side effects, it would be wise to limit their use to those few cases with unrelenting disease and, once the patients' condition stabilises, to switch them back to Aspirin or low dose indomethacin as soon as possible. In Rowe's
series\(^{(24)}\), the response to NSAIDS in patients was equally poor and most of the patients relapsed after a temporary initial improvement.

There was a better outcome for the sero-negative patients, more of whom became free of arthritis. They probably had a better anti-inflammatory response due to their immune competence.
CONCLUSIONS

1. There appears to be an increased occurrence of reactive arthritis associated with HIV infection. This is of particular interest because of the possible role of micro-organisms in the pathogenesis of the rheumatoid series of arthritides.

2. Reactive arthritis appears to be a distinct disease, clinically and pathologically distinguishable from other forms of arthritis. Reactive arthritis predominately affects the knee, ankle, elbow and wrist joints, often bilateral and is associated with bowel symptoms, particularly diarrhoea. There was chronic non-specific synovitis and effusion with white blood cells but sterile on culture. Few cases showed rheumatoid-like polyarthropathy.

3. HIV virus did not appear to be a specific trigger. Probably reactive arthritis is due to the antigenic effect of bacterial cell wall proteoglycans from infection in the body, notably the bowel and genito-urinary tract. The increased incidence of reactive arthritis in HIV-positive patients was probably due to the high prevalence of bacteremias especially from infection in the gut which makes them more susceptible to arthritis.
4. Aspirin and Indocid were found to be beneficial in controlling arthritic symptoms, although they did not offer a permanent cure. The response to these drugs was better in sero-negative patients.

5. It is suggested that future research in this field should be directed towards isolating and analysing specific mediators and elucidating their roles in the inflammatory response, as well as studying the symptomatology and measures of prevention and treatment. The possibility of a direct cause-effect of the HIV on the synovial membrane as a trigger of arthritis should equally be investigated.
REFERENCES


Fig. 1: Flow chart showing plan of management.
Fig 2: Pie charts showing percentages of patients in each group with the indicated number of involved joints.
Fig 3: Histogram showing the distribution of all involved joints in both groups (HIV-positive and HIV-negative) together.
Fig 4: Pie chart showing percentages of all involved joints in both groups (HIV-positive and HIV-negative) together.
Fig 5: Histogram showing the distribution of the main joint involved in both groups (HIV-positive and HIV-negative) together.
MAIN JOINT

Legend
K = Knee joint
H = Hand
P = Foot
E = Elbow joint
W = Wrist joint
MP= Metacarpo-phalangeal joint
S = Shoulder joint

HIV-positive

HIV-negative

Fig. 6: Pie charts showing the distribution of the main joint involved in HIV-positive and HIV-negative patients
Fig 7: Pie charts showing the side of involvement of the main joint (right, left or bilateral).
Fig 8: Pie charts showing final outcome in the HIV-positive and HIV-negative patients.
Fig 9: Photograph showing rheumatoid pattern of involvement of interphalangeal joints of right hand in HIV-seropositive patient with reactive arthritis. Normal left hand for comparison.
Fig 9b: Photograph showing swollen right knee in a 30-year-old seropositive man with reactive arthritis. Normal left knee for comparison.
Fig 10: Synovial biopsy from the knee of a 20-year-old female with reactive arthritis showing evidence of chronic inflammatory cells.