A RETROSPECTIVE ANALYSIS OF SPONDYLOARTHROPATHIES AT THE RHEUMATIC DISEASES UNIT, UNIVERSITY OF CAPE TOWN, OVER THE PERIOD 1988 - 1994.

VANESSA CELESTE BURCH

A Dissertation submitted to the Faculty of Medicine in the University of Cape Town in fulfilment of the requirements of Part III of the Degree of Master of Medicine.

ACKNOWLEDGEMENTS

I gratefully acknowledge the following :

- Dr A A Kalla, Supervisor, for inspiring me to undertake this project

- Professor Janet Seggie for encouragement and interest, always prepared to share her experience and listen to my ideas

- Mrs Indi Farmer for typing all the drafts, including the final copy, of this document

- Mrs Cynthia Woollgar for printing the figures in this document

- Mrs Josephine Bredenkamp for retrieving case notes and folders from the Records Department at Princess Alice Orthopaedic Hospital

- Mrs Merle Meier for assisting me in obtaining Outpatient Department statistics at Princess Alice Orthopaedic Hospital

- Sister Delicia Ward for assisting me in the use of the computerised database at Princess Alice Orthopaedic Hospital

DECLARATION

I declare that this dissertation is my own unaided work. It is being submitted for Part III of the degree of Master of Medicine in the University of Cape Town. It has not been submitted before for any degree or examination in any other university.

signature removed

Signed by candidate

23rd day of 19 96

To my friend, Martie

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aa	atlanto-axial
AAU	acute anterior uveitis
AC	arthritis clinic
AIDS	Acquired Immunodeficiency Syndrome
AS	ankylosing spondylitis
BCG	Bacillus Calmette Guerin
DISH	diffuse idiopathic skeletal hyperostosis
DMARD	disease-modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
EA	enteropathic arthritis
ECG	electrocardiogram
ESSG	European Spondyloarthropathy Study Group
GIT	gastrointestinal tract
GSH	Groote Schuur Hospital
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hsp	heat shock protein
IBD	inflammatory bowel disease
IgA	immunoglobin A
MCP	metacarpophalangeal
NASS	National Ankylosing Spondylitis Society
NSAID	non-steroidal anti-inflammatory drug
OPD	Outpatient Department
PAOH	Princess Alice Orthopaedic Hospital
PCR	polymerase chain reaction
PID	pelvic inflammatory disease
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RDU	Rheumatic Diseases Unit
ReA	reactive arthritis
SD	standard deviation
SpA	spondyloarthritis/arthropathy
STD	sexually transmitted disease
THR	total hip replacement
TKR	total knee replacement
UCT	University of Cape Town
UGT	urogenital tract
USpA	undifferentiated spondyloarthropathy

C H A P T E R O N E

INTRODUCTION AND LITERATURE REVIEW

1. SPONDYLOARTHROPATHY

   1.1 Traditional spectrum of disease

   1.2 Undifferentiated spondyloarthritis

   1.3 Juvenile-onset spondyloarthritis

2. THE HLA-B27 ASSOCIATION

3. BACTERIAL PATHOGENS AND SPONDYLOARTHROPATHY

4. SPONDYLOARTHRITIS IN AFRICA, AND SOUTH AFRICA IN PARTICULAR

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1. SPONDYLOARTHROPATHY

Seronegative spondyloarthropathy (1) is a term introduced in 1974 to describe a group of interrelated arthritides characterised by the following features (2) :

- spinal (including sacroiliac joint) involvement
- enthesitis
- asymmetric peripheral arthritis of predominantly the lower limbs
- familial tendency
- negative rheumatoid factor, and an
- Human Leukocyte Antigen (HLA)-B27 association.

This was amended to *spondyloarthropathy* later with the recognition that a small percentage of normal adult populations worldwide are rheumatoid factor positive, and that the prevalence thereof increases with advancing age (3).

1.1 Traditional spectrum of disease

Spondyloarthropathy embraces a spectrum of conditions (1,4,5) encompassing :

- ankylosing spondylitis
- psoriatic arthritis
- enteropathic arthritis
  and
- reactive arthritis, including Reiter's syndrome.

Classification and/or diagnostic criteria are well established for the above subgroups and are detailed in Appendix A (p.82-86).

1.2 Undifferentiated spondyloarthritis

Recently it has been recognised that the rigid confines of the spondyloarthropathy complex, as outlined above, artificially restrict the existing disease spectrum (15).

Consequently, some spondyloarthropathy patients lacking sufficient traditional criteria for one or other of the well-defined subgroups, have been excluded from epidemiological and clinical studies (16,17). The European Spondyloarthropathy Study Group (ESSG) addressed this issue in 1991 (15). They proposed preliminary criteria for the purpose of identifying the broader spectrum of spondyloarthropathies (Appendix B, p.87).

These criteria serve particularly to include the previously excluded group, which is now referred to as *undifferentiated spondyloarthropathy*. Inclusion of patients fulfilling criteria for undifferentiated spondyloarthropathy in current and future studies helps in identification of patterns of disease expression and understanding of the natural history of the disease. The likelihood exists that concepts long adhered to in the previously restricted spondyloarthropathy spectrum would need to be significantly altered. The following two examples emphasise this point :

(a) Isolated circumpolar Eskimo populations have an exceptionally high background prevalence of HLA-B27, of the order of 25-40% (18). A community-based

study of this group (19) demonstrated a 1.3% prevalence of spondyloarthritis in 464 patients examined. This is strikingly higher than the widely quoted prevalence of 0.2% for ankylosing spondylitis in Caucasian populations world-wide (17), and reflects the high HLA-B27 prevalence in Eskimos. Interestingly in this study, the prevalence of ankylosing spondylitis, reactive arthritis and undifferentiated spondyloarthritis was similar. Thus undifferentiated spondyloarthropathy, previously ignored, may assume the same status as ankylosing spondylitis in the broader spectrum of spondyloarthropathy, at least in certain populations.

(b) Amongst patients with undifferentiated spondyloarthritis, reviewed by Zeidler et al (16) in a long-term follow-up study, 25-59% developed ankylosing spondylitis within a ten-year period. As the authors suggest, the term *undifferentiated spondyloarthritis* is best considered a working diagnosis while this subgroup undergo further study in terms of pathogenesis and disease expression.

Clearly there is an ongoing need to study this particular subgroup of spondyloarthropathies more carefully.

1.3 Juvenile-onset spondyloarthritis

HLA-B27 associated rheumatic diseases of childhood onset also form part of the spondyloarthropathy complex, and

include juvenile-onset ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis and reactive arthritis (20). These conditions are often diagnosed retrospectively, since axial involvement (both clinically and radiologically) is present in less than one-quarter of patients at onset of disease (21), and the interpretation of radiographic sacroiliitis is limited by normal growth in childhood which causes blurring of the sacroiliac joint margins per se (22).

Owing to these limitations, the diagnosis of juvenile spondyloarthritis is best considered within the broad context of the seronegative enthesopathy and arthropathy (SEA) syndrome (23). The SEA syndrome includes all rheumatoid factor negative children, aged 16 years or less, presenting with arthralgia (in the presence or absence of objective signs of synovitis) and enthesitis. Long-term follow-up of these children, presenting with a constellation of musculoskeletal complaints for which a clinical diagnosis is not immediately apparent, has shown that a significant proportion go on to develop features characteristic of one or other spondyloarthropathy disorder. This is well illustrated by a recent study in which 75% of children presenting with an initial diagnosis of SEA syndrome, developed sufficient clinical and radiographic axial features to satisfy a diagnosis of ankylosing spondylitis within five years of disease onset (24).

Thus, as in adults, the spondyloarthritis spectrum has been expanded so as to identify as many clinically relevant patients as possible. This affords future research opportunities already alluded to in the context of adult-onset disease.

2. THE HLA-B27 ASSOCIATION

An association of the HLA-B27 (class I) antigen and spondyloarthropathy disorders, was described more than twenty years ago (25,26). In most Caucasian populations with ankylosing spondylitis, more than 90% of cases are HLA-B27 positive (27, quoted in 5). This contrasts strikingly with the general HLA-B27 prevalence in Caucasians of about 8% (27, quoted in 5).

A similar but slightly less striking association, (about 80% in most cases), has also been demonstrated in reactive arthritis (28,29).

In psoriasis and inflammatory bowel disease, spondylitis accompanied by sacroiliitis is almost as tightly associated with HLA-B27 as is ankylosing spondylitis. Peripheral arthritis in this setting is, however, not as closely associated with HLA-B27 (30).

In view of the strong overall HLA-B27 association, the spondyloarthropathies are referred to by some as *HLA-B27-associated diseases* in order to highlight the pivotal role that the histocompatibility antigen plays (30).

It is well recognised that the disorders, in particular ankylosing spondylitis, may also occur in the absence of HLA-B27 (31-34). This is true of population groups where the background prevalence of HLA-B27 is low, including genetically unmixed native populations of South America, Blacks and San Bushmen of Equatorial and Southern Africa, Aborigines of Australia, and people of the Eastern Polynesian Islands and Japan (35,36).

Black Americans have a background prevalence of HLA-B27 in the order of 2-4% (32,37) as compared to the previously quoted figure of 8% for American Caucasians. Only about 50% of American Blacks with ankylosing spondylitis are HLA-B27 positive (32), compared to more than 90% of Caucasian ankylosing spondylitis subjects. In circumstances of reduced HLA-B27 prevalence therefore, the association with ankylosing spondylitis is less impressive and the prevalence of HLA-B27 negative disease is correspondingly greater (17). This phenomenon is not restricted to Black populations, but has also been observed in certain European Caucasian groups; for example, an HLA-B27 prevalence of only 42.8% was recorded in ankylosing spondylitis subjects identified in a Dutch population survey (38).

The occurrence of spondyloarthropathy in the absence of an association with HLA-B27 has raised the question of clinical differences based on HLA-B27 status. This has been extensively debated in the literature, and the data to date has been reviewed by Linssen and Feltkamp (30). They conclude that in ankylosing spondylitis, aside from the positive

association of acute anterior uveitis with HLA-B27, the clinical and radiographic differences ascribed to HLA-B27 status largely reflect patient selection. Studies of ankylosing spondylitis in which patients with spondylitis associated with psoriasis and inflammatory bowel disease were included (39,40), tended to indicate a later age of disease onset, and a milder clinical course (judged by the development of 'bamboo spine' changes on radiographs) in HLA-B27 negative individuals. However, carefully conducted studies in North America (33) and Europe (34), which only included primary ankylosing spondylitis cases, failed to show any differences in age of onset, prevalence of peripheral arthritis, severity of pain and disability or spinal radiological abnormalities which could be ascribed to HLA-B27 status. These studies demonstrated the positive association between acute anterior uveitis and the presence of HLA-B27 antigen, and the absence of a relevant family history of spondylitis-associated disorders in HLA-B27 negative subjects.

Among reactive arthritis patients, including those with features of Reiter's syndrome, those positive for the HLA-B27 antigen show clinical heterogeneity reflected in increased severity and duration of peripheral arthritis (41-43), more frequent mucocutaneous features (42,44), an increased prevalence of back pain, radiological sacroiliitis and acute anterior uveitis (41-43) as well as a greater tendency to chronicity or a relapsing clinical course (44,13).

3. BACTERIAL PATHOGENS AND SPONDYLOARTHROPATHY

HLA-B27 associated reactive arthritis, aetiologically linked to a variety of microbial pathogens, serves as a good 'human disease model' (45) and has become the focus of intense research from which clues to the pathogenesis of other arthropathies could arise. Micro-organisms which are causally associated with reactive arthritis include : *Shigella flexneri* (46), *Salmonella enteritidus* (47,48), *Salmonella typhimurium* (49), *Yersinia enterocolitica* (14), *Yersinia pseudotuberculosis* (14), *Campylobacter jejuni* (50,51) and *Chlamydia trachomatis* (52). In most circumstances the infective aetiology is underscored by the presence of bacterial antigenic material in synovial tissue and/or synovial fluid. The cumulative data have been reviewed by Hughes and Keat recently (45).

Additionally, polymerase chain reaction (PCR) amplification to detect Chlamydial deoxyribonucleic acid (DNA) in a cohort of undifferentiated spondyloarthritis patients was performed in 1995 (53). In 41% of 27 synovial fluid samples taken from patients with no preceding history of urethritis, PCR amplification for *Chlamydia trachomatis* DNA was positive. These patients were all considered to have undifferentiated spondyloarthritis clinically, with no history to suggest an episode of reactive arthritis. This is exciting, since it suggests that an infective aetiology may also explain the pathogenesis of undifferentiated spondyloarthropathy.

Proof of infection as a trigger to reactive arthritis, and possibly undifferentiated spondyloarthritis too, raises the

possibility of antimicrobial therapy as definitive treatment. This avenue has long been explored: early studies have been reviewed by Hughes and Keat (45), who conclude that initial isolated reports of success with antibiotic treatment were largely anecdotal. Recent studies look more promising: the use of antibiotic therapy for recurrent urethritis in a Greenland population resulted in a significant reduction in the recurrence of reactive arthritis in treated patients (54), whilst the extended use of lymecycline (for a period of three months) shortened the duration of joint features in post-Chlamydial reactive arthritis (55). These findings support the notion that reactive arthritis may be treatable by definitive means, and thus holds prospect for potentially curable therapy. In light of this, traditional therapeutic approaches stand on the brink of change, and reflect the paradigm shift that the management of spondyloarthropathy is currently undergoing (56).

4. SPONDYLOARTHRITIS IN AFRICA, AND SOUTH AFRICA IN PARTICULAR

The prevalence and nature of rheumatic disorders in general, and spondyloarthropathies in particular, have been insufficiently documented from Africa (57). Only 20 cases of ankylosing spondylitis in Black Africans were known to the international community by 1980 (58-61). In view of the reduced HLA-B27 gene frequency, it is reasonable to assume that the prevalence of spondyloarthropathies in African Blacks would differ from populations with higher gene frequencies. It might also be considered plausible that the

data from American Blacks would reflect the situation in Africa. However, owing to racial admixture of about 15% among American Blacks (62), the background HLA-B27 prevalence of 2% (32) is significantly higher than the recorded values in Black Africans of Xhosa (0.83%) and Zimbabwean (0.68%) origin respectively (63). It is thus reasonable to predict that spondyloarthropathies in Africans would be poorly associated with HLA-B27 and less frequently seen. However, this remains largely unsubstantiated owing to the lack of facilities dedicated to the study and care of rheumatic diseases in Africa (57).

Nevertheless, in the last few years reports of spondyloarthropathy from sub-Saharan Africa have appeared in the literature (64-70). The numbers are small by comparison with series from Europe and North America, but it is apparent that the diseases are not as rare as previously believed.

Studies suggest a pattern in Black Africans of advanced ankylosing spondylitis without extra-articular manifestations, and predictably the majority of patients are HLA-B27 negative (59,61,67).

Psoriasis-related arthritis is rare in Black Africans (71), and the same holds true for inflammatory bowel disease (IBD)-related arthropathy (72).

Reactive arthritis and undifferentiated spondyloarthropathy in the African context are particularly interesting. Despite an abundance of urogenital and enteric pathogens

(known to be associated with the development of reactive arthritis), rheumatic sequelae of infections at these sites are not common (64-68,70). In a ten-month study conducted to identify all patients evaluated for rheumatic disease-related complaints at an academic referral hospital in Harare, Zimbabwe, only 3% of 411 patients had reactive arthritis (68)!

Reactive arthritis is known to complicate the course of human immunodeficiency virus (HIV) infection (73,74), and in the face of the Acquired Immunodeficiency Syndrome (AIDS) epidemic in Africa, reactive arthritis in HIV-infected individuals may be expected to emerge as an increasingly important rheumatological manifestation. Early data from Zimbabwe (75,76) and Togo (70) suggest this, but the data is sparse compared to the size of the population at risk. Once again, the lack of HLA-B27 association is evident (75) and may partly explain the relatively infrequent occurrence of reactive arthritis in Black Africans with AIDS.

South African spondyloarthropathy data is restricted to a handful of reports [see (a)-(e) below], creating the impression that spondyloarthropathies do not impact significantly on the health of local communities.

(a) An epidemiological survey of rheumatic disorders amongst urban and rural Blacks in the early 1970s identified only one case of ankylosing spondylitis in 1352 adults examined (58). The patient was a 62-year-old male. His HLA-B27 status was not known.

(b) A case report describing a Xhosa father and daughter with ankylosing spondylitis. Both subjects were HLA-B27 positive (59).

(c) A case series of eight Zulu Blacks (one female) from Natal with ankylosing spondylitis. Only one patient was HLA-B27 positive (61).

(d) Two case reports of Reiter's syndrome occurring in Black males. One of the subjects was HLA-B27 positive (64,65).

(e) A case series of psoriatic arthritis patients (White and Coloured) identified in a cohort of psoriasis patients attending a large university dermatology clinic. 42% of 58 patients had rheumatologic manifestations (77).

Such limited information does not do justice to the spectrum of disease managed in the health care facilities of South Africa. Furthermore, South Africa uniquely lends itself to the study of the disorders classified as spondyloarthropathy because the country has better established health care facilities in general, and rheumatology services in particular, when compared to most other African countries.

Most significantly, since HLA-B27 prevalence varies from extremely low to high, given the rich genetic diversity of the local population (Table 1), South Africa provides a potentially unique opportunity to explore the genetic predisposition to, patterns of, and aetiological relationships with the spondyloarthropathies in the spectrum as outlined earlier in this chapter.

TABLE 1 : HLA-B27 prevalence in South Africans of different ethnic origins

ETHNIC ORIGIN	HLA-B27 PREVALENCE (%)	REFERENCE(S)
San Bushmen	Unrecorded	35
Black (Xhosa)	0.29-0.83	63, 78
Coloured (Malay)*	2.9	63
Coloured (non-Malay)**	4.8	63
White ***	7.8-11.6	63, 78
Indian ****	2.21	#

* Descendants of unions between Khoisan (Hottentot and Bushmen), Whites, Malay and Black slaves (79)
** Descendants of unions between Khoisan (Hottentot and Bushmen), Whites and Black slaves (79)
*** Descendants of Dutch, French, German and British immigrants (79)
**** Descendants of immigrants from Indian subcontinent
\# Professor G Mody: Spondyloarthropathies - talk at "Rheumatology Focus" Conference, Johannesburg, 22 June 1996.

It is against this background that a study was designed to evaluate the clinical spectrum of spondyloarthritis at a referral centre representing a South African population.

CHAPTER TWO

STUDY DESIGN AND METHODS

1. OBJECTIVES

2. STUDY DESIGN

3. STUDY METHODS

   3.1 Case selection

   3.2 Case exclusion

   3.3 Data capture

4. ETHNICITY

5. DEFINITIONS

6. STATISTICAL ANALYSIS

7. SHORTCOMINGS OF THIS STUDY

CHAPTER TWO

STUDY DESIGN AND METHODS

1. OBJECTIVES

Given the paucity of epidemiological and clinical data representing the South African experience with the spondyloarthropathies, a study was designed to achieve a description of the spectrum of spondyloarthropathy in patients of different ethnic origin attending the Rheumatic Diseases Unit (RDU), University of Cape Town (UCT), in respect of differences in:

- clinical and/or radiographic expression of disease;
- gender
- HLA-B27 status, and
- choice of therapy and requirements for reconstructive orthopaedic surgical procedures.

2. STUDY DESIGN

The study comprised a retrospective descriptive review of all new cases of spondyloarthropathy seen at the RDU, UCT Medical School, from 1 January 1988 to 31 December 1994, who were consecutively identified from an analysis of the clinical records.

The RDU (UCT) is one of two principal referral centres for rheumatic-related diseases in the Western Cape region, and

provides clinical services at Groote Schuur Hospital (GSH, Observatory) and Princess Alice Orthopaedic Hospital (PAOH, Retreat) in Cape Town for an estimated population of 3.4 million (Western Cape), 55% (1.9 million) of whom are resident in the Cape Peninsula region (81). A minority of patients from further afield (Northern Cape and Eastern Cape) also attend the unit.

Approximately 12 500 patients attend PAOH Outpatient Department (OPD) annually, of which 35% are seen by the RDU staff each year (average values calculated from attendance registers for the period 1 January 1988 to 31 December 1994). New patients constitute about 6% of all patients seen by the RDU per annum (Table 2). Statistical data were not available from the OPD Arthritis Clinic (AC) at GSH, but similar proportions would be expected, since both clinics are staffed by the same complement of doctors and operate under similar circumstances at both venues.

TABLE 2 : PAOH Outpatient Department statistics

	Outpatients seen per annum mean (range)
All OPD clinics	12 525
RDU OPD clinics	4 255 (4130-4617)
RDU new patients	275 (195-346)

3. STUDY METHODS

3.1 Case selection

For the period 1988-1994, potential cases of spondylo-arthropathy were identified by computer-assisted search of an established database maintained at PAOH. All patients in whom one of the following diagnoses was recorded were traced :

- ankylosing spondylitis
- psoriatic arthritis
- Reiter's syndrome
- reactive arthritis
- IBD-related arthritis
- seronegative arthritis
- *'other'* arthritides

Additional potential cases were also selected from amongst patients attending the outpatient AC at GSH. A dedicated rheumatic diseases database did not exist at this facility at the time of study, and precluded a systematic search to identify all suitable patients. Only patients identified in the course of routine clinic visits could be considered for study.

The clinic records of 120 potential cases identified were subject to review by the investigator, and 100 cases were identified for further study.

3.2 Case exclusion

Figure 1 indicates the reasons for exclusion of 20 potential cases by virtue of wrong diagnosis, insufficient data or disputed diagnosis.

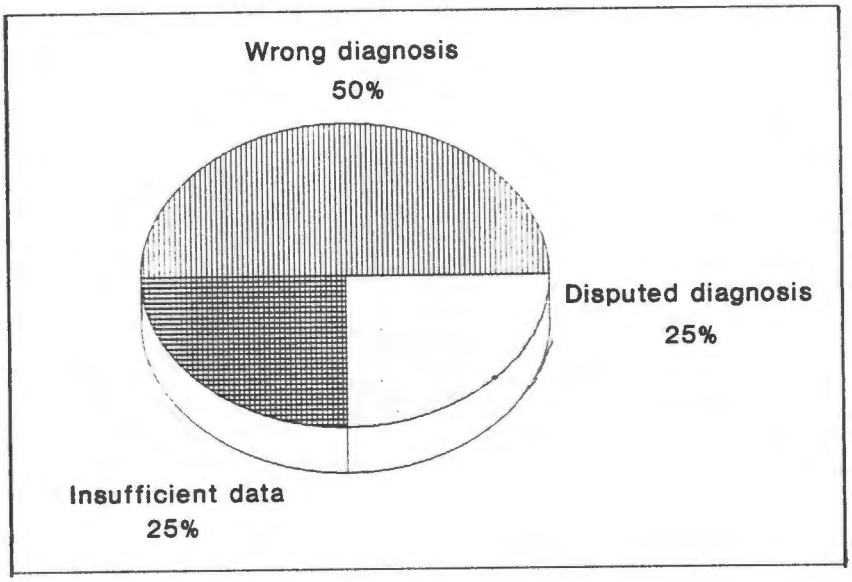


Figure 1 : Reasons for exclusion from study

(a) **Wrong diagnosis :** Fibromyalgia (2), unspecified arthralgia (4), seronegative rheumatoid arthritis (RA) (3) and gout (1).

(b) **Insufficient data :** Three cases of ankylosing spondylitis referred to PAOH during the study period were seen by the Department of Orthopaedic Surgery with a view to arthroplasty surgery. These patients did not undergo full rheumatological evaluation by a staff member of the RDU since such had been done at another facility. This information was not available in the PAOH notes.

The case folders of a further two patients could not be traced.

(c) **Disputed diagnosis :** Three cases of presumed ankylosing spondylitis were rejected because advanced age of disease-onset raised concern regarding the possible diagnosis of diffuse

idiopathic skeletal hyperostosis (DISH), a non-inflammatory arthropathy occurring predominantly in aging males (80).

(d) Post-infectious sequelae not usually recognised as part of the reactive arthritis spectrum (11) : One patient had post-rubella synovitis of the wrists, and another had post-streptococcal synovitis.

3.3 Data capture

A data capture sheet was designed to record demographic, historical, clinical, serological, radiological, microbiological and management-related details (Appendix C, p.88-91). All recorded information was obtained from clinic records kept from the time of initial patient evaluation until last seen or the time of data collection (March-May 1995), whichever occurred first.

Clinic records kept by the RDU reflect clinical, radiological and special investigation(s) findings from the time when first seen in a 'New Patient' clinic were evaluated by a senior house officer or medical registrar, undergoing training in rheumatic-related diseases, and reviewed by a consultant rheumatologist. Periodic review by the consultant staff at follow-up visits is achieved as required. The typewritten records thus largely reflect the opinion of a consultant rheumatologist, and were particularly suitable (detailed and legible) for purposes of retrospective data review.

Each selected case was assigned a clinical diagnosis from within the spondyloarthropathy spectrum according to well-established definitions and/or diagnostic criteria contained in Appendices A and B :

- ankylosing spondylitis (AS)
- psoriatic arthritis (PsA)
- enteropathic arthritis (EA)
- reactive arthritis (ReA)*
- undifferentiated spondyloarthritis (USpA).

* including Reiter's syndrome.

4. ETHNICITY

Note was taken of the race of the patient as defined in the hospital administration records, and patients were thus defined as Black, White, Coloured or Asian.

The term *'Asian'* as used in this study refers to Indian people (largely South African by birth) whose forefathers originally emigrated from the Indian subcontinent in the last century to take up residence in South Africa, and is used to conform to race classifications used in South African population statistics.

In this study *'Coloured'* is taken to mean South Africans of mixed ethnic origin, who are of Malay or non-Malay descent (refer to Chapter One: Introduction and Literature Review - Table 1, page 13), as described by Botha and Pritchard (79). Clinic records do not permit accurate distinction of these two Coloured subgroups, and so all patients of mixed ethnic origin are simply referred to as *'Coloured'*.

An estimate of the expected racial-mix of the group studied here was derived through analysis of :

(a) the population composition of the Western Cape, and more specifically of the Cape Peninsula (Figures 2(a) and (b))

(b) the racial-mix of patients attending the OPDs of the major State-funded hospitals in the Cape Peninsula (Table 3), and

(c) the racial-mix of patients attending the RDU 'New Patient' clinics at PAOH.

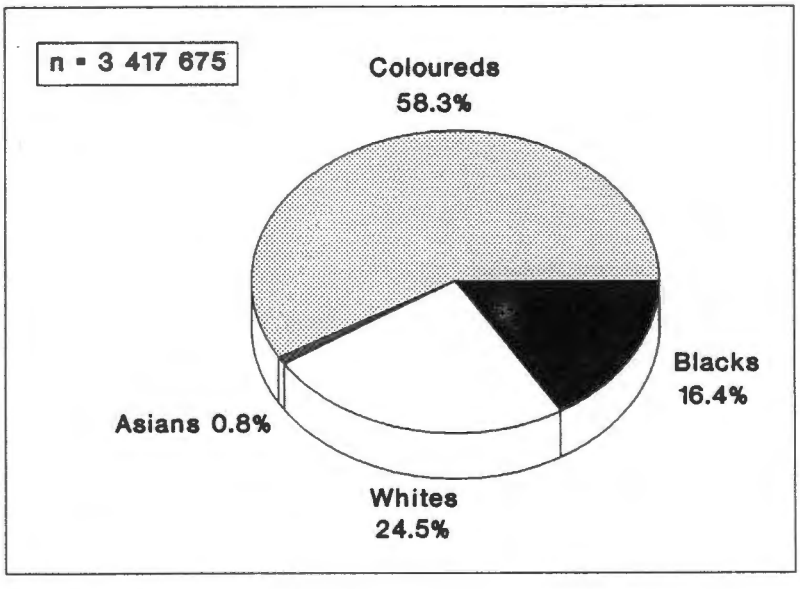
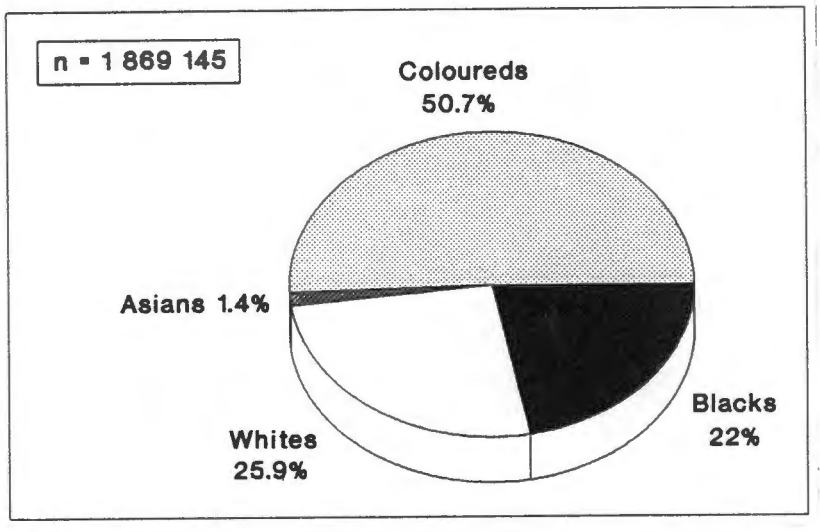


Figure 2(a) : Population composition - Western Cape 1991 (81)



Cape Peninsula = magisterial districts of Cape Town, Bellville, Goodwood, Simon's Town and Wynberg (including Khayelitsha, Nyanga, Guguletu, Athlone, Mitchell's Plain)

Figure 2(b) : Population composition - Cape Peninsula 1991 (81)

From this data it is seen that during the period of interest, Coloured people made up at least 50% of the regional population, while Whites comprised about one-quarter and Blacks about one-fifth. Asians (largely Indians) comprised a small minority of less than 2%. Regarding the data relating to Black people, it is highly probable that the population head count significantly underestimated the actual figures, owing to the difficulties in obtaining correct data in the setting of large communities of informal housing (squatter camps), political unrest and violence, and an ever-increasing influx of Black people from the rural areas of the former Transkei and Ciskei. Thus a figure of 22%, although a useful guide, has to be viewed with caution, since it largely represented Blacks housed in formal settlements at the time of the 1991 population census.

TABLE 3 : Outpatient head count per population group attending Cape Peninsula hospital OPDs - 1989/90 and 1990/91 (82)

	TOTAL OPD HEAD COUNT PER YEAR	WHITE %	COLOURED %	ASIAN %	BLACK %
Somerset, Green Point	127 259	26.1	48.2*		25.7
Conradie, Pinelands	105 861	5.8	45.5*		48.7
Victoria, Wynberg	58 529	23.3	56.0*		20.7
Princess Alice Retreat	12 525	30.6	69.4**		
False Bay, Fish Hoek	21 941	39.6	60.4**		
Groote Schuur, Mowbray	963 164	16.1	62.5*		21.3
Tygerberg, Bellville	503 192	24.6	67.0	0.3	8.1
AVERAGE HEAD COUNT PER ANNUM***	1 589 595	13.1	65.4		21.5

* Combined value - separate Coloured and Asian statistics not available.

** Combined value - separate Coloured, Asian and Black statistics not available .

*** Average values calculated excluded PAOH and False Bay Hospital because separate non-White racial statistics were not available.

The racial-mix of patients attending State-funded hospital OPDs was roughly proportional to that of the overall population composition. It may be presumed that Whites were under-represented at State hospitals since the more affluent sector were likely to attend private medical facilities. The inflated Coloured/Asian figure represented combined data, while the 21.5% figure for Blacks reflected data similar to that obtained from population statistics. Only one hospital

(Tygerberg, Bellville) was able to provide a statistic for Asian patients, and this value reflected a similar minority figure to that obtained from local population data.

Analysis of the racial-mix of patients attending the RDU 'New Patient' clinics, showed that 180 Black patients were seen in the seven-year study period. Thus about 10% (26 of 275 per year) of new referrals per annum were Black patients. Data for the other race groups could not be accurately defined from the patient booking/attendance registers.

Based on analysis of the presented data, it was estimated that the racial-mix of the group of spondyloarthropathy patients studied would be in the order of :

TABLE 4 : Predicted racial-mix of 100 spondyloarthropathy patients studied

ETHNIC GROUP	PREDICTED PREVALENCE (%)
Coloured	50-60
White	20
Black	10-20
Asian	< 5

5. DEFINITIONS

All terms used in the data capture sheet relating to clinical, radiological and seriological features are defined in Appendix D (p.92-101).

6. STATISTICAL ANALYSIS

All information gathered was entered on a personal computer (486DX, IBM-compatible) using the spreadsheet facilities of *Quattro Pro version 5.00*. Statistical methods of choice were based on sample size. Continuous variables were compared using the Student's t-test, for variables of equal or unequal variance, as appropriate. Chi-squared analysis was used for evaluation of categorical data. The assessment of significance of differences was determined at a probability of 95%.

7. SHORTCOMINGS OF THIS STUDY

Retrospective studies, having multiple problems and inadequacies, are not well suited to study specific issues of interest. Rather, they serve as a useful tool to gain initial insight into previously poorly documented problems, and thereby promote further prospective study of identified matters of importance. To that end this retrospective study provides some useful clinical data relating to the spondylo-arthritis (SpA) disease spectrum as seen in an urban South African setting. However, the findings of this study can only be evaluated once the reader is familiar with the limitations of the work presented.

(a) **Incomplete data capture:** The absence of a database facility at GSH, at the time of study, precluded inclusion of <u>all</u> new SpA patients evaluated by the RDU, and thus the findings of this study largely reflect a cohort of patients seen at PAOH.

Since prospective patient evaluation, according to a study protocol, was not performed, all investigations (radiological, serological and microbiological) of interest were not performed in every case, causing a series of missing data in the results.

(b) **Small subgroup sizes:** An obvious consequence of incomplete data capture is a reduction in the number of cases within any specific disease/ethnic subgroup. Such small subgroups, lacking statistical power, frustrate data interpretation in some situations in this study (appropriately highlighted in the subsequent text).

(c) **Referral bias:** A hospital OPD-based study tends to select patients at the severe end of the disease spectrum. This is clearly not an ideal situation, but in the absence of any other local data, information such as is obtained from this study is useful to define at least an initial impression of local disease patterns.

(d) **Poor documentation of the aetiology of ReA:** Synovitis (oligoarticular, asymmetric) in the absence of any other obvious cause (such as sepsis, gout or trauma), accompanied by an appropriate history, was sufficient to make a diagnosis of ReA in this study. Unfortunately, in routine clinical practice, precipitating aetiological infections were not pursued in the majority. Thus the

aetiology of ReA remains unanswered by this study, but interesting future research options are highlighted in the discussion text.

(e) **Absence of HLA-B27 subtyping:** Nine HLA-B27 subtypes are currently recognised (35), and it is apparent that the frequency of any given one varies within different population groups. There is, however, uncertainty regarding the association, or lack thereof, with certain subtypes of SpA (discussed in detail in Chapter Four: Discussion - 1: SpAs are uncommon in Black South Africans, p.58-63). Given the enormous genetic diversity in South Africa (alluded to in Chapter One: Introduction and literature review - 4. SpA in Africa, and South Africa in particular, p.12), accurate survey of HLA-B27 subtypes in the patients in this study may have been expected to yield particularly interesting results.

(f) **Poor characterisation of the distribution of small joint arthritis:** Distinct clinical patterns of joint disease in PsA are well described (9): (i) predominant involvement of distal interphalangeal joints, (ii) arthritis mutilans, (iii) symmetric polyarthritis, (iv) asymmetric oligoarticular arthritis and (v) axial involvement. Unfortunately the data collection technique in this study did not permit detailed analysis of the patterns of joint disease in PsA patients. Such data may have been useful to evaluate and compare local disease patterns with those highlighted above.

CHAPTER THREE

RESULTS

For ease of comprehension on the part of the reader, the results of the study are reported under the headings :

I. Patterns of disease - the broad picture

II. Influence of ethnicity on patterns of disease (Appendix E)

III. Influence of gender on patterns of disease (Appendix F)

IV. Influence of HLA-B27 on patterns of disease (Appendix G)

Differences observed are highlighted in each subchapter, whilst the overall results of the survey, for detailed perusal, are provided in the form of tables and figures in complementary appendices.

I. PATTERNS OF DISEASE - THE BROAD PICTURE

1. **PREVALENCE**

2. **DEMOGRAPHY**

3. **FAMILY HISTORY**

4. **AGE OF DISEASE-ONSET, PRESENTATION AND DURATION**

5. **PATTERNS OF DISEASE**

   5.1 Spondylitis
   5.2 Peripheral arthritis
   5.3 Tenosynovitis and enthesitis
   5.4 Extra-articular manifestations

6. **LATE COMPLICATIONS**

7. **HLA-B27 STATUS**

8. **LABORATORY AND RADIOGRAPHIC DATA**

   8.1 Rheumatoid factor
   8.2 Microbiological evaluation
   8.3 Spinal radiographs
   8.4 Sacroiliac joint radiographs
   8.5 Peripheral joint radiographs

9. **MANAGEMENT**

   9.1 Medical therapy
   9.2 Orthopaedic surgical procedures

I. PATTERNS OF DISEASE - THE BROAD PICTURE

1. PREVALENCE

100 Patients were identified as having spondyloarthropathy, and fell into disease groups as depicted in Figure 3. Nine patients in the cohort had juvenile-onset disease (AS=3, PsA=4, USpA=2). The diagnosis was made retrospectively in seven cases presenting initially in early adulthood. Only two PsA patients were seen at disease-onset. Two cases classified as USpA when first seen in early adulthood, would have been considered to have had SEA syndrome if seen at disease-onset in adolescence.

90% of the selected cases came from PAOH. Therefore, spondyloarthropathy patients constitute about 5% of all <u>new patients</u> seen annually by the RDU at PAOH; expressed as a ratio, about 1:20 <u>new</u> patients seen can be expected to have a spondyloarthropathy disorder.

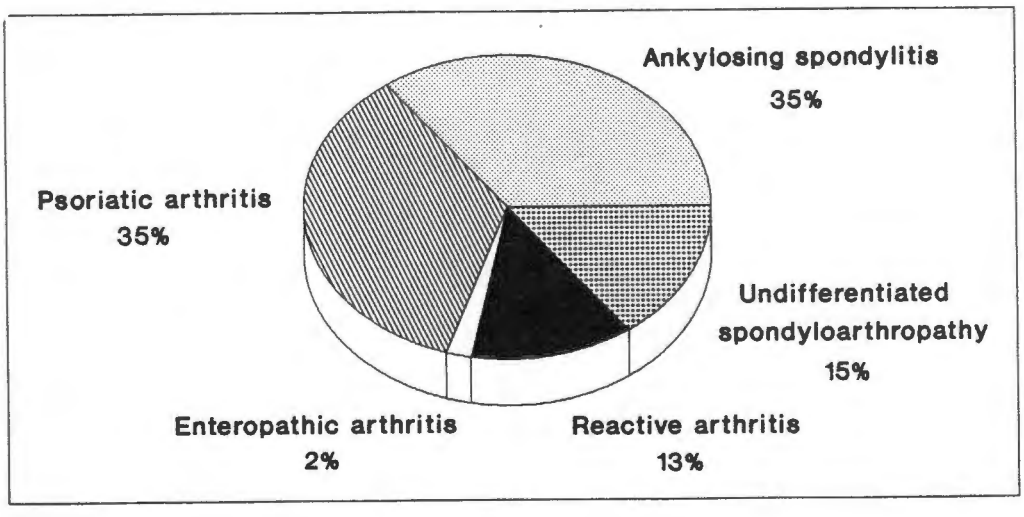


Figure 3 : Spondyloarthropathy disease subgroups

- Ankylosing spondylitis (AS): 32 fulfilled the New York criteria and 3 fulfilled the Rome criteria in the absence of sacroiliac joint radiograph reports (Appendix A)
- Psoriatic arthritis (PsA) : Appendix A
- Enteropathic arthritis (EA) : Appendix A
- Reactive arthritis (ReA) : Fan et al (11) in Appendix A
- Undifferentiated spondyloarthropathy (USpA) : ESSG criteria (Appendix B)

2. DEMOGRAPHY

White and Coloured patients were well represented in the study cohort (93%), while the paucity of Black and Asian patients was striking (Figure 4).

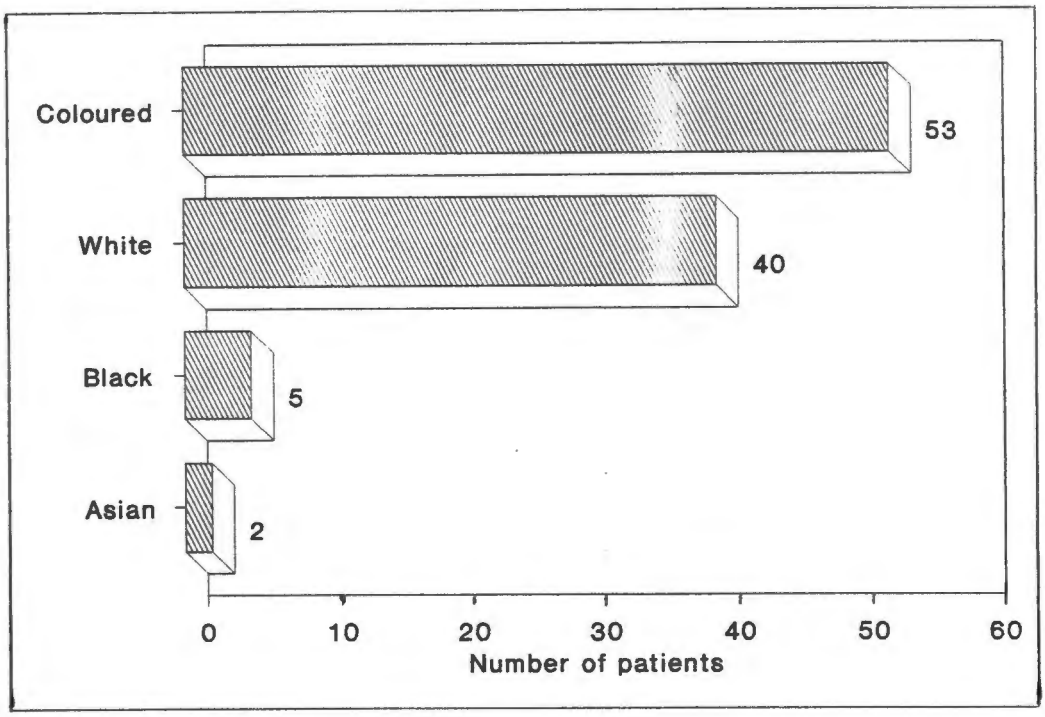


Figure 4 : Ethnic composition of spondyloarthritis study group

TABLE 5 : Demography of 100 spondyloarthropathy patients

MALES (n=71)						FEMALES (n=29)				
AS	PsA	EA	ReA	USpA		AS	PsA	EA	ReA	UspA
3			2		Black (n=5)					
11	8		4	5	White (n=40)	2	6		1	3
15	11	1	5	4	Coloured (n=53)	4	8	1	1	3
	2				Asian (n=2)					
29	21	1	11	9	TOTAL	6	14	1	2	6

Overall male dominance was demonstrated by a male:female ratio of 2.5:1, which was prominent in AS (4.8:1) and ReA (5.5:1), relatively unimpressive in PsA (1.5:1) and USpA (1.5:1), and equal in EA males and females (Table 5).

3. FAMILY HISTORY

Although 22 of the patients reported a family history of arthritis, only 8 (4 Whites and 4 Coloureds) had a history relevant to the index disease case, specifically :

- AS : one case with a family history of AS
- PsA : 5 cases with family histories of psoriasis
- USpA: one case with a family history of IBD and one with a family member having AS.

The remaining 14 patients reported a family member with unspecified arthritis. Black and Asian patients did not report any family history of rheumatic disease.

4. AGE AT DISEASE-ONSET, PRESENTATION AND DURATION

TABLE 6 : Age at onset, age at presentation and duration of disease in 100 spondyloarthritis patients

	AS (n=35)	PsA (n=35)	EA (n=2)	ReA (n=13)	USpA (n=15)	TOTAL (n=100)
Age at onset mean (± SD)	28.7 (±15.1)	35.3 (±17.8)	42.5	29.4 (±10.2)	27.9 (± 8.3)	31.3 (±14.9)
range (yrs)	13-82	10-74	32-53	17-55	13-40	10-82
Age at presentation mean (± SD)	38.7 (±14.8)	43.9 (±17.1)	50.5	31.2 (± 9.4)	32.9 (±10.8)	38.9 (±15.2)
range (yrs)	18-82	15-84	38-63	19-55	13-50	13-84
Disease duration mean (± SD)	10.1 (± 9.3)	8.5 (±9.9)	8	2 (±2.9)	5.1 (±6.6)	7.7 (±8.9)
range (yrs)	0.5-41	0.5-46	6-10	0.5-11	0.5-23	0.5-46

The age at symptom-onset was similar across the spondylo-arthropathy spectrum (Table 6). Although the EA group was slightly older, the size of the group was too small to permit valid comment. The ReA patients were younger than the mean age at presentation (p=0.018), and had a significantly shorter duration of disease (p=0.022). These differences persisted even after exclusion of the juvenile-onset sub-group (n=9) from the analysis.

5. PATTERNS OF DISEASE

The clinical patterns at presentation with spondyloarthritis, as studied in 100 patients, are detailed below in terms of :

- spondylitis
- peripheral arthritis
- tenosynovitis and enthesitis
- extra-articular manifestations.

5.1 Spondylitis

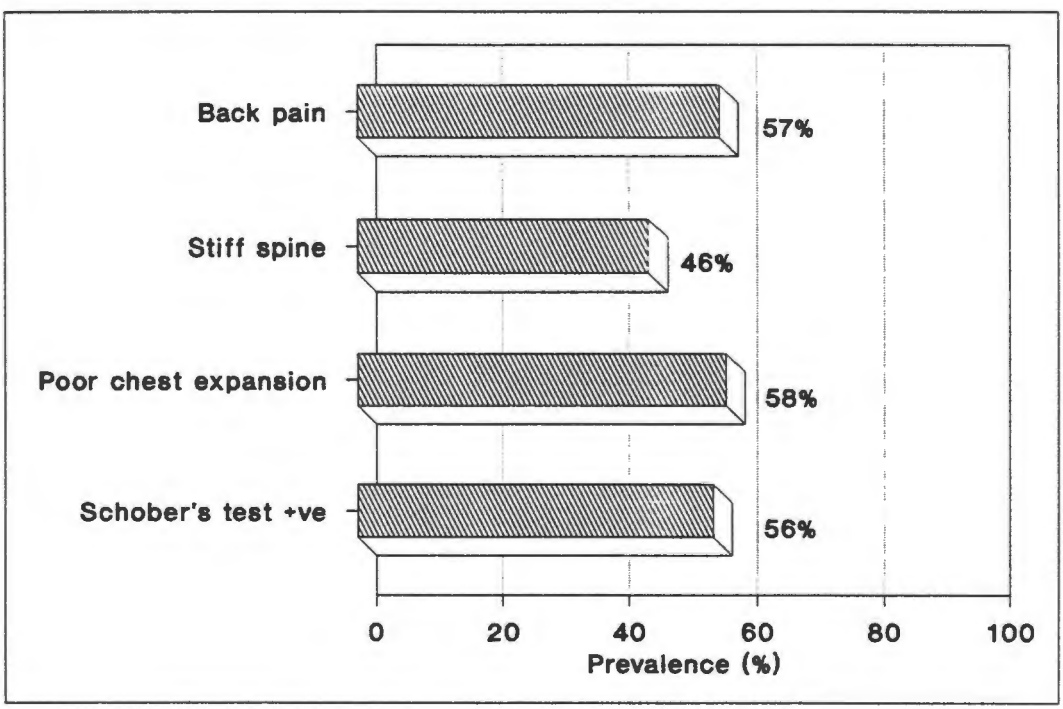


Figure 5 : Clinical features of spondylitis in 100 spondyloarthropathy patients

Approximately 50% of the total cohort had clinical features of spondylitis (Figure 5). Inflammatory back pain accompanied by the three clinical signs of advanced spondylitis were more common in AS when compared to PsA and ReA ($p<0.005$) (Figure 6). A small clustering of spondylitis features was also observed in USpA.

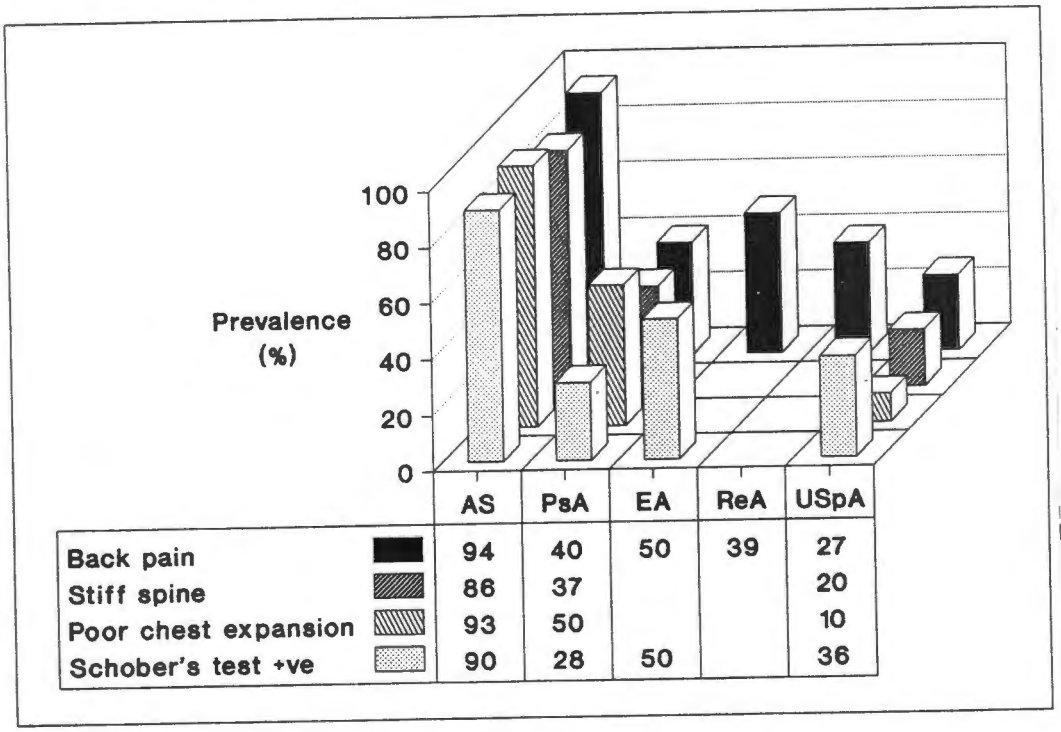


Figure 6 : Distribution of spondylitis features across spondyloarthopathy spectrum

5.2 Peripheral arthritis

Figure 7 shows that while spondylitis prevailed in AS, peripheral arthritis was dominant in PsA, ReA and USpA. Overall, therefore, peripheral joint disease was more common than axial involvement ($p<0.005$).

Large joint peripheral arthritis was more common overall ($p<0.005$), and small joint disease was mostly recorded in PsA patients (Figure 8).

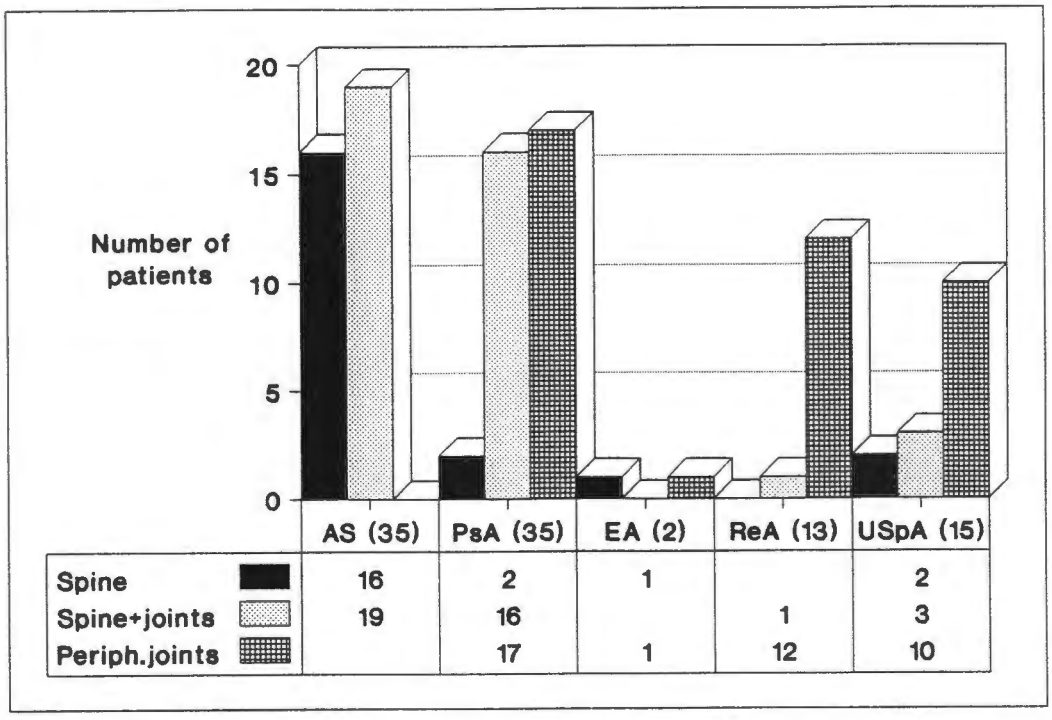


Figure 7 : Patterns of joint involvement across the spondyloarthropathy disease spectrum

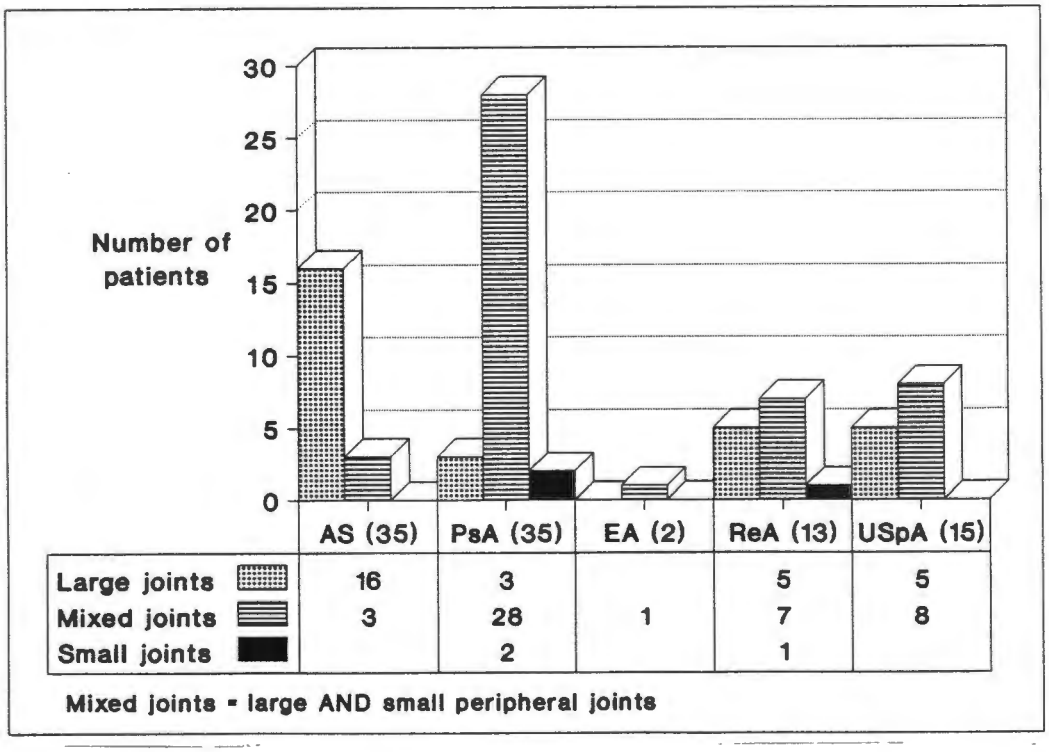


Figure 8 : Peripheral arthritis patterns in spondyloarthritis

5.3 Tenosynovitis and enthesitis

Tenosynovitis, commonest in PsA and ReA, was present in 16 patients (Figure 9).

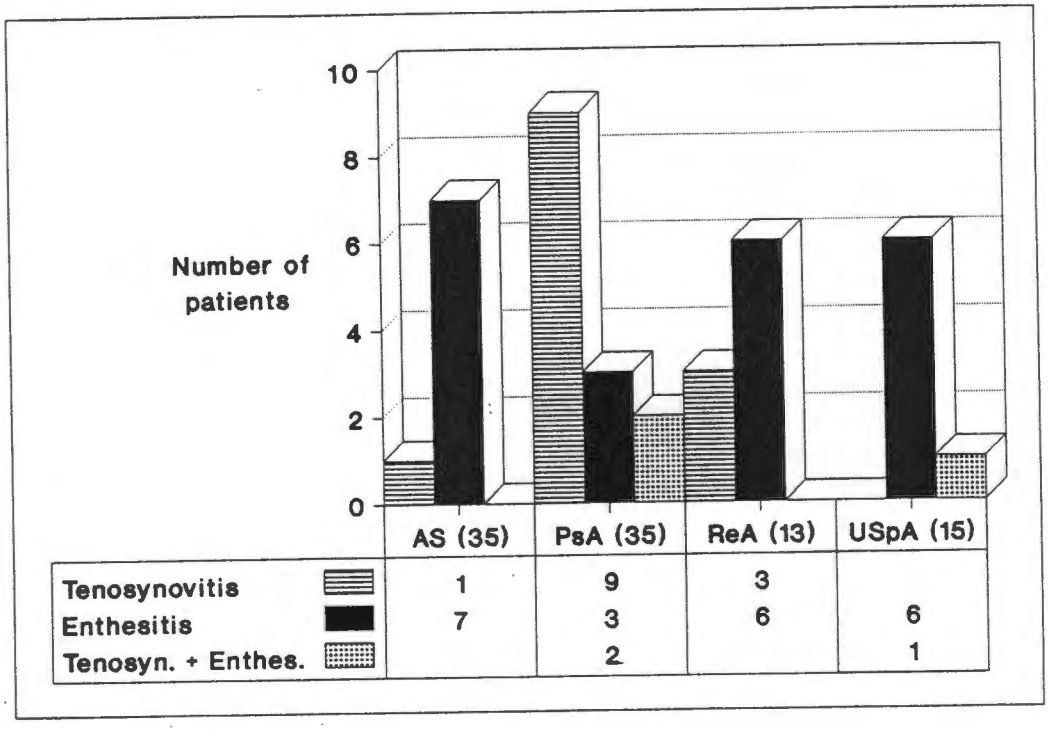


Figure 9 : Non-articular musculoskeletal features

Enthesitis at the insertion of the Achilles tendon or plantar fascia insertion was recorded in 25 cases, and occurred with similar frequency in AS, ReA and USpA, but was less frequent in PsA (Figure 9).

5.4 Extra-articular manifestations

Extra-articular features are tabulated in Table 7. Of note, acute anterior uveitis (AAU) was more common in AS than PsA ($p<0.05$), and mucocutaneous features occurred in less than one-quarter of ReA patients.

In reactive arthritis, rheumatological manifestations were more often preceded by urethritis (9/13) than diarrhoea (4/13) ($p<0.05$).

TABLE 7 : Extra-articular features in spondyloarthritis

	AS (n=35)	PsA (n=35)	ReA (n=13)	USpA (n=15)
Conjunctivitis			2	2
Anterior Uveitis	6	1		
Keratoderma blenorrhagica			1	
Circinate balanitis			2	
Aortic regurgitation		1*		1

* 84-year-old patient. Not investigated to exclude other causes of aortic regurgitation.

6. LATE COMPLICATIONS

Cervical myelopathy was present in one of three PsA cases with radiological atlanto-axial cervical spine disease. No reports of apical pulmonary fibrosis (in the absence of previous pulmonary tuberculosis), cauda equina syndrome or spinal fractures were noted.

7. HLA-B27 STATUS

Tissue typing, specifically for HLA-B27 antigen, was carried out in 45 patients, amongst whom 51.1% were positive (Table 8).

TABLE 8 : HLA-B27 status

	AS (n=35)	PsA (n=35)	ReA (n=13)	USpA (n=15)
HLA-B27 +ve	12/20	1/7	6/7	4/11
	(60)	(14.3)	(85.7)	(36.4)

percentage indicated in parentheses

8. LABORATORY AND RADIOGRAPHIC DATA

8.1 Rheumatoid factor

Serological tests for rheumatoid factor were available on 51 patients. In only two patients was the result positive (4%). These two patients had features consistent with SpA rather than RA :

(i) a 40-year-old HLA-B27 negative Coloured male with AS as evidenced by: peripheral arthritis, spondylitis (inflammatory back pain, limitation of lumbar spine motion in three planes, and limited chest expansion), radiographic sacroiliitis, and spinal radiongraphs showing advanced disease with 'bamboo spine' changes.

(ii) a 34-year-old HLA-B27 positive Coloured male with PsA as evidenced by: characteristic skin rash of psoriasis, peripheral resorptive arthritis, spondylitis (inflammatory back pain and limitation of lumbar spine motion in three planes), radiographic sacroiliitis, and spinal radiographs showing evidence of spondylitis.

8.2 Microbiological evaluation

Results of relevant serology and/or stool culture were recorded in 7 cases. A White patient with ReA had a stool culture result positive for *Yersinia enterocolitica*.

8.3 Spinal radiographs

45 Spinal radiograph reports were recorded across the disease spectrum. Radiographic abnormalities were reported in 80% (36/45) of available radiographs, and

77.8% (28/36) of these findings were considered to be causally related to the underlying spondyloarthropathy.

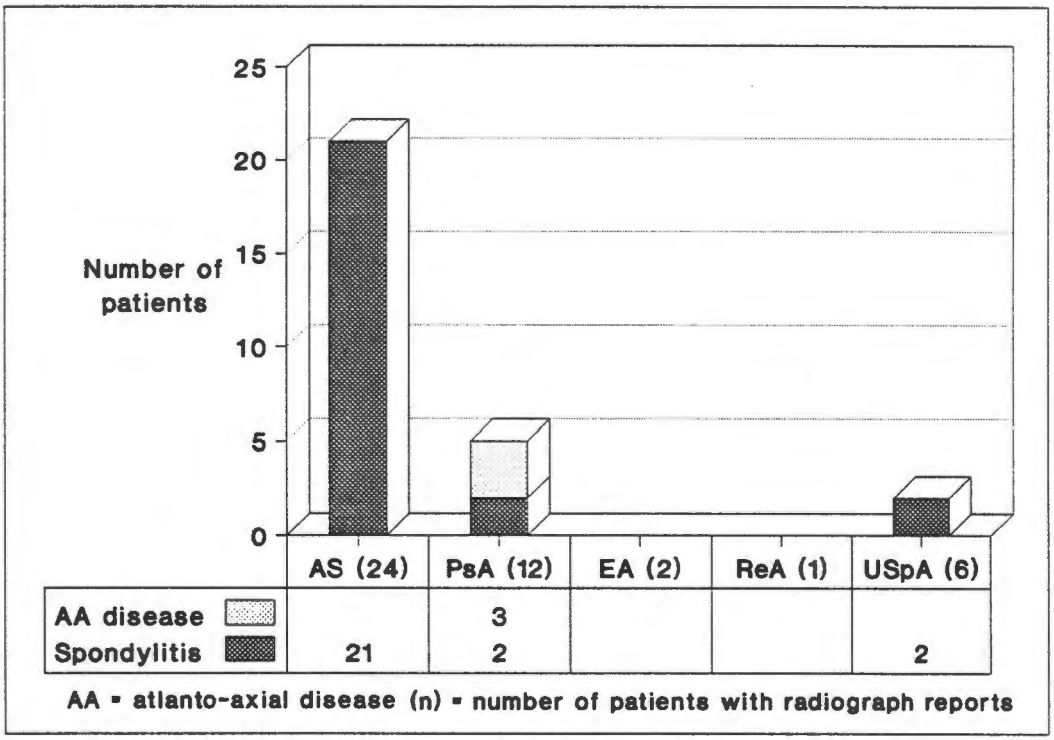


Figure 10 : Spinal radiographic features relevant to spondyloarthritis

Radiographic spondylitis was dominant in AS, of similar but reduced prevalence in PsA and USpA, and was not reported in EA or ReA. Atlanto-axial disease was present in three PsA patients only (Figure 10), but neck radiographs were not performed routinely in all patients.

8.4 Sacroiliac joint radiographs

Radiographic analysis of sacroiliac joint pathology was available in 69 cases overall. 60.9% (42/69) of radiographs were considered to demonstrate sacroiliiitis, which was bilateral in 35 cases, and unilateral in the remaining 7 cases (refer to Figure 11).

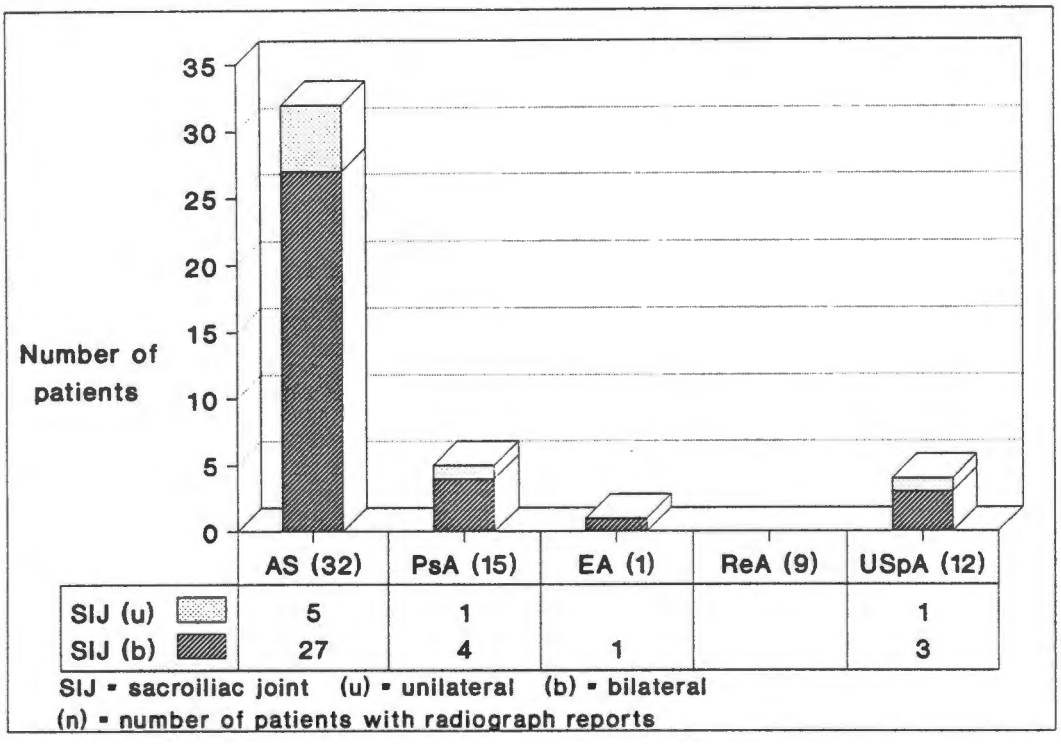


Figure 11 : Radiographic sacroiliitis

8.5 Peripheral joint radiographs

Radiographic evaluation of the peripheral joints was available for 61 cases. 67% (41/61) of reports documented abnormal findings in keeping with, though not specific for, the underlying type of SpA. Radiographic evidence of peripheral joint damage was largely restricted to AS and PsA compared with ReA ($p<0.005$) and USpA ($p<0.05$). As many as 80% of the peripheral joint radiographic changes were compatible with advanced cartilage damage. Resorptive changes were not common (7.3%). (Refer to Figure 12.)

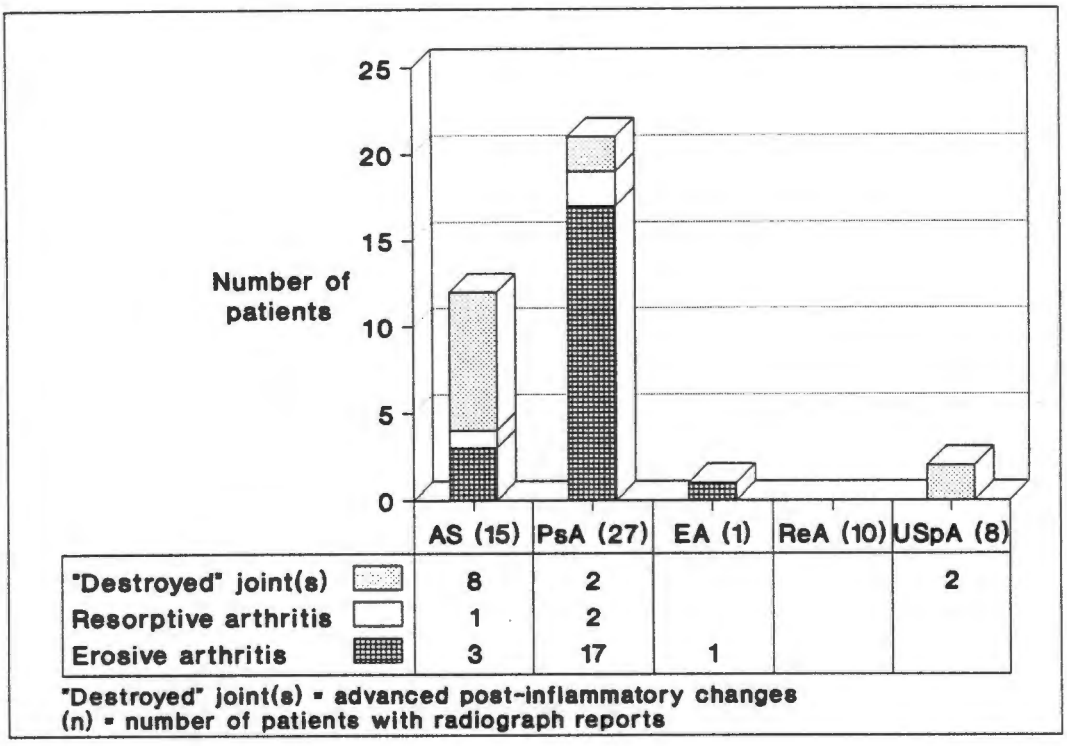


Figure 12 : Distribution of radiographic changes indicating peripheral joint damage

9. MANAGEMENT

Most patients were managed with drug therapy. Surgical intervention was uncommon.

9.1 Medical therapy

Symptomatic therapy only (analgesia, NSAIDs) was prescribed for 80 patients, while just 16 patients (10 Coloured, 6 White) received disease modifying anti-rheumatic drugs (DMARD), 11 (69%) of whom had PsA (see Table 9).

TABLE 9 : Medical therapy prescribed in spondyloarthritis patients

	AS (n=35)	PsA (n=35)	EA (n=2)	ReA (n=13)	Uspa (n=15
Symptomatic Rx	29 (82.9)	24 (68.6)	1	11 (84.6)	15 (100)
+ steroids	1 (2.9)				
DMARD + symptomatic Rx	2 (5.7)	10 (28.6)	1		
DMARD + steroids	2 (5.7)	1 (2.9)			

Percentage indicated in parentheses
Rx = therapy

Weekly oral methotrexate was most commonly used (75% of prescriptions), while sulphasalazine was taken by three patients, and one patient received parenteral gold therapy. This patient, with AS, was also the only person in this cohort to have received three courses of radiation therapy at disease onset in 1947.

Data from Table 10 (see overleaf) shows that DMARD use was more common in patients with PsA, prolonged disease duration and erosive OR resorptive changes on peripheral joint radiographs.

Gender, ethnic origin and HLA-B27 status, as expected, were not significantly associated with DMARD use. Sub-group analysis of age at disease onset in PsA patients requiring DMARDs, as compared with those not requiring DMARD therapy, showed a tendency towards a younger age at disease onset ($p=0.054$) in those using DMARDs.

TABLE 10 : Comparison of selected clinical and radiographic features in spondyloarthritis patients using DMARDs and/or symptomatic therapy

	DMARD USE (n=16)	NO DMARD USE (n=84)	p-VALUE
Age at symptom-onset			
mean (±SD)	27.8 (±11.9)	31.9 (±15.5)	ns
range (yrs)	10-53	13-82	
Disease duration			
mean (±SD)	13.5 (±10)	6.6 (±8.2)	0.004
range (yrs)	2-41	0.5-46	
SpA subgroup:			
- AS	4 (25)	31 (37)	
- PsA	11 (68.8)	24 (28.6)	<0.005
- EA	1 (6.3)	1 (1.2)	
- ReA		13 (15.5)	
- USpA		15 (17.9)	
Peripheral joint radiographs:	(n=13)	(n=48)	
- Erosive	8 (61.5)	13 (27.1)	<0.025
- Resorptive	3 (23.1)		<0.005
- 'Destroyed'	1 (7.7)	11 (22.9)	

Percentage indicated in parentheses

Antimicrobial therapy was reported to have been used (repeated courses of tetracycline) in one case of ReA only.

Chemical synovectomy using mustine was attempted in the knees of one PsA patient, with good success.

9.2 Orthopaedic surgical procedures

15 Patients underwent a total of 28 orthopaedic surgical procedures as outlined in Table 11. More than one-quarter (8/28) of all joint arthroplasty procedures were performed in three juvenile-onset SpA

patients (one patient required revision of bilateral total hip arthroplasties).

TABLE 11 : Orthopaedic surgical procedures

	AS (n=35)		PsA (n=35)		USpA (n=15)		ALL PROCEDURES PERFORMED
	pts	proc	pts	proc	pts	proc	
THR							
- bilateral	7	16	1	2	2	4	22
- unilateral	2	2			1	1	3
TKR							
- bilateral			1	2			2
Swanson's arthroplasty (MCP joints)			1	1			1
TOTAL	9	18	3	5	3	5	28

pts = patients proc = procedure THR = total hip replacement TKR = total knee replacement MCP = metacarpophalangeal

Table 12 (see overleaf) shows that large joint arthroplasty was more commonly performed in patients who had AS, early-onset disease, prolonged disease duration, and peripheral joint radiographs showing features of 'destroyed' joint(s).

Gender, ethnic origin and HLA-B27 status did not influence joint arthroplasty requirements. Since almost 30% of large joint arthroplasties were performed in juvenile disease-onset patients, analysis of the comparison in Table 12 was also performed after exclusion of all juvenile disease-onset patients. The tendency to prolonged disease duration in arthroplasty

patients persisted, but failed to achieve statistical significance, while the other findings (except age at onset) remained unchanged.

TABLE 12 : Selected clinical and radiographic features in spondyloarthritis patients requiring arthroplasty surgery as compared to patients not requiring surgery.

	ARTHROPLASTY PATIENTS * (n=14)	NO SURGERY (n=85)	p-VALUE
Age at symptom-onset			
mean (±SD)	23.5 (±8.5)	32.5 (±15.5)	0.003
range (yrs)	10-53	13-82	
Disease duration			
mean (±SD)	12.1 (±7.1)	6.9 (±8.9)	0.042
range (yrs)	2-23	0.5-46	
SpA subgroup:			
- AS	9 (64.3)	26 (30.6)	<0.025
- PsA	2 (14.3)	32 (37.6)	
- EA		2 (2.3)	
- ReA		13 (15.3)	
- USpA	3 (21.4)	12 (13.9)	
Peripheral joint radiographs:	(n=13)	(n=48)	
- Erosive	3 (23.1)	18 (37.5)	
- Resorptive	1 (7.7)	2 (4.2)	
- 'Destroyed'	9 (69.2)	3 (6.2)	<0.005

Percentage indicated in parentheses

* Large joint arthroplasty only

II. INFLUENCE OF ETHNICITY ON PATTERNS OF DISEASE

Data analysis was performed to assess the influence of ethnic origin on the overall picture of spondyloarthritis in our cohort of 100 patients. The results of detailed analysis are contained in Appendix E, (p.95-7) and only the important differences are discussed in this section.

While age of disease-onset and presentation did not differ significantly, Table 13 shows 5 Black patients who presented early and with relatively short duration of disease. The two Indian males were older both at the time of disease-onset and presentation, when compared to the mean values of the group as a whole.

TABLE 13 : Age at disease-onset, presentation and duration in spondyloarthritis patients of differing ethnic origin

	WHITE (n=40)	COLOURED (n=53)	BLACK (n=5)	ASIAN (n=2)
Age at onset	32.2	30.2	28	49.5
mean (±SD)	(±17.3)	(±12.4)		
range (yrs)	10-82	13-63	17-64	41-58
Age at presentation	40.4	37.8	31.8	55
mean (±SD)	(±17.1)	(±12.8)		
range (yrs)	13-84	15-69	19-70	
Disease duration	8.3	7.7	3.9	5.5
mean (±SD)	(±9.8)	(±8.7)		
range (yrs)	0.5-41	0.5-46	0.5-4	

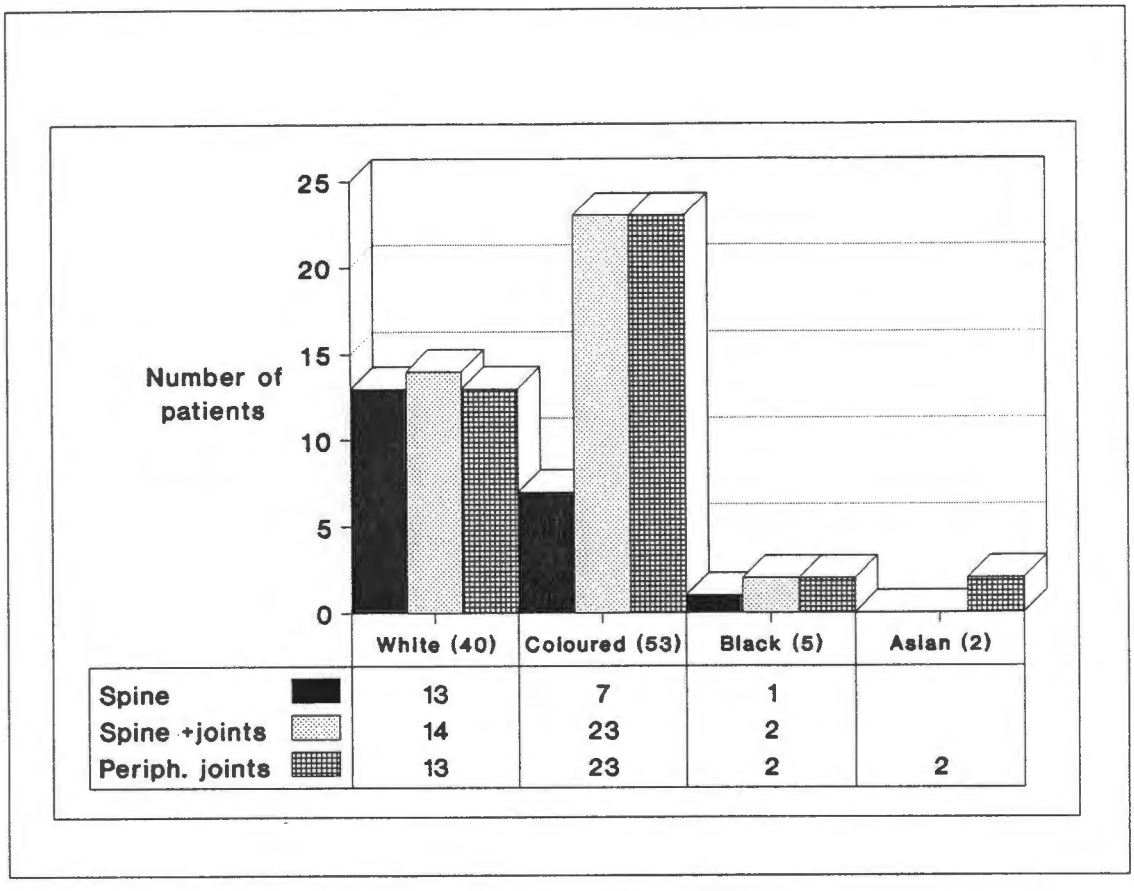


Figure 13 : Patterns of disease in spondyloarthropathy patients of varying ethnic origin

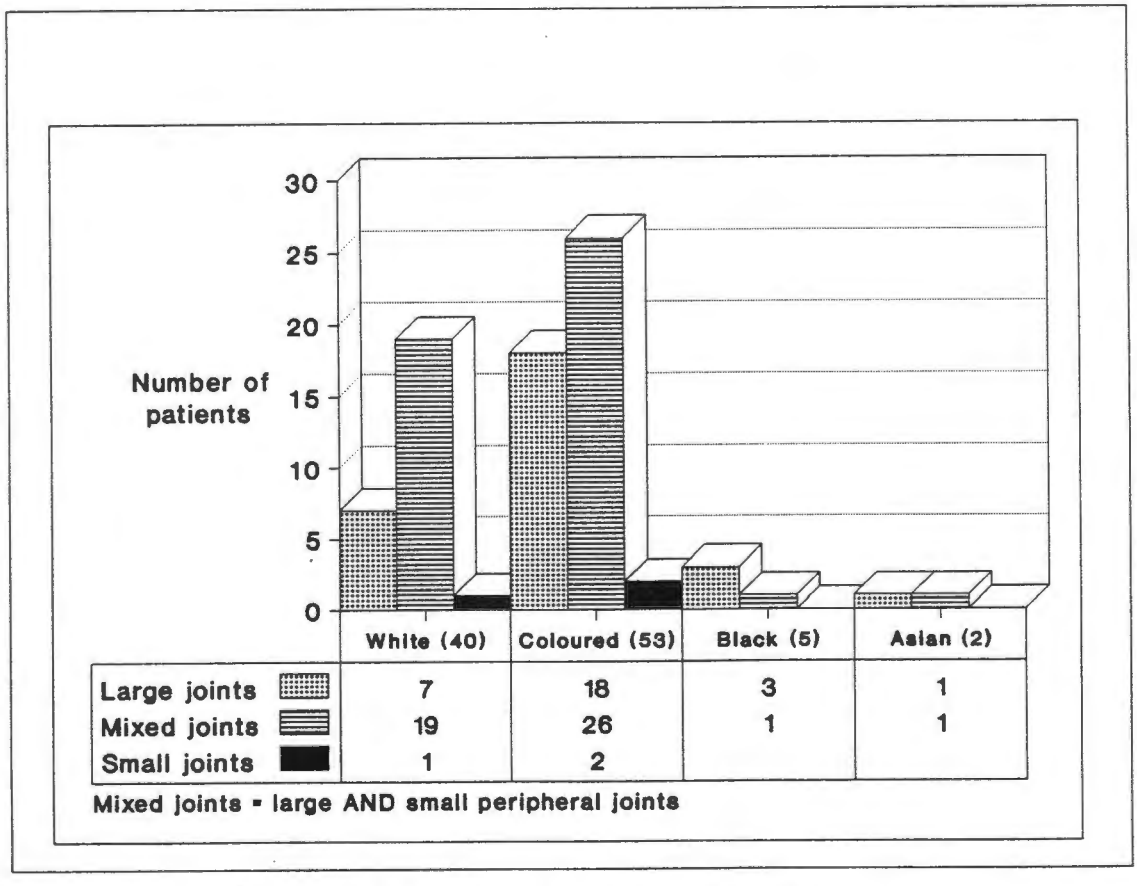


Figure 14 : Peripheral arthritis patterns

Analysis of joint disease patterns, according to ethnic origin, demonstrates that while spondylitis and peripheral arthritis (both large and small joints) were seen with similar frequency in Whites, there was a clear excess of peripheral arthritis (large joints) in the Coloured patient subgroup ($p<0.005$). There was a similar trend in Black patients, but numbers were too few in the Black and Asian groups to permit valid comments (refer to Figures 13 and 14).

Ethnicity was also linked to an increased prevalence of enthesitis, as compared to tenosynovitis ($p<0.05$), observed in Coloured patients only (Table 14).

TABLE 14 : Non-articular musculoskeletal system features in spondyloarthritis patients of different ethnic origins

	WHITE (n=40)	COLOURED (n=53)	BLACK (n=5)	ASIAN (n=2)
Tenosynovitis	8	6	1	1
Enthesitis	11	13		1

Triggers to the onset of ReA (urethritis, diarrhoea) were also found to vary according to ethnic origin. While urethritis (cervicitis in females) preceded all cases of ReA in Coloureds, it accounted for only half of the White patients, the remainder of whom had diarrhoea prior to the onset of rheumatic manifestations. One of two Black patients had diarrhoea and the other had urethritis preceding the onset of ReA.

Peripheral joint radiological features also showed variation based on ethnic heterogeneity. Peripheral joint erosive changes occurred in eight of nine White patients with spondyloarthritis in whom radiological reports were available. In contrast, only half of Coloured patients (12/24) had features of erosive arthropathy on X-rays (Appendix E: Tables 20(a) and (b) p.103).

Advanced changes ('destroyed' joints) were reported in Coloured (10/24) and Black (2/4) patients only (Appendix E: Tables 20(b) and (c), p.103-4).

TABLE 15 : Large joint arthroplasty surgery performed in patients of varying ethnic origin

Large joint arthroplasty	WHITE (n=40)	COLOURED (n=53)	BLACK (n=5)	ASIAN (n=2)
No. of patients	3	10	1	
No. of procedures	6	20	1	

Of 27 large joint arthroplasties performed in 14 patients, 74% of procedures were performed in Coloured patients, while the remaining seven procedures were performed in three Whites and one Black patient ($p<0.005$). Despite the increased number of Coloureds requiring arthroplasty, ethnic origin per se did not influence joint replacement surgery requirements (p-value not significant - see Table 16).

TABLE 16 : DMARD use and arthroplasty surgery performed in in spondyloarthritis patients of differing ethnic origin

DMARD USE (n=16)	NO DMARD USE (n=84)		ARTHROPLASTY* (n=14)	NO SURGERY (n=85)
6 (37.5)	34 (40.5)	White (n=40)	3 (21.4)	37 (43.5)
10 (62.5)	43 (51.2)	Coloured (n=53)	10 (71.4)	42 (49.4)
	5 (5.9)	Black (n=5)	1 (7)	4 (4.7)
	2 (2.4)	Asian (n=2)		2 (2.3)

Percentage indicated in parentheses
* Large joint arthroplasty only

Similarly, Table 16 also shows that Coloured patients accounted for 62.5% of DMARD use, but race per se was not significantly associated with DMARD use (p-value not significant).

Also, the clinical and radiographic features of spondylitis, prevalence of radiographic sacroiliitis, extra-articular manifestations and HLA-B27 prevalence were not influenced by ethnicity (refer to Appendix E: Tables 17 - 20(c) p.102-4).

III. INFLUENCE OF GENDER ON PATTERNS OF DISEASE

The influence of gender on disease patterns in spondyloarthritis patients was evaluated in the 100 cases studied. All the data reviewed is contained in Appendix F (p.105-8), and only important differences are highlighted in this section.

Females had a notably later age of disease-onset and presentation, the mean age for females exceeding that of males by ten years or more. This was true of all disease subgroups except USpA, where age of disease-onset was similar in males and females (refer to Table 21 and Figure 15).

TABLE 21 : Gender-based differences in 100 spondyloarthropathy patients reviewed

MALES (n=71)		FEMALES (n=29)
	Age at onset *	
28.1 (±11.8)	mean (±SD) (yrs)	39.1 (±19)
10-64	range	15-82
	Age of presentation**	
35.4 (±12.6)	mean (±SD) (yrs)	47.5 (±17.6)
13-70	range	15-84
	Disease duration	
7.3 (±7.6)	mean (±SD) (yrs)	8.6 (±11.5)
0.5-31	range	0.5-46

* p=0.006
** p=0.001

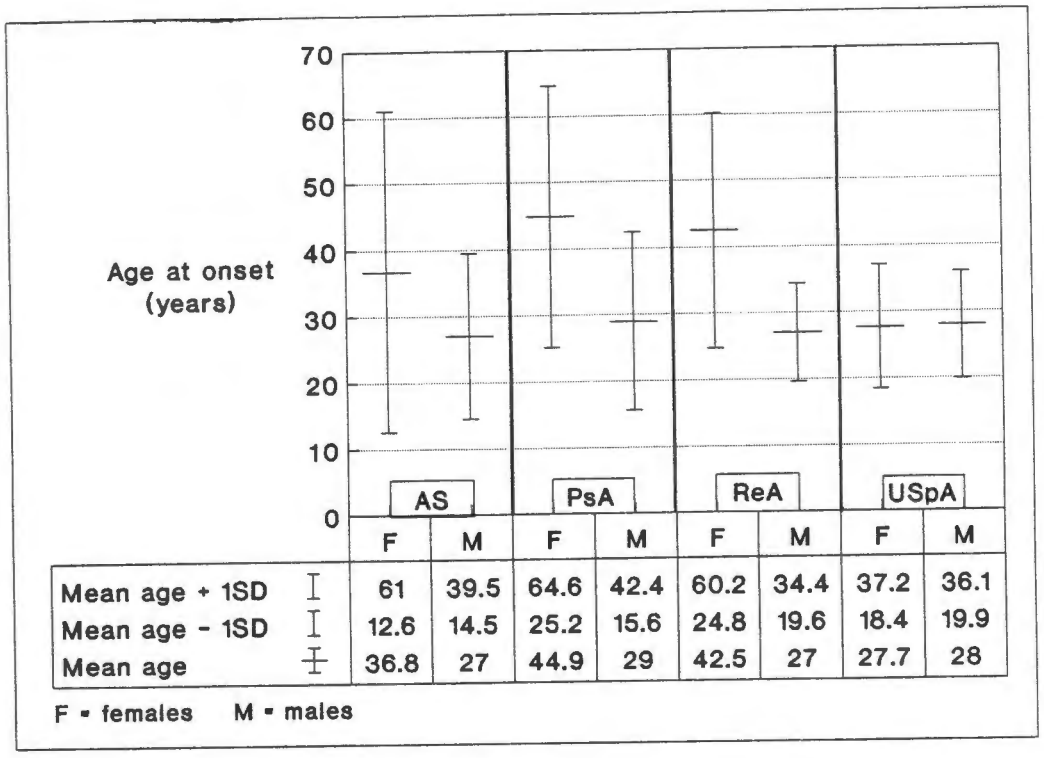


Figure 15 : Comparison of age of disease-onset in males and females of different spondyloarthropathy disease subgroups

While the overall pattern of joint disease did not differ significantly in males and females (Appendix F: Figure 16, p.105), it was observed that inflammatory back pain was more common in males (Table 22(a)). Disease-based subgroup comparison (Table 22(b)) showed that the increased prevalence of spondylitis observed in males was restricted to PsA patients.

No other features regarding non-articular musculoskeletal system features, extra-articular features, HLA-B27 prevalence, radiographic data including sacroiliitis, or large joint arthroplasty requirements differed significantly on the basis of gender (refer to Appendix F: Tables 23-27 and Figures 16 and 17, p.105-8).

TABLE 22(a) : Clinical features of spondylitis

MALES (n=71)		FEMALES (n=29)
45/71 (63.4)	Inflammatory back pain*	13/29 (44.8)
34/69 (49.3)	Reduced spinal mobility	9/25 (36)
26/44 (59.1)	Reduced chest expansion	6/10 (60)
30/53 (56.6)	Schober's test positive	7/13 (53.8)

Denominator = number of patients in whom presence/absence of feature was recorded
* p<0.005
Percentage in parentheses

TABLE 22(b) : Comparison of selected clinical features of spondylitis in male and female PsA patients

	PsA MALES (n=21)	PsA FEMALES (n=14)	p-VALUE
Inflammatory back pain	12/21	2/14	<0.025
Reduced spinal mobility	9/19	1/11	<0.05

IV. INFLUENCE OF HLA-B27 ON PATTERNS OF DISEASE

Comparison of spondyloarthritis patients on the basis of HLA-B27 status was performed so as to evaluate the influence of this genetically-determined variable.

TABLE 28 : Demographic data for spondyloarthritis patients according to HLA-B27 status

HLA-B27 +ve (n=23)					HLA-B27 -ve (n=22)			
AS	PsA	ReA	USpA		AS	PsA	ReA	USpA
1				Black (n=2)	1			
4		3	3(1)	White (n=21)	5	3(2)		3(1)
7(1)	1	3	(1)	Coloured (n=22)	2	3(1)	1	4(1)
12(1)	1	6	4(2)	TOTAL	8	6(3)	1	7(2)
6.7:1				overall male:female ratio	3.4:1			

(n) = number of females in group

The demographic data of 45 patients whose HLA-B27 status was known, is seen in Table 28. AS (60%) and ReA (85.7%) cases were strongly associated with the HLA-B27 antigen, whilst the majority of patients with PsA (85.7%) were HLA-B27 negative; less than half of patients with USpA (36.4%) were HLA-B27 antigen positive.

TABLE 29 : HLA-B27 related differences in spondyloarthritis

HLA-B27 +ve (n=23)		HLA-B27 -ve (n=22)
24 (±7.4) 13-41	Age at disease-onset mean (±SD), range (yrs)	33 (±15.3) 16-74
31.7 (±9.6) 13-51	Age at presentation mean (±SD), range (yrs)	36.6 (±17.1) 17-84
	Clinical spondylitis : *	
17/23	- inflammatory back pain	10/22
14/23	- reduced spinal mobility	7/22
11/16	- reduced chest expansion	6/16
13/16	- Schober's test positive	6/18
12/15	Radiographic spondylitis *	2/9
3	Anterior uveitis	
2	Diarrhoea	
5	Urethritis OR cervicitis	1

* Denominator = number of patients in whom presence/absence of feature was recorded.

In patients with spondyloarthritis, the presence of the HLA-B27 antigen was associated with an earlier age of disease-onset ($p=0.03$) and a tendency towards earlier presentation, and proved predictive of clinical but, more especially, of radiographic spondylitis ($p<0.01$), and of anterior uveitis as an extra-articular feature (Table 29).

As most cases of ReA were HLA-B27 carriers, triggers to the disease in this category (diarrhoea, urethritis) were linked to positive HLA-B27 status (Table 29).

Conversely, HLA-B27 negativity (majority of PsA patients) was associated with small joint disease (Figure 18).

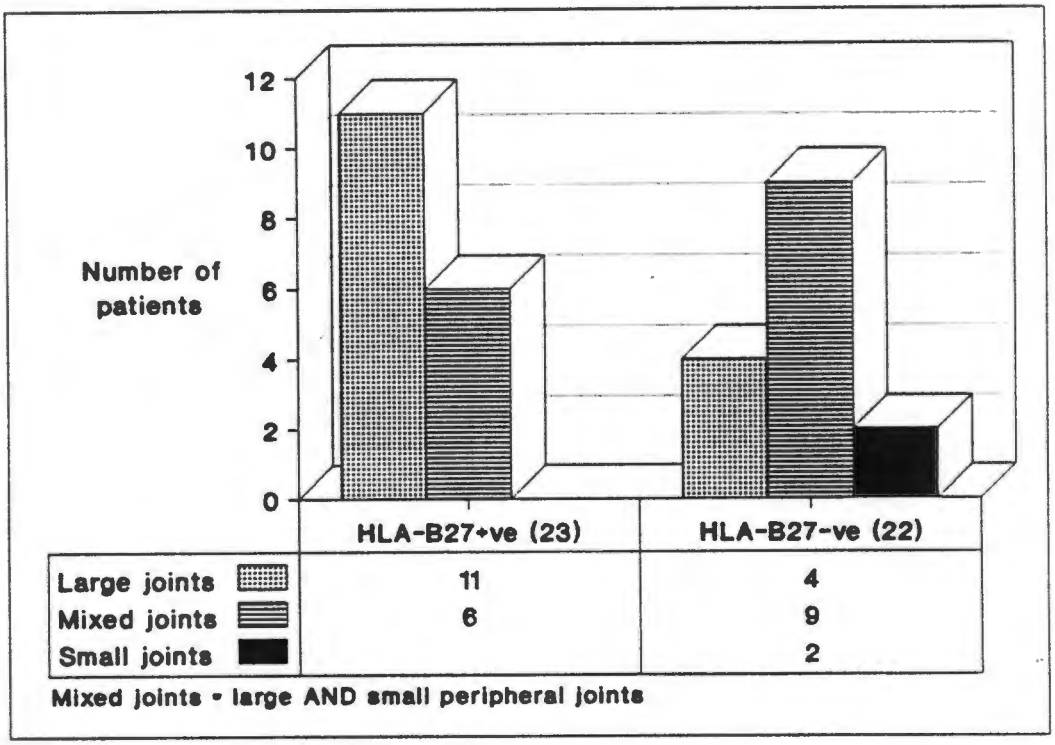


Figure 18 : Patterns of peripheral joint disease in spondyloarthritis patients of differing HLA-B27 status

In view of data relating to HLA-B27-based comparisons in spondyloarthritis (refer to Chapter One: Introduction and Literature Review, p.6-7), a separate analysis of AS was performed.

As shown in Table 30, carriage of the HLA-B27 antigen in AS patients had only a modest influence on the age of disease-onset (p-value not significant), and was predictive of anterior uveitis as an extra-articular manifestation.

TABLE 30 : A comparison of selected features in AS patients of differing HLA-B27 status

HLA-B27+ve AS (n=12)		HLA-B27-ve AS (n=8)
24.6 (±8.8) 13-41)	Age of disease-onset mean (±SD), range	30 (±15) 19-64
3	Anterior uveitis	

In contrast to the findings with regard to spondyloarthropathy in general, in AS patients the clinical and radiographic features of spondylitis did not differ in relation to HLA-B27 status (Appendix G: Tables 31-32(b), p.109-110).

Finally, neither the prevalence of radiographic sacroiliitis, nor peripheral joint radiographic findings nor the ultimate management of patients appeared to be influenced by HLA-B27 status (refer to Appendix G: Tables 32(a)-33, p.109-110).

CHAPTER FOUR

DISCUSSION

Discussion of this study focuses on four distinct aspects of the results, and addresses each in turn.

1. **Spondyloarthropathies are uncommon in Black South Africans.**

   The reduced prevalence of SpA in South African Blacks, as seen in Black communities elsewhere in Africa, is discussed, and possible reasons for this finding are explored.

2. **The clinical picture of spondyloarthritis in urban South Africans.**

   The broad clinical spectrum of spondyloarthritis, as documented in this report of urban South Africans, is compared with published international data. The striking overall similarities are highlighted, and potential explanations for observed differences are offered. Also, the influences of ethnicity, gender and HLA-B27 are examined in the light of existing data.

3. **The management of spondyloarthropathies in a South African university-based Rheumatic Diseases Unit.**

   The pharmacological and surgical management options utilised by the RDU, UCT largely reflect international trends and this is discussed in some detail.

Explanations accounting for the apparent increased prevalence of joint arthroplasty locally are examined.

4. **Why the paucity of reactive arthritis?**

The striking paucity of reactive arthritis in a developing African country such as South Africa, where urethritis and diarrhoea are common clinical problems, is highlighted and theoretical explanations for this phenomenon proposed.

1. SPONDYLOARTHROPATHIES ARE UNCOMMON IN BLACK SOUTH AFRICANS

This study, and other similar reports, indicate that up to 7% of African patients, presenting with rheumatic disease-related symptoms, have spondyloarthritis (SpA) (Table 34).

TABLE 34 : Prevalence of spondyloarthritis in Africa

		SpA prevalence (%)*	
		HIV negative	HIV positive
Zimbabwe, 1990 (66) **	• 6 months, prospective • Blacks, n=141	7.8	8.5
Zimbabwe, 1991 (68)	• 10 months, prospective • Blacks, n=411	5.3	6.3
Togo, 1993 (70)	• 27 months, retrospective • Blacks, n=2020	1.1	0.5
South Africa, 1994	• 72 months, retrospective • Multi-racial, n=1925	5 ***	

* All data derived from hospital-based studies
** Study included patients known to the hospital - not representative of prevalence of spondyloarthritis in a "New Patient" clinic
*** HIV status not assessed, but no patient was reported to have features suggestive of HIV infection including progressive unexplained loss of weight, chronic unexplained diarrhoea, peripheral lymphadonopathy, oral candidiasis or oral hairy leukoplakia.

Despite the crude nature of these prevalence data, the presence of SpA in Africa is confirmed, and the, until recently, under-estimated burden of rheumatic disease on this continent highlighted (57,92).

There is a striking paucity of Black patients in this South African study, in spite of White, Coloured and Asian patient numbers being fairly representative of both the population residing in the Cape Peninsula and those attending State-funded hospital OPDs in the region (Table 35).

TABLE 35 : Ethnic composition of the resident population, and State-funded hospital OPD attendance, in the Cape Peninsula - 1991

	Resident Population (%) (81)	Hospital OPDs (%) (82)*	Cape Town SpA study (%)
White	25.9	13.1	40
Coloured	50.7	65.4**	53
Black	22	21.5	5
Asian	1.4	0.3***	2
TOTAL NUMBER	1 869 145	1 589 595	100

* Average calculated from 1989/90 and 1990/91 data
** Composite figure for Coloured and Asian - separate statistics poorly defined (82)
*** Data derived from Tygerberg Hospital OPD count only

Indeed, White patients comprised a greater than expected proportion of the cohort, probably reflecting the increased prevalence of HLA-B27-associated disorders in an ethnic group having a significantly higher background prevalence of HLA-B27 when compared with other South African ethnic groups (refer to Chapter One: Introduction and literature review - Table 1, p.13). Also, the increased use of State-funded, and university-linked, rheumatological services by more affluent sectors of the community, consequent upon the limited availability of such expertise nationally (93), may have contributed an element of referral bias.

Although the size of the Coloured patient cohort of this study was proportional to the population composition of the Cape Peninsula in the early 1990s, it may constitute a relative over-representation, given the reduced background prevalence of HLA-B27 in Coloured when compared to White South Africans (refer to Chapter One: Introduction and literature review - Table 1, p.13).

This may be due to referral bias, since PAOH is situated in close proximity to a former 'Coloured housing zone'. However, good transport facilities by both road and rail from all areas of the Cape Peninsula, and the referral nature of the hospital services are likely to have largely protected the data from major influence from this potential confounding variable.

National population statistics indicate that, during the time period of this study, 78% of Asians were resident in Natal (including KwaZulu), while only 4.6% stayed in the Cape Province (Western and Eastern regions) (94). Differential geographical distribution therefore accounts for the small minority of Asian patients in this study.

In contrast, Black people constituted at least 22% of the resident Cape Peninsula population in 1991 (refer to Chapter Two: Study Design and Methods - Figure 2b, p.21), and represented 21.5% of patients attending State-funded hospital OPDs at that time (refer to Chapter Two: Study Design and Methods - Table 3, p.22). In the light of these data it is improbable that the reduced number of Black SpA patients observed can be attributed to financial or geographical constraints. Rather, this pattern is compatible with a truly diminished prevalence of HLA-B27-associated SpA in Black South Africans.

It is recognised that health service-based data collection, particularly in developing countries, is fraught with difficulty (important factors listed in Table 36) and, in its

turn, is liable to create false impressions of actual disease prevalence. While such influences are relevant to this study, they do not entirely explain the demographic phenomenon observed; other factors such as genetic make-up, environmental influences and host immune responses need to be considered. These will be amplified in the subsequent text.

TABLE 36 : Factors influencing public health service-based data collection

* Limited/inaccessible health care facilities
* Inadequate primary health care evaluation
* Restricted access to specialist opinion/care
* Budget restrictions curtailing use of extensive and/or expensive diagnostic investigations

The prevalence of SpA correlates in a positive manner with the background prevalence of HLA-B27 in the specific population group being considered (27 quoted in 5, 28, 32). Hence the scarcity of this HLA haplotype in African Blacks (Table 37) should account for the virtual absence of Blacks in this SpA study cohort. However, fewer than 50% of recorded SpA cases are HLA-B27-associated in communities having a reduced background HLA-B27 prevalence (Table 37).

TABLE 37 : HLA-B27 prevalence in populations of Black African descent

	HLA-B27 prevalence (%)	
	Population group	SpA cases
American Blacks (32, 95*)	2-4	48
Zimbabwean Blacks (63, 67)	0.68	0
South African Blacks (61, 63, 68)	0.29-0.68	12.5

* Data quoted in (32)

Also, recent data from The Gambia demonstrate that, despite a local HLA-B27 prevalence figure of 6% (96) resembling the 8% prevalence in White North European communities (27, quoted in (5)), no case of SpA was detected in 1115 subjects examined (96). This finding has previously been attributed to regional dominance (in West Africa) of the HLA-B*2703 subtype which, of nine recognised B27 allotypes (35), is thought not to be associated with SpA (97). However, Brown et al have shown that whilst 50% of HLA-B27 positive Gambian subjects (without AS) were subtype B*2703 positive, the remainder were B*2705 positive (96). This is an unexpected finding since the B*2705 allotype commonly occurs in SpA patients of White North European population groups (35). Thus it is clear that HLA-B27 antigen status is not the only important factor in the pathogenesis of SpA (32, 34, 36, 45), and ongoing research is needed to identify additional protective factors accounting for the diminished prevalence of SpA in selected population groups, locally and elsewhere.

Currently, additional HLA class I and II alleles, which appear to be relevant to the development of SpA, AS and ReA in particular, have been identified (98, 99). However, such

preliminary data, of additional genetically-mediated influences, require better definition before it is possible to implicate that the absence of such genetic factors is able to confer protection against onset of SpA in identified ethnic groups.

2. THE CLINICAL PICTURE OF SpA IN SOUTH AFRICANS

The SpA disease spectrum, as recorded in South Africans in this study, is concordant with that described in the international rheumatology literature. Comparison of Tables 38 and 39 confirm the similarities, and highlight several interesting points.

TABLE 38 : Clinical patterns of disease in 100 spondyloarthritis patients studied in Cape Town (1988-1994)

	AS (n=35)	PsA (n=35)	EA (n=2)	ReA (n=13)	USpA (n=15)
Age at onset, mean (range) (yrs)	29 (13-82)	35 (10-74)	42 (32-53)	29 (17-55)	28 (13-40)
Gender males:females	4.8:1	1.5:1	1:1	5.5:1	1.5:1
Prevalence (%)					
Spondylitis	100	51	50	8	33
Peripheral arthritis	54	94	50	100	87
Sacroiliitis	100	33	100		33
Enthesitis	20	14		46	47
Tenosynovitis	3	31		23	7
Uveitis	17	3			
Aortic regurgitation		3			7
HLA-B27 positive	60	14		86	36

TABLE 39 : Clinical patterns of disease in spondyloarthritis - international data

	AS	PsA	EA	ReA	USpA
Mean age at onset (yrs)	17-40	20-50	15-50	18-45	16-23
Gender males:females	4.6:1	± 1:1	1:1	10:1(UGT) 1:1(GIT)	1.4:1
Prevalence (%)					
Spondylitis	all	20-40	<15	<23	±20
Peripheral arthritis	±33	>80	>80	>80	>80
Sacroiliitis	all	20-40	±15	20-30	16-30
Enthesitis	20	40		10-20	20-28
Tenosynovitis		20-30		10-20	
Uveitis	20-40	3	rare	<5	
Aortic regurgitation	4-5	1	rare	1	7
HLA-B27 positive (White populations)	90	PA <20 Sp ±50	PA <20 Sp >50	70-85	80

PA = peripheral arthritis
Sp = spondylitis

References : AS : 2, 100-108
PsA: 9, 77, 109-114
EA : 10, 115, 116
ReA: 5, 11, 12, 28, 29, 117, 118
USpA: 107, 119, 120

- The wide range of age at disease-onset in South African SpA patients, is accounted for by the inclusion of 9 cases with juvenile-onset disease and three AS patients with disease-onset beyond 50 years of age. Although late-onset AS is uncommon, this has been well documented in a French case series of ten males (121), and was also recorded in four of eight African Blacks with AS, as reported by Chalmers (61).

- Figure 19 demonstrates the shift in emphasis with respect to articular features that occurs across the SpA spectrum; AS prevails at the spondylitis end of the spectrum, progressing through PsA, USpA and ReA toward

the peripheral arthritis end of the spectrum. Data from Table 39 confirms that this pattern is also observed internationally. Understanding SpA in terms of a broad spectrum, with varying emphasis on axial or peripheral manifestations, is in line with the current trend of broadening the overall disease concept and thereby accommodating patients previously excluded by rigid classification criteria (15).

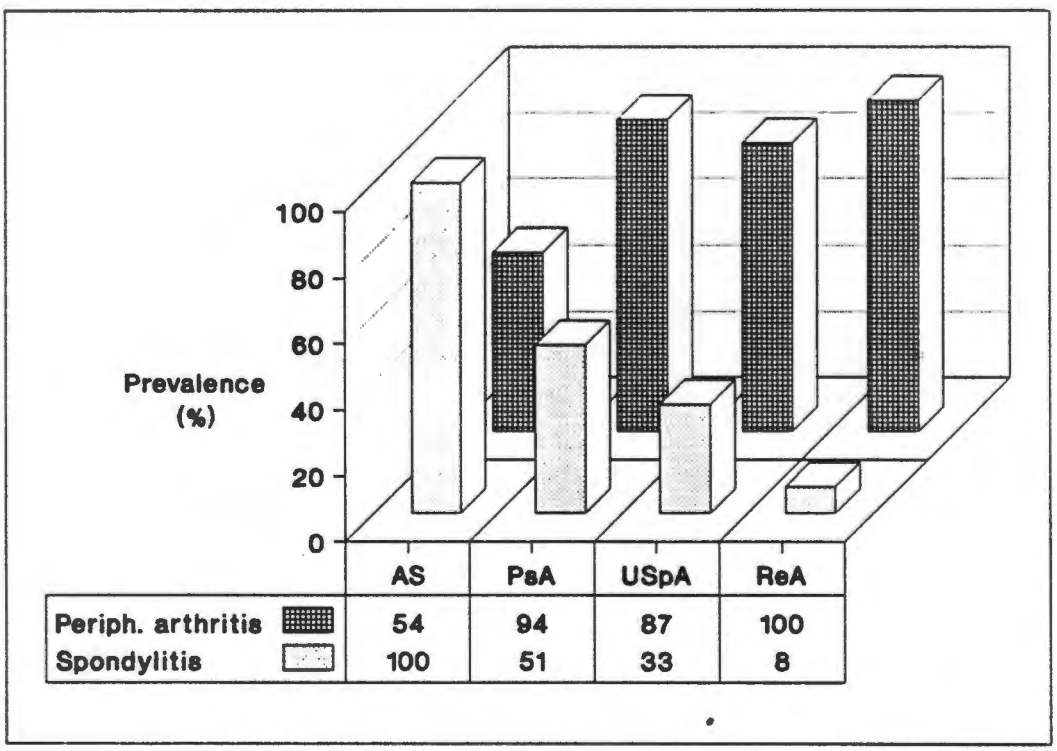


Figure 19 : The spondyloarthropathy disease spectrum

- The local prevalence of spondylitis in PsA cases was greater than usually reported elsewhere (109, 110, 113). However, this figure does vary in the literature, as illustrated by a previous study conducted by the RDU (UCT), in which spondylitis was reported in 88% of psoriasis patients with arthritis (77).

- In this study both spondylitis and sacroiliitis were more frequently recorded in USpA cases than is generally quoted in the literature (107, 120). However, reports regarding this subset of SpA are few, and the clinical picture is still emerging. Explanations at this point would thus be premature.

- An alarming number of PsA patients (70.4%) were noted to have radiographic evidence of erosive, deforming arthritis in the Cape Town data. Recent studies are however highlighting the aggressive nature of PsA, reporting erosive, deforming radiographic changes in up to 57% of series (77, 109, 110).

- 'Destroyed' peripheral joints indicating advanced post-inflammatory features (obliteration of the joint space with/without ankylosis of the joint) were recorded in 53% of AS patients for whom radiograph reports were available. These patients generally required large joint arthroplasty procedures. Possible explanations for this observation are discussed in detail later.

- An unusually high percentage of bilateral sacroiliitis was observed in the PsA subset of local SpA patients. In general, this feature is largely restricted to HLA-B27 positive PsA subjects (about 85% of cases), in which circumstance more than half have bilateral sacroiliac changes (110). While the only HLA-B27 positive patient in this study had bilateral sacroiliitis, HLA typing was not available for the remaining four PsA patients with

bilateral sacroiliitis. Conclusions regarding this feature of the study are thus limited.

TABLE 40 : Variations in spondyloarthritis disease patterns as determined by selected genetic variables

ETHNIC ORIGIN

- tendency to present earlier; shorter disease duration (B)
- peripheral arthritis more common than spondylitis (C)
- peripheral joint radiographs :
  - erosive changes (W)
  - erosive changes and 'destroyed' joints (C)
- 74% of arthroplasties (C)

GENDER

- delayed age of onset (f)
- increased prevalence of back pain (m)

HLA-B27 STATUS

- earlier age of onset (+)
- increased prevalence of :
  - spondylitis (+)
  - small joint peripheral arthritis (-)
  - anterior uveitis (+)

(B) = Blacks, (W) = Whites, (C) = Coloureds
(f) = females, (m) = males
(+) = HLA-B27 positive, (-) = HLA-B27 negative

The influence of selected, genetically-determined variables on the SpA disease profile observed in this study, are highlighted in Table 40. Several interesting observations are made :

- The small cohort of Black patients reported in this study did not present with advanced, neglected longstanding disease, supporting the concept that delayed and/or limited access to health care facilities were not significant factors accounting for their under-representation in this study.

- It is surprising that, despite a probable element of referral bias accounting for both White and Coloured patient numbers in this RDU study (as discussed earlier in this chapter), the excess of peripheral arthritis, particularly advanced disease requiring arthroplasty, was observed predominantly in Coloured patients. Although this may suggest that aggressive peripheral joint disease in SpA is more common in Coloured South Africans, a statement such as this could only be made with any measure of confidence after review of all arthroplasties performed in SpA patients in both State-funded and private local medical facilities. Such co-ordinated data collection is not available, and thus interpretation of this observation is limited.

- The delayed onset of SpA observed in females ($p=0.006$) requires careful consideration. Disease-based subgroup analysis shows that the overall trend to delayed onset was only significant in the PsA subgroup ($p=0.015$), while small sample size in the other subgroups precluded useful comparison. Since the onset of arthritis in psoriasis occurs across a wide age range, approximately 8-80 years (77, 109), the delayed disease-onset in females, as recorded in this study, may represent a non-specific finding.

- Back pain and restricted spinal mobility, two features of spondylitis, were more frequently recorded in males, specifically of the PsA subgroup. This observation has

been recorded elsewhere (109, 110, 112), and Torre Alonso, et al (110) have shown that the spondylitic form of PsA, predominant in males, is associated with increased levels of immunoglobulin A (IgA), suggesting a possible relationship between AS and psoriatic spondylitis. While a similar clinical finding is reflected in this study, IgA levels were not studied.

- HLA-B27 positivity, in this study, was associated with early age of disease-onset, spondylitis and anterior uveitis. Review restricted to the AS subgroup shows that only the prevalence of anterior uveitis varies with HLA-B27 status. This matter has been intensely debated in the literature, and was discussed earlier (Chapter One: Introduction and literature review; - 2. The HLA-B27 Association, p.5-7). It transpires that differences in clinical disease profiles, incorrectly ascribed to HLA-B27 status, merely reflect the heterogenous nature of the various disorders constituting the SpA spectrum (30).

- The association of small joint disease and HLA-B27 negativity reported in this study, is easily explained by the observation that small joint involvement featured prominently in PsA cases, most of whom were HLA-B27 negative (85%).

Based on the observations of this descriptive study, therefore, the conclusion is that SpA disease patterns in

urban South Africans largely reflect those seen in Europe and North America. This is consistent with observations in Southern Africa relating to other rheumatic diseases, such as rheumatoid arthritis (RA); urbanised Africans display RA disease patterns similar to those described in First World centres (122).

3. THE MANAGEMENT OF SPONDYLOARTHRITIS IN A SOUTH AFRICAN UNIVERSITY-BASED RHEUMATIC DISEASES UNIT

Therapeutic management strategies utilised by the RDU (UCT) in the management of SpA are summarised in Table 41.

TABLE 41 : Management of Spondyloarthritis, RDU, Cape Town

	Prevalence (%)				
	AS (n=35)	PsA (n=35)	EA (n=2)	ReA (n=13)	USpA (n=15)
Symptomatic therapy only	83	69	50	85	100
DMARD	11	31			
Corticosteroid	9	3			
Large joint arthroplasty	26	8			20

Symptomatic treatments (analgesics and NSAIDs) were prescribed in the majority of patients, reflecting the internationally recognised efficacy of these agents in relief of symptoms in SpA patients (123).

Similarly, DMARD use in the RDU (Cape Town) also reflects international trends, where most experience exists in the use

of sulphasalazine in AS and methotrexate in PsA (cumulative data summarised in (123) and (124)).

The high prevalence of erosive, deforming arthritis observed in this series of PsA patients (70.4%) and similar data from other centres (77, 109, 110), together with reports of severe functional impairment (American Rheumatology Association Class III-IV) in up to 19% of cases (109, 110), more than justifies the use of DMARDs in PsA patients locally and abroad (109). Based on current observations, earlier, more aggressive use of DMARDs is being advocated in an attempt to alter the unfavourable outcome of PsA in a significant percentage of cases (109, 110).

Methotrexate (low-dose oral weekly therapy) was the DMARD of choice in the management of PsA in this study. Therapeutic efficacy of this agent was first demonstrated in a parenterally administered double-blind placebo-controlled trial in 1964 (125), and subsequently low-dose oral therapy has been shown to be of variable benefit (43-80%) in small open trials and retrospective reports, as reviewed by Creemers et al (124). More recently, a multicentre trial using low-dose (7.5-15 mg) oral weekly therapy showed a favourable response, although the difference failed to achieve statistical significance (126). While methotrexate is currently the favoured agent, positive reports on the use of azathioprine and cyclosporin A are also appearing in the literature (127).

Sulphasalazine use was restricted to AS and EA patients in this study. While the benefit of this agent in the management of IBD and related SpA has been previously documented (10), meta-analysis of five randomised double-blind placebo-controlled studies has also demonstrated efficacy and safety in the short term (three to six months) use of sulphasalazine in AS (128). Despite achieving only modest benefit, largely due to extended disease duration prior to the use of sulphasalazine in a significant number of cases (129), data such as this may promote earlier use of DMARDs in AS too. Furthermore, preliminary data suggesting efficacy of other DMARDs, including methotrexate, azathioprine and cyclophosphamide (124) may soon broaden the spectrum of therapeutic options in SpA.

The role of corticosteroids remains questionable, and limited use (<10%) in this study probably reflects this uncertainty. While data suggesting benefit from short course pulse methylprednisone in acute severe attacks of AS exists (130), chronic long-term use of oral corticosteroids is generally not recommended in AS (123) or PsA (127).

Radiation therapy, administered to only one patient in the study cohort, was abandoned in the 1960s (despite efficacy) owing to the associated increased risk of malignancy [reviewed in (123) and (124)].

TABLE 42 : Prevalence of large joint arthroplasty in AS patients - international data

	Large joint arthroplasty prevalence (%)	
Khan, et al (33)	8.9	(n=78)
Calin, et al (131)	6	(n=1500)*
	8	(n=50)
McKenna, et al (132)	6	(n=123)
Wordsworth, et al (133)	6	(n=100)

(n) = size of cohort studied)
* patients from National Ankylosing Spondylitis Society (NASS)

Large joint arthroplasty was performed in 14% of the Cape Town SpA cohort. The commonest indication for joint replacement was a radiographically 'destroyed' joint (obliterated joint space with varying degrees of joint ankylosis) accompanied by disability. Table 41 indicates that one-quarter of all the AS patients studied required total hip replacement (THR), while data from Europe and North America suggest that only 6-8% of AS cases require THR (Table 42). However, it is internationally recognised that joint arthroplasty procedures are more frequently required in juvenile-onset AS (17%) as compared with adult-onset AS (4%) (134). Thus the fact that one-third (6/18) of all total hip arthroplasties in AS patients were performed in two juvenile disease-onset patients, partly accounts for the apparently increased frequency of arthroplasty surgery in AS patients in this study. An element of bias is, however, also relevant, and is addressed in the subsequent text.

Since the data in Table 42 are derived from hospital-based records (except where indicated), selection bias owing to the

hospital-based nature of the Cape Town data does not appear to account for the observed difference. Furthermore, the data of Calin et al (131), gathered by administering a self-answered postal questionnaire to members of the National Ankylosing Spondylitis Society (NASS), demonstrate that even community-based surveys provide similar prevalence data (large joint arthroplasty) when compared with hospital-based studies.

In the Western Cape, restriction of State-funded surgical expertise to two regional centres only, resulting in aggregation of selected patients at these centres, is a more tenable explanation for the difference between local and international data. In Europe and North America, in contrast, greater numbers of centres manage such patients, tending to spread the surgical load, rather than 'clustering patients' at one or two centres, as is the situation locally.

Similarly, the arthroplasty requirements of PsA and USpA patients in this study are subject to the potential "patient clustering" phenomenon previously described. However, the 20% prevalence of large joint prostheses in USpA patients studied in Cape Town, has not been noted in other studies of this disease subgroup to date. Such data requires further evaluation in other centres to confirm this unexpected high morbidity figure, in a previously 'ignored' patient population. Follow-up data suggesting that a significant percentage of USpA go on to develop classical AS over a

period of several years (16), tends to support the credibility of the observation made in this study. It seems plausible that an otherwise previously undefined cohort of young patients with neglected large joint (predominantly hip) disease, may present for the first time when requiring arthroplasty surgery.

TABLE 43 : Disease profile of AS/PsA patients prescribed DMARDs and/or requiring large joint arthroplasty RDU, Cape Town

- Early age of onset
- Prolonged disease-duration
- Radiographic joint damage

Table 43 reflects the disease profile of high-risk SpA patients, as identified in this observational study. Early identification of such SpA patients, prior to the development of advanced clinical and radiographic joint damage, would afford clinicians the opportunity of instituting DMARD management earlier, thereby permitting better evaluation of the disease-modifying (retarding) efficacy of the various agents. Ultimately, this should achieve a reduction in arthroplasty requirements, and preserve patients' financial and physical independence. The personal and national benefits are obvious, especially in a developing country such as South Africa.

Encouraging 'early referral of all cases of synovitis' identified by South African primary health care facilities to

a regional RDU referral centre has potential to detect at-risk patients early, allowing for more effective management and a potentially better outcome. Most referred cases would ultimately have RA, but SpA patients would certainly form part of the referred cohort (approximately 5% according to this study) with the potential for similar benefit as in RA. In the broader vision of future health care in South Africa, including widely accessible primary care facilities, encouraging early referral and intervention has the potential to improve the long-term outcome of rheumatic disease in an African country enormously privileged to have specialist rheumatology services. An "Early Synovitis Clinic" has recently been established by the RDU (Cape Town), but large scale community awareness and education is required for such a facility to demonstrate benefit in the long-term. Hence, education of primary medical care-givers (for example, nurse practitioners) in the recognition of symptoms and signs of rheumatic-related diseases should currently be given priority.

A limited programme geared to training nursing professionals in the recognition and limited management (treatment, follow-up and monitoring of DMARD-related toxicity) of rheumatic diseases has been established in the Western Cape under the auspices of the Nursing Education Division, GSH. Such programmes should enjoy wide publicity and support, especially from the local rheumatology fraternity, since they have potential to impact on the quality of accessible health care in the wider community of South Africa.

4. WHY THE PAUCITY OF REACTIVE ARTHRITIS?

The striking discrepancy between the observed prevalence of ReA, and the plethora of potential precipitating infections on the African continent, a recent focus of attention (57), is the most interesting observation recorded in this study. If ReA is expected to occur in 1-3% (20% if HLA-B27 positive) of individuals presenting with urogenital tract or enteric infections known to trigger rheumatic manifestations (12), then the number of cases reported from Africa is astonishingly low (Table 44).

TABLE 44 : Prevalence of ReA in Africans presenting with rheumatic-type symptoms

	ReA prevalence (%)*
Zimbabwe, 1990 (66)	3.5
Zimbabwe, 1991 (68)	3.4
Togo, 1993 (70)	0.3
South Africa, 1994	0.6 (1.1)**

* HIV negative subjects only
** Prevalence of ReA in Black subjects in study only

In the metropolitan area of Cape Town alone, approximately 33 000 people attended municipal Sexually Transmitted Diseases (STD) Clinics in 1993 (135). More than 50% of patients were new cases (approximately 15/1000 population incidence rate), and less than one-third of reported sexual contacts were treated (135). Non-gonococcal urethritis, most commonly *Chlamydia trachomatis*-related (136), represented more than half of cases treated, whilst gonococcal disease (co-infection with *Chlamydia trachomatis* in 15-50% (136, 137))

constituted the majority of the remainder. Municipal clinic data underestimate the true size of the infected population by a considerable margin, but even these conservative figures make it very difficult to account for only thirteen new cases of ReA seen by the RDU (UCT) over seven years, whilst in excess of 100 000 new cases of STD (*Chlamydia trachomatis*-related in the majority) were treated in Cape Town in the same time period (135). This hypothetical estimate of the local 'population at risk' for ReA does not even take into account the prevalence of common ReA-precipitating enteric infections, *Salmonella* and *Shigella* species in particular; such data would merely underscore the already glaring hundredfold disparity between the predicted and observed data.

While inaccuracies of health service-based data collection (previously outlined in Table 36), incomplete data capture owing to the retrospective nature of this study, and the diminished prevalence of HLA-B27 in non-White South Africans may partly account for the above observation, other relevant factors should also be considered.

Indeed, recent observations in the Gambia by Brown et al (96) (refer to Chapter Four: Spondyloarthropathies are uncommon in Black South Africans, p.62), have led to speculation that genetic (HLA-B27 heterogeneity or non-HLA-B27) or environmental factors may act to protect certain populations from the development of SpA-related disorders. Therefore it seems reasonable to suggest that diverse environmental

microbial antigen exposure may influence the genetically-determined, immune-mediated human response in circumstances of pathogenic antigen challenge, thereby favourably modulating the clinical consequences of such microbial encounters. In support of this suggestion it has been shown in a murine model that vaccination with mycobacterial 65kDa heat shock protein (hsp), prior to *Mycobacterium tuberculosis* exposure, protects against the development of adjuvant arthritis (138). Heat shock proteins, such as those used in this study, are phylogenetically highly conserved potentially immunogenic proteins in prokaryotes and eukaryotes (139), and are consequently eminently suitable candidate antigens to mediate cross-reactive immune responses between unrelated microbial pathogens. Furthermore, since *Mycobacterium tuberculosis*, responsible for an estimated 90 million cases of tuberculosis in the final decade of this century (140), is the most important single pathogen known to man, its hsp is an ideal antigen to consider, and further explore, in the clinical setting. While mycobacterial hsp has more commonly been considered to cross-react with human 60kDa hsp (both members of the hsp60 family), thereby implicated in the pathogenesis of auto-immune-mediated diseases such as RA (141, 142), this has not been a consistent experimental finding (143-145). Alternatively, it is tempting to suggest that mycobacterial hsp encountered in the form of *Mycobacterium bovis* Bacillus Calmette Guerin (BCG) vaccination and environmental or disease-related exposure may promote a protective host immune response upon exposure to other pathogens producing antigenically similar hsps. Such

influences on immune responses may be particularly relevant in areas of the world where tuberculosis has reached epidemic proportions, including South Africa where the current annual incidence rate for new cases of tuberculosis in Cape Town is of the order of 500-800/100 000 population in local Coloured and Black communities respectively (146).

Chlamydia trachomatis, already identified in preceding discussion as a major South African pathogen in the STD setting, also produces a 60kDa hsp; thus it seems plausible that a cross-reactive hsp60-specific memory T-cell-based immune response promoting rapid and efficient containment of chlamydial organisms at their portal of entry (urethra or cervix) may prevent haematogenous dissemination to peripheral joint, and so account for the limited prevalence of ReA within a vast pool of people in whom it is known precipitating infections for ReA are common.

It is hoped to pursue this hypothesis in further prospective research.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

1. The spectrum of spondyloarthropathy at the University of Cape Town represents the world-wide experience with respect to demography, clinical features, radiography, therapeutic requirements and the need for arthroplasty.

2. Spondyloarthritis is uncommon in Blacks for reasons that are not fully explained.

3. Reactive arthritis is rare in relation to the frequency of sexually transmitted diseases in the Cape Peninsula.

RECOMMENDATIONS

1. Future prospective studies are needed to see the long-term outcome of undifferentiated spondyloarthropathy in South African patients.

2. The paucity of spondyloarthritis in Blacks may hold some clues about the pathogenesis of this group of diseases, and this merits further study.

3. Molecular studies, focusing on mycobacterial and related heat shock proteins, may elucidate some reasons for reactive arthritis being uncommon in our cohort of patients.

APPENDIX A

DISEASE CLASSIFICATION CRITERIA AND/OR DEFINITIONS

1. **ANKYLOSING SPONDYLITIS** (adapted from 5)

1.1 **Rome, 1961** (6)

Clinical criteria

1. Lower back pain and stiffness (more than three months), not relieved by rest.
2. Pain and stiffness in the thoracic region.
3. Limited motion in the lumbar region.
4. Limited chest expansion.
5. History or evidence of iritis or its sequele.

Radiologic criterion

6. Radiographs showing bilateral sacroiliac changes characteristic of ankylosing spondylitis (this would exclude bilateral sacroiliac joint osteoarthritis).

Definite ankylosing spondylitis defined by grade 3-4 bilateral sacroiliitis and at least one clinical criterion OR at least four clinical criteria in the absence of radiographic sacroiliitis.

1.2 New York, 1966 (7)

Clinical criteria

1. Limitation of the lumbar spine in all three planes: anterior flexion, lateral flexion and extension.
2. Pain at the dorsolumbar junction or in the lumbar spine.
3. Limitation of chest expansion to 2.5 cm or less measured at the level of the 4th intercostal space.

Grading of radiographs

0 : normal

1 : suspicious

2 : minimal sacroiliitis

3 : moderate sacroiliitis

4 : ankylosis

Definite ankylosing spondylitis defined by grade 3-4 bilateral sacroiliitis with at least one clinical criterion OR grade 3-4 unilateral or grade 2 bilateral sacroiliitis with clinical criterion 1 or both clinical criteria 2 and 3.

Probable ankylosing spondylitis defined as bilateral sacroiliitis in the absence of any clinical criteria.

1.3 **Modified New York criteria, 1984** (8)

1. Low back pain of at least three months duration improved by exercise and not relieved by rest.
2. Limitation of motion of the lumbar spine in sagittal and frontal planes.
3. Chest expansion decreased relative to normal values for age and sex.
4. Bilateral sacroiliitis grade 2-4.
5. Unilateral sacroiliitis grade 3-4.

Definite ankylosing spondylitis defined as unilateral grade 3-4, or bilateral grade 2-4 sacroiliitis and at least one of the three clinical criteria.

2. **PSORIATIC ARTHRITIS** (9)

Definition : psoriasis, associated with an inflammatory arthritis, which is usually rheumatoid factor negative.

3. **ENTEROPATHIC ARTHRITIS** (10)

Definition : an inflammatory arthritis induced by, or occurring in, the presence of intestinal disease. The spectrum of intestinal disease includes :

- inflammatory bowel disease (IBD)
  - ulcerative colitis
  - Crohn's disease
- Whipple's disease
- intestinal bypass surgery
- miscellaneous, including :
  - coeliac disease
  - collagenous colitis

4. REITER'S SYNDROME

4.1 Reiter, 1916 (adapted from 11 and 12)

A clinical triad of urethritis, arthritis and conjunctivitis following dysentry was first described by Stoll in 1776. This same triad was noted to follow venereal infection, as reported in 1818 by Brodie. Reports by Reiter in 1916, and Feissinger and Leroy in the same year, again described the same clinical observations following urogenital and gastro-intestinal infections, respectively. The syndrome was finally formally described by Bauer and Engelman in 1942.

4.2 American Rheumatism Association, 1981 (13)

Definition : an episode of peripheral arthritis of more than one month duration, occurring in association with urethritis and/or cervicitis.

5. REACTIVE ARTHRITIS

5.1 Ahvonen et al, 1969 (14)

Definition : an episode of acute arthritis developing soon after, or during, an infection elsewhere in the body, but in which the micro-organism does not enter the joint.

5.2 Fan et al, 1993 (11)

Definition : an episode of peripheral arthritis occurring in relation to an infection at a distant site in the body. The infectious organism cannot be cultured from joint fluid or synovium. The term is restricted to conditions frequently associated with HLA-B27, and does not include rheumatic fever, Lyme arthritis, parasitic infections and post-viral arthritides.

APPENDIX B

THE EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP (ESSG) CRITERIA FOR THE CLASSIFICATION OF SPONDYLOARTHROPATHY (15)*

i. Inflammatory spinal pain

OR

ii. Synovitis

- asymmetric
  OR
- predominantly in the lower limbs

AND

one or more of the following :

- positive family history of any one of the following :
  - ankylosing spondylitis
  - psoriasis
  - acute uveitis
  - reactive arthritis
  - IBD
- psoriasis
- IBD
- urethritis, cervicitis or acute diarrhoea within one month before onset of arthritis
- alternating buttock pain
- enthesitis
- radiographic unilateral (grade 3-4) or bilateral (grade 2-4) sacroiliitis**

* *Specifications of all variables of the ESSG criteria for spondyloarthropathy are as defined in Appendix D.*

** *Radiographic grading of sacroiliitis according to the New York criteria, 1966 (7) as detailed in Appendix A.*

APPENDIX C

SERONEGATIVE SPONDYLOARTHROPATHY : DATA CAPTURE SHEET

Z1. Study number Z1 [| | |]

A1. Surname A1 [| | | | | | | | | | | | |]

A2. Initial A2 [ ]

A3. Hospital number A3 [| | | | | | | |]

A4. Ethnic group A4 [ ]
1: Black
2: White
3: Coloured
4: Asian
5: Oriental

A5. Date of birth A5 [| | | | | |]

A6. Gender A6 [ ]
1: Male
2: Female

B1. Age at onset of symptoms B1 [|]

B2. Age at time of diagnosis B2 [|]

C1. Distribution of arthritis C1 [ ]
1. large joints
2. small joints
3. spine
4. large and small joints and spine
5. large and small joints
6. large joints and spine
7. small joints and spine
8. no evidence of arthritis

C2. Non-articular musculoskeletal system features C2 [ ]
1. tenosynovitis
2. enthesitis
3. tenosynovitis and enthesitis
4. absent/not recorded

C3. Gastrointestinal tract features C3 [ ]
1. diarrhoea
2. IBD
3. Whipple's disease
4. absent/not recorded

C4. Ophthalmic features C4 ☐
1. uveitis or conjunctivitis
2. absent/not recorded
(**indicate in Comments section whether conjunctivitis or uveitis present)*

C5. Urogenital tract features C5 ☐
1. urethritis or cervicitis
2. genital ulcers
3. urethritis or cervicitis and genital ulcers
4. absent/not recorded

C6. Respiratory features C6 ☐
1. apical pulmonary fibrosis (previous TB)
2. apical pulmonary fibrosis (no TB)
3. chest radiograph normal
4. chest radiograph not done/not recorded

C7. Cardiac features C7 ☐
1. aortic and/or mitral regurgitation
2. conduction disturbance (ECG)
3. normal examination
4. underlying cardiac disease

C8. Dermatologic features C8 ☐
1. psoriasis with/without nail changes
2. keratoderma blenorrhagica or pyoderma gangranosum
3. normal skin/no comment regarding skin
4. circinate balanitis

D1. Inflammatory back pain D1 ☐
1. present
2. absent/not recorded

D2. Limitation of lumbar spine movement D2 ☐
1. yes
2. no
3. not recorded

D3. Modified Schober's test D3 ☐
1. normal
2. reduced
3. not recorded

D4. Chest expansion D4 ☐
1. normal
2. reduced
3. not recorded

E1. Complications E1 ☐
1. spinal fracture
2. cauda equina syndrome
3. myelopathy
4. none recorded

F1. Family history F1 ☐

1. ankylosing spondylitis
2. psoriasis
3. IBD
4. unspecified arthritis
5. relevant family history absent/not recorded

G1. Rheumatoid factor G1 ☐

1. positive
2. negative
3. not recorded

G2. HLA-B27 status G2 ☐

1. positive
2. negative
3. not recorded

G3. Microbiological evaluation G3 ☐

- Chlamydia
- Salmonella
- Shigella
- Yersinia
- Campylobacter

(**ring relevant organism/s*)

1. positive
2. negative
3. not recorded

H1. Radiographic features: spine H1 ☐

1. normal
2. spondylitis
3. degenerative changes only
4. not recorded/not done
5. atlanto-axial disease

H2. Radiographic features: sacroiliac joints H2 ☐

1. normal
2. unilateral abnormality
3. bilateral abnormalities
4. suspicious
5. not recorded/not done

H3. Radiographic features: peripheral joints H3 ☐

1. normal
2. periarticular osteopaenia (with/without joint space narrowing and erosions)
   (**ring osteopaenia, if present on its own*)
3. resorptive changes
4. not done/not recorded
5. advanced changes ('destroyed' joint)
6. other findings
   (***indicate findings (6) in Comments section*)

I1. Medical therapy I1 ☐

1. no therapy prescribed in clinic notes
2. symptomatic
3. corticosteroid
4. DMARD
5. symptomatic and corticosteroid
6. symptomatic and DMARD
7. corticosteroid and DMARD
8. symptomatic, corticosteroid and DMARD

I2. Disease modifying anti-rheumatic drug (DMARD) I2 ☐

1. not used
2. sulphasalazine
3. methotrexate
4. chloroquine sulphate
5. combination of agents
   (** *indicate agents used in combination (5) in Comments section*)

J1. Joint replacement surgery J1 ☐

1. unilateral hip
2. bilateral hip
3. other
   (** *indicate joint replaced (3) in Comments section*)
4. no joint replacement surgery

K1. Clinical diagnosis K1 ☐

1. ankylosing spondylitis
2. psoriatic arthropathy
3. enteropathic arthritis
4. reactive arthritis
5. undifferentiated spondyloarthropathy

L1. Was diagnosis changed during course of illness? L1 ☐

1. yes
2. no

M1. Duration of disease (years) M1 ☐☐

ADDITIONAL COMMENTS :

_____

_____

_____

_____

_____

_____

APPENDIX D

DEFINITIONS OF TERMS USED ON DATA CAPTURE SHEET

B1. **Age at onset of symptoms** : age at which one or more of the following symptoms were first noted :

- joint-related pain and/or swelling and/or stiffness
- early morning stiffness of at least one hour duration
- inflammatory back pain (defined below)

B2. **Age at time of diagnosis** : age at the time of initial evaluation by the RDU at either PAOH or GSH.

C1. **Distribution of arthritis** :

Peripheral Arthritis : the presence of joint tenderness and/or swelling with or without a capsular pattern of limitation of movement at a given joint

OR

the presence of established joint deformity(ies) due to previous disease activity, excluding trauma.

Large joint : hip, knee, ankle, shoulder, elbow, wrist

Small joint : metacarpophalangeal, interphalangeal, metatarsophalangeal

Spondylitis (Spine) : a history of inflammatory back pain (defined in D1) AND limitation of spinal range of movement in any plane OR limitation of lumbar spine movement in three planes (defined in D2), a positive modified Schober's test (defined in D3) or reduced chest expansion (defined in D4).

C2. **Non-articular musculoskeletal system features** :

Tenosynovitis : tenderness on palpation of a particular tendon accompanied by pain on resisted movement relevant to the particular tendon

OR

sausage-shaped digits (dactylitis) due to flexor tenosynovitis (83).

Enthesitis : an *enthesis* (84) is the site of ligamentous insertion onto bone occurring at multiple sites in the body (eg. attachment of the Achilles tendon to the calcaneus). Non-granulomatous inflammation at these sites, *enthesitis* (85), results in local fibre disruption with subsequent reactive bone formation creating a new enthesis with the eroded end of the ligament. Over a period of time ossification of ligaments and tendons produces radiographically recognisable 'whiskering' at the relevant sites (86). For the purposes of this study enthesitis was limited to the respective sites of insertion of the Achilles tendon and the plantar fascia onto the calcaneus as suggested by the ESSG spondyloarthropathy criteria (15). A clinic record of spontaneous pain or compression tenderness at the site of a relevant enthesis was considered indicative of enthesitis at that site.

C3. **Extra-articular features : gastrointestinal tract**

Diarrhoea : an episode of diarrhoea occurring within one month before onset of arthritis (15).

Inflammatory bowel disease : ulcerative colitis or Crohn's disease defined by radiographic barium study and/or histology.

Whipple's disease : defined by histologic features on biopsy in the appropriate clinical setting.

C4. **Extra-articular features : ophthalmic**

Conjunctivitis : spontaneous onset of a painful red eye with preserved visual acuity when seen by a member of the RDU

OR

history of such a presentation to a medical practitioner.

Uveitis : spontaneous onset of a painful red eye with impaired visual acuity as assessed by an opthalmologist

OR

history of such a presentation and ophthalmological opinion.

C5. **Extra-articular features : urogenital tract**

Urethritis : an episode of urethral discharge occurring within one month before onset of arthritis (15).

Cervicitis : an episode of pelvic inflammatory disease (PID) requiring medical attention occurring one month before onset of arthritis (15).

C6. **Respiratory features**

Apical pulmonary fibrosis as reported on the chest radiograph findings was recorded separately in the presence or absence of a reported history of *pulmonary tuberculosis.* A history of previous therapy for tuberculosis was considered to indicate previous tuberculosis. In the absence of a history of anti-tuberculosis therapy the presence of apical pulmonary fibrosis could not be considered to be exclusively related to previous tuberculosis. In the absence of a report of apical

pulmonary fibrosis, the chest radiograph was recorded as ***normal***, ie. other miscellaneous findings on the radiograph were not recorded for the purposes of this study.

C7. **Cardiac features**

Aortic and/or mitral regurgitation or an isolated ***conduction disturbance*** as reported from an electrocardiogram (ECG), in the **absence** of a history of underlying cardiac disease (hypertension, rheumatic heart disease, ischaemic heart disease or congenital heart disease) was recorded as an extra-articular manifestation in the setting of spondyloarthritis.

C8. **Dermatologic features**

The presence of skin signs (with or without nail changes) characteristic of ***psoriasis*** OR mucocutaneous features compatible with a diagnosis of ***keratoderma blenorrhagica***, ***pyoderma gangranosum*** or ***circinate balanitis*** as diagnosed by a physician.

D1. **Inflammatory back pain** : a history of back pain with at least four of the following features (87) :

- onset before age 45
- insidious onset
- improved by exercise
- associated with morning stiffness, or
- at least three months duration.

D2. **Limitation of lumbar spine movement** : limitation of lumbar spine mobility in three planes: anterior flexion (as defined by the modified Schober's test), extension and lateral flexion as defined by the New York criteria (7).

D3. **Modified Schober's test** : a minimum length of 20 cm achieved (between the upper and lower marks of a pre-measured 15 cm lumbar spine segment) on maximal anterior flexion (88) indicating at least 5 cm distraction in the lumbar spine segment. A recorded value of less than the above was considered to be abnormal (89).

D4. **Chest expansion** : a chest circumference increase of at least 5 cm on full inspiration as measured in the 4th intercostal space. A value of less that the above was considered to be reduced, as defined by the New York criteria (7).

E1. **Complications**

Spinal fractures : a description in the clinic notes of a radiologically identified segment of spinal architectural irregularity owing to the presence of a vertebral fracture accompanied by a history of pain relevant to the site of observed pathology. Vertebral fracture should have had no other identifiable cause (eg. underlying malignancy with bony secondary deposits), but may have been related to trivial trauma.

Cauda equina syndrome : a description in the clinic notes of the slow spontaneous onset of neurological dysfunction related to the lower lumbar and sacral dermatomes. Clinical features recorded should include (90) :

- sensory disturbance (in the relevant dermatomes)
- urinary and/or rectal sphincter dysfunction
- lower limb weakness, and
- pain in the lower extremities.

Myelopathy : a description in the clinic notes of the spontaneous onset of neurological dysfunction of pyramidal tract origin below a level of radiologically identifiable vertebral column pathology compatible with the term spondylitis (defined in Section H1) and in the absence of any other recognised cause. Clinical features recorded should include :

- sensory disturbance relevant to the involved dermatomes
- motor weakness and reflex disturbances relevant to the level of involvement, and
- urinary and/or rectal sphincter dysfunction dependent upon the level of pathology.

F1. **Family history**

Ankylosing spondylitis, psoriasis or inflammatory bowel disease was recorded to be present in a family member of the index case, only if such a diagnosis had been made by a medical practitioner and confirmed by the relevant investigations. Unsubstantiated reports of arthritis in a family member of the index case was recorded as ***unspecified arthritis***.

G1. **Rheumatoid factor**

Rheumatoid factor assayed by sheep cell agglutination (SCAT) and latex agglutination was recorded as **positive** for any detectable titre.

G2. **Human leukocyte antigen (HLA)-B27 status**

The presence of HLA-B27 was recorded as ***positive*** if present.

G3. **Microbiological evaluation**

Chlamydia trachomatis : a four fold rise in serum titre or an initial titre greater than 1 in 256 was recorded as a ***positive*** finding.

Salmonella, Shigella, Yersinia and ***Campylobacter*** : a positive stool culture was recorded as a ***positive*** finding.

RADIOGRAPHIC FEATURES

Specific attention is drawn to the fact that skeletal radiographic changes were recorded and classified according to descriptive terms used in the clinical notes. Specific grading systems, such as the New York grading of sacroiliitis (7) or the Larsen index (91) of peripheral joint changes, were not utilised since radiographs were not routinely reported upon in this manner in the patient records used in this study.

H1. **Spine**

Spondylitis was defined by descriptions of: (i) squaring of vertebral bodies and/or (ii) syndesmophyte formation or (iii) 'bamboo' spine changes.

Degenerative changes was defined by descriptions of: (i) vertebral body osteophyte formation and/or (ii) vertebral disc space narrowing and/or (iii) loss of anterior vertebral body height.

Atlanto-axial disease was defined by descriptions of (i) radiological evidence of atlanto-axial instability as demonstrated by flexion and extension views of the cervical spine (measurement of the atlanto-dens interval) or (ii) radiographic evidence of anterior atlanto-axial subluxation and/or (iii) radiologically visible erosion of the odontoid peg.

H2. **Sacroiliac joints**

Abnormal sacroiliac joints were defined by descriptions of (i) widening or narrowing of the joint space, accompanied by (ii) irregular joint margins or (iii) complete ankylosis of the sacroiliac joints. ***Unilateral*** or ***bilateral*** changes were recorded separately.

Descriptions expressing concern regarding the normality of one or both sacroiliac joint(s) were recorded as ***'suspicious'***.

H3. **Peripheral joints**

Descriptions of (i) *periarticular osteopaenia* with (ii) *joint space narrowing and joint margin erosions* were recorded as ***'erosive' changes***.

Descriptions of (i) 'pencil-in-cup' deformities and/or (ii) distal phalangeal resorption or (iii) gross disturbances of joint architecture due to bone loss of a resorptive nature were recorded as ***resorptive changes***.

Descriptions of advanced non-traumatic post-inflammatory joint damage including obliteration of the joint space with or without features of joint ankylosis were recorded as ***advanced changes ('destroyed' joint)***.

Miscellaneous other radiographic changes reported in peripheral joints were recorded as ***other findings*** which were detailed in the Comments section at the end of the data capture sheet.

I1. **Medical therapy**

Drug therapy as prescribed on prescription charts in the clinic notes was recorded in one or more of the following categories :

(i) ***symptomatic*** : included all forms of analgesia (non-opiate and opiate) and non-steroidal anti-inflammatory agents.

(ii) ***corticosteroid*** : included all prescriptions of oral therapy. Intra-articular injections of corticosteroid therapy were not included in this group.

(iii) ***disease-modifying anti-rheumatic drug (DMARD)*** : included sulphasalazine, methotrexate, oral or injectable gold preparations and chloroquine sulphate.

J1. **Joint replacement surgery**

Records of total ***hip*** replacement surgery, either ***unilateral*** or ***bilateral***, were recorded as such.

Replacement of any other joint, or surgical procedure was recorded as ***other***, and detailed in the Comments section at the end of the data capture sheet.

K1. **Clinical diagnosis**

Each patient was assigned a clinical diagnosis from within the recognised spondyloarthropathy complex. Details of diagnostic criteria or definitions for each disorder are listed in Appendices A and B. A ***change in diagnosis*** during the course of illness was recorded separately.

M1. **Duration of disease**

Defined as the time (in years) that had elapsed between the onset of symptoms and initial presentation to the RDU, rounded off to the nearest six months.

APPENDIX E

COMPARATIVE DATA : INFLUENCE OF ETHNICITY ON PATTERNS OF DISEASE

TABLE 17 : Clinical features of spondylitis

	WHITE (n=40)	COLOURED (n=53)	BLACK (n=5)
Inflammatory back pain	25/40 (62.5)	29/53 (54.7)	3/5 (60)
Reduced spinal mobility	16/38 (42.1)	24/49 (49)	3/5 (60)
Reduced chest expansion	15/24 (62.5)	13/25 (52)	3/4 (75)
Schober's test positive	15/27 (55.6)	19/33 (57.6)	3/4 (75)

Percentage in parentheses
Denominator = number of patients in whom presence/absence of feature was recorded

TABLE 18 : Extra-articular manifestations

	WHITE (n=40)	COLOURED (n=53)	BLACK (n=5)
Circinate balanitis	1	1	
Keratoderma blenorrhagica		1	
Anterior uveitis	3	4	
Conjunctivitis		2	2

TABLE 19 : HLA-B27 prevalence

	AS (n=20)	PsA (n=7)	ReA (n=7)	USpA (n=11)
White (n=21)	4/9	0/3	3/3	3/6
Coloured (n=22)	7/9	1/4	3/4	1/5
Black (n=2)	1/2			

(n) = all patients within a subgroup for whom HLA-B27 results were available.

TABLE 20(a) : Radiographic features in White patients

	AS (n=13)	PsA (n=14)	EA (n=5)	ReA (n=8)	TOTAL (n=40)
Sacroiliac joints	12/12 (b=9)	2/6 (b=1)	0/2	1/5 (b=1)	15/25 (b=11)
Spine	6/8	1/4	0/1	0/4	7/17
Peripheral joints	2/4	7/9	0/5	0/3	9/21
(i)	2	6			8
(ii)					
(iii)		1			1

* Sacroiliac joints (b) = bilateral
* Spine (aa) = atlanto-axial disease
* Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

TABLE 20(b) : Radiographic features in Coloured patients

	AS (n=19)	PsA (n=19)	EA (n=2)	ReA (n=6)	Uspa (n=7)	TOTAL (n=53)
Sacroiliac joints	17/17 (b=16)	3/8 (b=3)	1/1 (b=1)	0/5	3/7 (b=2)	24/38 (b=22)
Spine	13/14	4/8 (aa=3)	0/2		0/2	17/26 (aa=3)
Peripheral joints	8/8	13/17	1/2	0/3	2/5	24/35
(i)	1	10	1			12
(ii)	6	2			2	10
(iii)	1	1				2

* Sacroiliac joints (b) = bilateral
* Spine (aa) = atlanto-axial disease
* Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

TABLE 20(c) : Radiographic features in Black and Asian patients

	BLACK		ASIAN
	AS (n=3)	ReA (n=2)	PsA (n=2)
Sacroiliac joints	3/3 (b=2)	0/1	
Spine	2/2		
Peripheral joints	2/3	0/2	1/1
(i)			1
(ii)	2		
(iii)			

* Sacroiliac joints (b) = bilateral
* Spine (aa) = atlanto-axial disease
* Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

A P P E N D I X F

COMPARATIVE DATA : INFLUENCE OF GENDER ON PATTERNS OF DISEASE

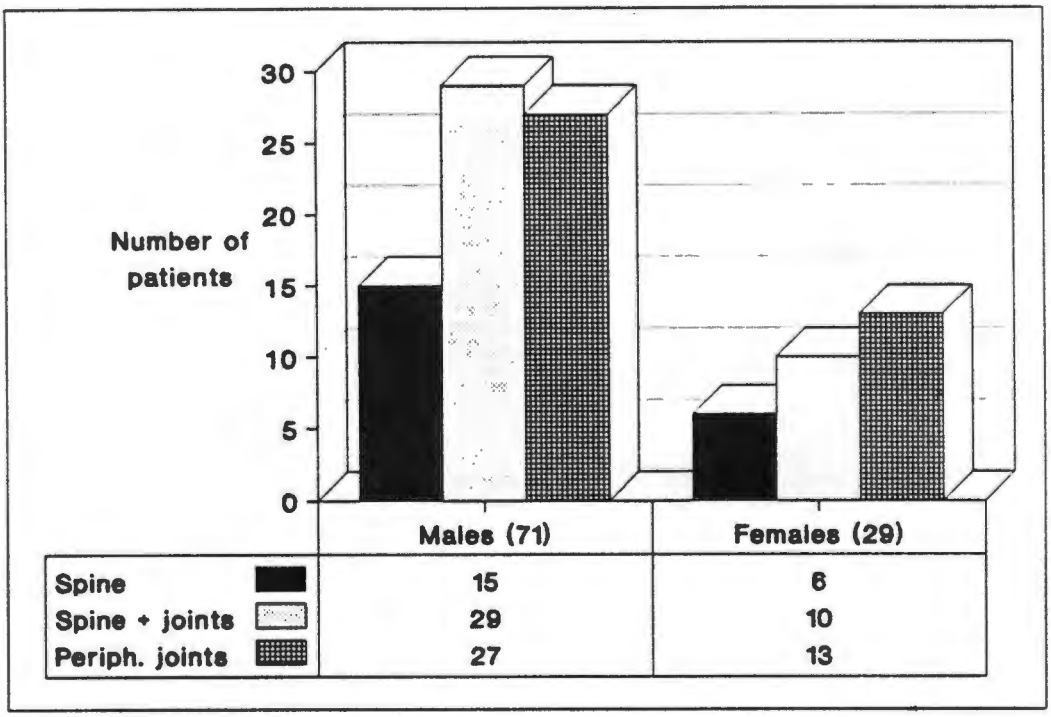


Figure 16 : Patterns of disease

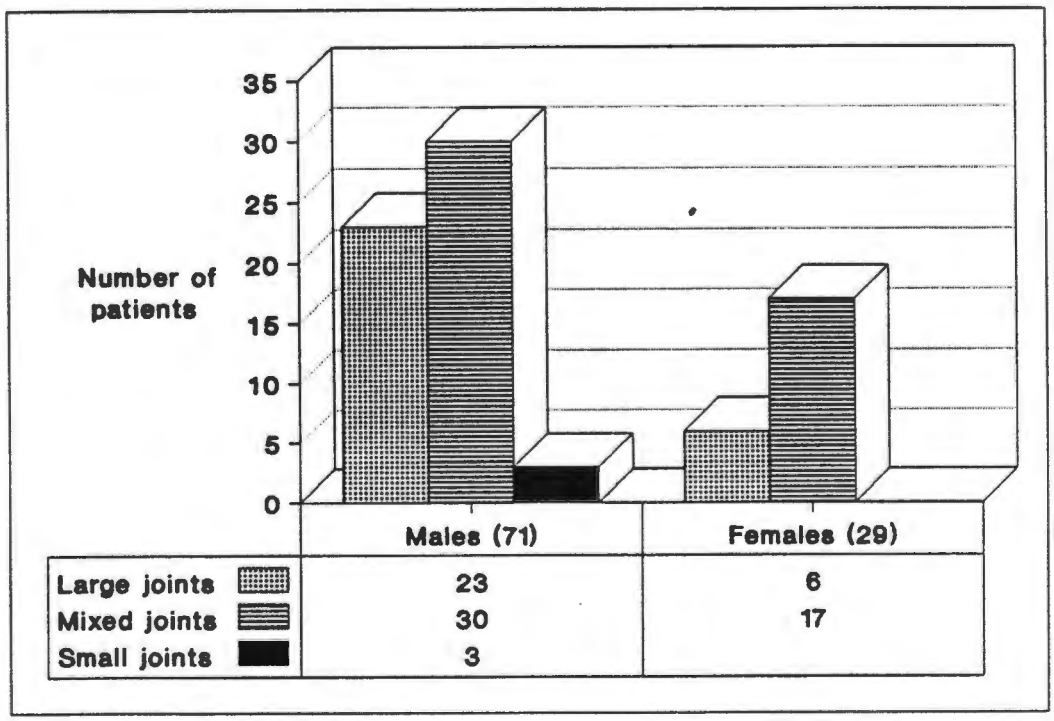


Figure 17 : Peripheral arthritis patterns

TABLE 23 : Non-articular musculoskeletal system features

MALES (n=71)		FEMALES (n=29)
10 (14.1)	Tenosynovitis	2 (7)
19 (26.8)	Enthesitis *	10 (34.5)

* Enthesitis more common than tenosynovitis in males ($p<0.005$) and females ($p<0.005$)
Percentage in parentheses

TABLE 24 : Extra-articular manifestations

MALES (n=71)		FEMALES (n=29)
3	Diarrhoea	1
8	Urethritis OR cervicitis	1
2	Circinate balanitis	
1	Keratoderma blenorrhagica	
5	Anterior uveitis	2
3	Conjunctivitis	1

TABLE 25 : HLA-B27 prevalence

	AS (n=20)	PsA (n=7)	ReA (n=7)	USpA (n=11)
Males (n=37)	11/19	1/4	6/7	2/7
Females (n=8)	1/1	0/3		2/4

(n) = all patients within a subgroup for whom HLA-B27 results were available.

TABLE 26(a) : Radiographic features in males

	AS (n=29)	PsA (n=21)	EA (n=1)	ReA (n=11)	USpA (n=9)	TOTAL (n=71)
Sacroiliac joints	26/26 (b=21)	5/11 (b=5)		0/9	3/7 (b=2)	34/53 (b=28)
Spine	17/20	3/7 (aa=1)	0/1	0/1	0/3	20/32 (aa=1)
Peripheral joints	8/11	12/15	1/1	0/9	1/6	22/42
(i)		9	1			10
(ii)	7	2			1	10
(iii)	1	1				2

Sacroiliac joints (b) = bilateral
Spine (aa) = atlanto-axial disease
Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

TABLE 26(b) : Radiographic features in females

	AS (n=6)	PsA (n=14)	EA (n=1)	ReA (n=2)	USpA (n=6)	TOTAL (n=29)
Sacroiliac joints	6/6 (b=6)	0/4	1/1 (b=1)		1/5 (b=1)	8/16 (b=8)
Spine	4/4	2/5 (aa=2)	0/1		0/3	6/13 (aa=1)
Peripheral joints	4/4	9/12		0/1	1/2	14/19
(i)	3	8				11
(ii)	1				1	2
(iii)		1				1

Sacroiliac joints (b) = bilateral
Spine (aa) = atlanto-axial disease
Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

TABLE 27 : Management

MALES (n=71)			FEMALES (n=29)	
37	(80.1)	Symptomatic therapy	22	(75.9)
10	(14.1)	DMARDs	6	(20.7)
		Large joint arthroplasty :		
9	(12.7)	- number of patients	5	(17.2)
21	(7.4)	- number of procedures	6	(5.2)

Percentage in parentheses

APPENDIX G

COMPARATIVE DATA : INFLUENCE OF HLA-B27 ON PATTERNS OF DISEASE

TABLE 31 : Clinical features of spondylitis in AS patients of differing HLA-B27 status

HLA-B27 +ve AS (n=12)		HLA-B27 -ve AS (n= 8)
12/12	Inflammatory back pain	7/8
12/12	Reduced spinal mobility	5/8
10/10	Reduced chest expansion	5/7
11/11	Schober's test positive	5/7

Denominator = number of patients in whom presence/absence of feature was recorded

TABLE 32(a) : Radiographic features in HLA-B27 positive patients

	AS (n=12)	PsA (n=1)	ReA (n=6)	USpA (n=4)	TOTAL (n=23)
Sacroiliac joints	9/9 (b=9)	1/1 (b=1)	0/5	0/2	10/17 (b=10)
Spine	11/12	1/1	0/1	0/1	12/15
Peripheral joints	2/3	1/1	0/5	1/2	4/11
(i)					
(ii)	2			1	3
(iii)		1			1

* Sacroiliac joints (b) = bilateral
* Spine (aa) = atlanto-axial disease
* Peripheral joints = (i) erosive changes
  (ii) advanced post-inflammatory changes
  (iii) resorptive changes

TABLE 32(b) : Radiographic features in HLA-B27 negative patients

	AS (n=8)	PsA (n=6)	ReA (n=1)	USpA (n=7)	TOTAL (n=22)
Sacroiliac joints	8/8 (b=5)	0/4	0/1	2/7 (b=1)	10/20 (b=6)
Spine	2/3	0/2		0/4	2/9
Peripheral joints	2/3	3/5		0/4	5/12
(i)		3			3
(ii)	1				1
(iii)	1				1

* Sacroiliac joints (b) = bilateral
* Spine (aa) = atlanto-axial disease
* Peripheral joints = (i) erosive changes
(ii) advanced post-inflammatory changes
(iii) resorptive changes

TABLE 33 : Management of spondyloarthritis patients of differing HLA-B27 status

HLA-B27 +ve (n=23)		HLA-B27 -ve (n=22)
18 (78.3)	Symptomatic therapy	21 (95.4)
3 (13)	DMARDs	1 (4.5)
	Large joint arthroplasty :	
4 (17.4)	- number of patients	2 (9.1)
9 (39.1)	- number of procedures	4 (18.2)

Percentage in parentheses

REFERENCES

1. Moll J M H, Haslock I, Macrae I F, Wright V: Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Behcet's syndrome. Medicine (Baltimore). 1974;53:343-64.

2. Wollheim F A: Ankylosing spondylitis. In: Kelley W N, Harris E D, Ruddy S, Sledge C D (eds). Textbook of Rheumatology. Philadelphia: W B Saunders. 1993:943-60.

3. Carson D A: Rheumatoid factor. In: Kelley W N, Harris E D, Ruddy S, Sledge C D, (eds). Textbook of Rheumatology. Philadelphia: W B Saunders. 1993:155-60.

4. Arnett F C: Seronegative spondyloarthropathies. Bull Rheum Dis 1987;37:1-12.

5. Khan M A, van der Linden S: Ankylosing spondylitis and other spondyloarthropathies. Rheum Dis Clin North Am 1990;16:551-79.

6. Kellgren J H, Jeffery M R, Ball J: The Epidemiology of Chronic Rheumatism. (I. Proceedings, 356; II. Atlas of Standard Radiographs of Arthritis, 44pp). Oxford: Blackwell Scientific Publications. 1963:326-7.

7. Bennett P H, Burch T A: The epidemiological diagnosis of ankylosing spondylitis. In: Bennett P H, Wood H N (eds). The 3rd International Symposium of Population Studies of the Rheumatic Diseases, Proceedings of New York 1966. New York: Excerpta Medica Foundation, 1968:305-13 and 456-7.

8. Van der Linden, S M, Valkenburg H A, Cats A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.

9. Moll J M H, Wright V: Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.

10. Wollheim F A: Enteropathic arthritis. In: Kelley W N, Harris E D, Ruddy S, Sledge C D (eds). Textbook of Rheumatology. Philadelphia: W B Saunders. 1993:985-97.

11. Fan, P T, Yu D T Y: Reiter's syndrome. In: Kelley W N, Harris E D, Ruddy S, Sledge C D (eds). Textbook of Rheumatology. Philadelphia: W B Saunders. 1993:961-73.

12. Calin A: Reiter's syndrome; epidemiology and immunogenetics. Scand J Rheumatol 1980;32 (suppl):178-83.

13. Willkens R F, Arnett F C, Bitter T, Calin A, Fisher L, Ford D K, Good A E, Masi A T: Reiter's syndrome: Evaluation of preliminary criteria for definite diagnosis. Arthritis Rheum 1981;24:844-9.

14. Ahvonen P, Sievers K, Aho K: Arthritis associated with Yersinia enterocolitica infection. Acta Rheum Scand 1969;15: 232-53.

15. Dougados M, van der Linden S, Juhlin R, Huitveldt B, Amor B, Calin A, Cats A, Dijkmans B, Olivieri I, Pasero G, Veys E, Zeidler H: The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondylo-arthropathy. Arthritis Rheum 1991;34:1218-27.

16. Zeidler H, Mau W, Khan M A: Undifferentiated spondylo-arthropathies. Rheum Dis Clin North Am 1992;18:187-202.

17. Gran J T, Husby G: The epidemiology of ankylosing spondylitis. Semin Arthritis Rheum 1993;22:319-34.

18. Hansen J A, Lanier A P, Nisperos B, Michelseon E, Dahlberg S: The HLA system in Inupiat and Central Yupik Alaskan Eskimos. Hum Immunol 1986;16:315-28.

19. Erdesz S, Shubin S V, Shoch B P, Krylov M Y, Mylov N M, Chekalina N A, Benevolenskaya L I: Spondyloarthropathies in circumpolar populations of Chukotka (Eskimo and Chukchi): epidemiology and clinical characteristics. J Rheumatol 1994; 21:1101-4.

20. Petty R E: HLA-B27 and rheumatic diseases of childhood. J Rheumatol 1990;(suppl.26)17:7-10.

21. Burgos-Vargas R, Petty R E: Juvenile ankylosing spondylitis. Dis Clin North Am 1992;18:123-42.

22. Ladd J R, Cassidy J T, Martel W: Juvenile ankylosing spondylitis. Arthritis Rheum 1971;14:579-90.

23. Rosenberg A M, Petty R E: A syndrome of seronegative enthesopathy and arthropathy in children. Arthritis Rheum 1982;25: 1041-7.

24. Burgos-Vargas R, Clark P: Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. J Rheumatol 1989;16: 192-7.

25. Brewerton, D A, Caffrey M, Hart F D, James D C O, Nicholls A, Sturrock R D: Ankylosing spondylitis and HL-A27. Lancet 1973;1:904-7.

26. Schlosstein L, Terasaki P I, Bluestone R, Pearson C M: High association of an HL-A antigen, w27, with ankylosing spondylitis. N Eng J Med 1973;288:704-6.

27. Khan M A: HLA and ankylosing spondylitis. In: Calabro J J, Dick C (eds). Ankylosing spondylitis: New Clinical Applications in Rheumatology. Lancaster (England): MTP Press Limited. 1987:23-44.

28. Brewerton D A, Caffrey M, Nicholls A, Walters D, Oates J K, James D C O: Reiter's disease and HL-A27. Lancet 1973;2:996-8.

29. Fox R, Calin A, Gerber R C, Gibson D: The chronicity of symptoms and disability in Reiter's syndrome. Ann Int Med 1979;91:190-3.

30. Linssen A, Feltkamp T E W: B27 positive diseases versus B27 negative diseases. Ann Rheum Dis 1988;47:431-39.

31. Khan M A, Braun W E, Kushner I: Low frequency of HLA-B27 in American Blacks with ankylosing spondylitis. Clin Res 1976;24:331A.

32. Khan M A, Braun W E, Kushner I, Grecek D E, Angus Muir W, Steinberg A G: HLA-B27 in ankylosing spondylitis: differences in frequency and relative risk in American Blacks and Caucasians. J Rheumatol 1977; (suppl.3) 4:39-43.

33. Khan M A, Kushner I, Braun W E: Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. Arthritis Rheum 1977;20:909-12.

34. Van der Linden J M J P, de Ceulaer K, van Romunde L K J, Cats A: Ankylosing spondylitis without HLA-B27. J Rheumatol 1977;4(suppl 3):54-6.

35. Khan M A: HLA-B27 and its subtypes in world populations. Editorial review. Curr Opinion Rheumatol 1995;7:263-69.

36. Gofton J P: Epidemiology, tissue type antigens and Bechterow's syndrome (ankylosing spondylitis) in various ethnical populations. Scand J Rheumatol 1980;32 (suppl):166-68.

37. Payne R, Feldman M, Cann H, Bodmer J G: A comparison of HLA data of the North American black with African black and North American caucasoid populations. Tissue Antigens 1977;9:135-47.

38. Van der Linden S M, Valkenburg H A, de Jongh B M, Cats A: The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. Arthritis Rheum 1984;27:241-9.

39. Moller P, Vinje O, Berg K: HLA antigens, psoriasis and acute anterior uveitis in Bechterew's syndrome (ankylosing spondylitis). Clin Genet 1982;21:215-21.

40. Wagener P, Mau W, Zeidler H, Eckert G, Robin-Winn D, Deicher H: HLA-B27 and clinical aspects of ankylosing spondylitis: results of prospective studies. Immunol Rev 1985;86:93-9.

41. Aho K, Ahvonen P, Lassus A, Sievers K, Tiilikainen A: HL-A27 in reactive arthritis: a study of yersinia arthritis and Reiter's disease. Arthritis Rheum 1974;17:521-6.

42. Leirisalo M, Skylv G, Kousa M, Voipio-Pulkki L-M, Soutranta H, Nissilü M, Hvidman L, Nielsen E D, Svejgaard A, Tiilikainen A, Laitinen O: Follow up study on patients with Reiter's disease and reactive arthritis with special reference to HLA-B27. Arthritis Rheum 1982;25:249-58.

43. Laitinen O, Leirisalo M, Skylv G: Relation between HLA-B27 and clinical features in patients with yersinia arthritis. Arthritis Rheum 1977;20:1121-4.

44. McClusky O E, Lordon R E, Arnett F C: HL-A27 in Reiter's syndome and psoriatic arthritis: a genetic factor in disease susceptibility and expression. J Rheumatol 1974;1:263-8.

45. Hughes R A, Keat A C: Reiter's syndrome and reactive arthritis: a current view. Semin Arthritis Rheum 1994;24:190-210.

46. Paronen I: Reiter's disease: a study of 344 cases observed in Finland. Acta Med Scand 1948;212(suppl):1-112.

47. Warren C P W: Arthritis associated with Salmonella infections. Ann Rheum Dis 1970;29:483-87.

48. Hannu T J, Leirisalo-Repo M: Clinical picture of reactive salmonella arthritis. J Rheumatol 1988;15:1668-71.

49. Vartiainen J, Hurri L: Arthritis due to Salmonella typhimurium. Report of 12 cases of migratory arthritis in association with Salmonella typhimurium infection. Acta Med Scand 1964;175:771-6.

50. Urman J D, Zurier R B, Rothfield N F: Reiter's syndrome associated with Campylobacter fetus infection. Ann Int Med 1977;86:444-5.

51. Weir W, Keat A C, Welsby PD: Reactive arthritis associated with Campylobacter infection of the bowel. J Infect 1979; 1:281-4.

52. Keat A, Thomas B J, Taylor-Robinson D: 'Chlamydial infection in the aetiology of arthritis. Br Med Bull 1983;39:168-74.

53. Bas S, Griffais R, Kvien T K, Glennas, A, Melby K, Vischer T: Amplification of plasmid and chromosome Chlamydia DNA in synovial fluid of patients with reactive arthritis and undifferentiated spondyloarthropathies. Arthritis Rheum 1995;7:1005-13.

54. Bardin T, Enel C, Cornelis F, et al: Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. Arthritis Rheum 1992;35:190-4.

55. Lauhio A, Leirisalo-Repo M, Lahdevirta J, Saikka P, Repo H: Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. Arthritis Rheum 1991;34:6-14.

56. Bardin T, Schumacher H R: Should we treat postvenereal Reiter's syndrome by antibiotics? J Rheumatol 1991;18:1780-2.

57. Adebajo A O, Davis P: Rheumatology on the dark continent: not as dark as it was. J Rheumatol 1992;19:195-7.

58. Solomon L, Beighton P, Valkenburg H A, Robin G, Soskolne C L: Rheumatic disorders in the South African Negro. Part I: Rheumatoid arthritis and ankylosing spondylitis. South Afr Med J 1975;49:1292-96.

59. Klemp P, Meyers O L: Ankylosing spondylitis in a Xhosa father and daughter. South Afr Med J 1976;50:1439-41.

60. Mulley G P: Ankylosing spondylitis in blacks. Lancet 1977;1: 1209.

61. Chalmers I M: Ankylosing spondylitis in African Blacks. Arthritis Rheum 1980;23:1366-9.

62. Baum J, Ziff M: The rarity of ankylosing spondylitis in the black race. Arthritis Rheum 1971;14:12-18.

63. Klemp P, Meyers O L, du Toit E D: HLA-B27 and ankylosing spondylitis in African blacks. (Letter) Arthritis Rheum 1982;25:716.

64. Seedat Y K, Duminiet H: Reiter's syndrome in a black patient. South Afr Med J 1982;61:289.

65. Methven P G, Swift P J: Reiter's syndrome in a black patient. A case report. South Afr Med J 1985;68:597-8.

66. Stein M, Davis P: Rheumatic disorders in Zimbabwe: a prospective analysis of patients attending a rheumatic diseases clinic. Ann Rheum Dis 1990;49:400-2.

67. Stein M, Davis P, Emmanuel J, West G: The spondylo-arthropathies in Zimbabwe: a clinical and immunogenetic profile. J Rheumatol 1990;17:1337-9.

68. Stein M, Svoren B, Davis P, Blankenberg B: A prospective analysis of patients with rheumatic diseases attending referral hospitals in Harare, Zimbabwe. J Rheumatol 1991; 18:1841-44.

69. Adebajo A O: Spondyloarthropathies in Subsaharan Africa. J Rheumatol 1991;18:1115.

70. Mijiyawa M: Spondyloarthropathies in patients attending the rheumatology unit of Lome Hospital. J Rheumatol 1993;20: 1167-9.

71. Lamuerezo B R: Psoriatic arthritis amongst Ugandan Africans. East Afr Med J 1989;57:855-60.

72. Stein C M, Levy L M: Ulcerative colitis in Zimbabwe. Cent Afr J Med 1982;28:363-5.

73. Rynes R I: Painful rheumatic syndromes associated with Human Immunodeficiency Virus infection. Rheum Dis Clin North Am 1991;17:79-87.

74. Solomon G M Brancato L, Winchester R: An approach to the Human Immunodeficiency Virus-positive patient with a spondylo-arthropathic disease. Rheum Dis Clin North Am 1991;17:43-58.

75. Davis P, Stein M, Latif A, Emmanuel J: Acute arthritis in Zimbabwean patients: possible relationship to human immuno-deficiency virus infection. J Rheumatol 1989;16:346-8.

76. Davis P, Stein M: Human immunodeficiency virus-related connective tissue diseases: a Zimbabwean perspective. Rheum Dis Clin North Am 1991;17:89-97.

77. Green L, Meyers O L, Gordon W, Briggs B: Arthritis in psoriasis. Ann Rheum Dis 1981;40:366-9.

78. Du Toit E D, MacGregor K J, Taljaard D G, Oudshoorn M: HLA-A, B, C, DR and DQ polymorphisms in three South African population groups: South African Negroes, Cape Coloureds and South African Caucasoids. Tissue Antigens 1987;31:109-25.

79. Botha M C, Pritchard D: Blood group gene frequencies: an indication of the genetic constitution of population samples in Cape Town. South Afr Med J 1972;46 (suppl):1-27.

80. Yagan R, Khan M A: Confusion of roentgenographic differential diagnosis between ankylosing hyperostosis (Forrestier's disease) and ankylosing spondylitis. Clin Rheumatol 1983; 2:285.

81. Provincial Statistics Report for Western Cape: 1994. Report number 00/90/01, page 7. Based on 1991 census data. Issued by Central Statistics Service, Pretoria.

82. Provincial Statistics Report for Western Cape: 1989/90 - Annexure I, 1990/1991 - Annexure P. Issued by Central Statistics Service, Pretoria.

83. Michet C J: Psoriatic arthritis. In: Kelly W N, Harris E D, Ruddy S, Sledge C D (eds). Textbook of Rheumatology. Philadelphia: W B Saunders. 1993:974-84.

84. Keat A: Spondyloarthropathies. BMJ 1995;310:1321-4.

85. Ball J: The Heberden Oration, 1970. Enthesopathy of rheumatoid and ankylosing spondylitis. Ann Rheum Dis 1971;30:213-23.

86. Ball G V: Ankylosing spondylitis. In: McCarty D, Koopman W J (eds) Arthritis and Allied Conditions: A Textbook of Rheumatology. Philadelphia: Lea and Febiger. 1993:1051-60.

87. Calin A, Porta J, Fries J F, Schurman D J: Clinical history as a screening test for ankylosing spondylitis. JAMA 1977; 237:2613-4.

88. Macrae I F, Wright V: Measurement of back movement. Ann Rheum Dis 1969;28:584-9.

89. Moll J M H, Wright V: Normal range of spinal mobility. An objective clinical study. Ann Rheum Dis 1971;30:381-6.

90. Tullous M W, Skerhult H E I, Story J L, Brown W E, Eidelberg E, Dadsetan M R, Jinkins J R: Cauda equina syndrome of longstanding ankylosing spondylitis. Case report and review of the literature. J Neurosurg 1990;73:441-7.

91. Larsen A, Dale K, Eek M: Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol 1977;18:481-91.

92. Adebajo A O: Rheumatology in the Third World. Ann Rheum Dis 1990;49:813-6.

93. Huskisson I D: The need for rheumatologists in South Africa. Rheumatol News 1996;9:4-5.

94. South African Statistics: 1994. Chapter One: Population - pages 1-6. Issued by Central Statistics Service, Pretoria.

95. Albert E D, Mickey M R, Terasaki P I: Genetics of the HLA system in four populations: American Caucasians, Japanese Americans, American Negroes and Mexican Indians. In: Dausset J, Colombani J (eds). Histocompatibility Testing. Copenhagen: Munksgaard. 1973:233-40.

96. Brown M A, Jepson A M Young A, Greenwood B, Wordsworth B P: Spondyloarthritis in the Gambia - evidence for a non-HLA-B27 protective effect. Br J Rheumatol 1996; 35(suppl.1):113.

97. Hill A S V, Allsopp C E M, Kwiatkowski D, Anstey N M, Greenwood B M, McMichael A J: HLA Class I typing by PCR: HLA-B27 and an African B27 subtype. Lancet 1991;337:640-2.

98. Westman P, Leirisalo-Repo M, Partanen J, Koskimies S: A comparative study of HLA genes in HLA-B27 positive ankylosing spondylitis and HLA-B27 positive peripheral reactive arthritis. Arthritis Rheum 1996;39:943-9.

99. Cornelis F, Enel C, Lathrop M, Bardin T: Genetic predisposition to post-venereal Reiter syndrome in Greenland involves more than one allele. Arthritis Rheum 1995;suppl: S381.

100. West H F: The aetiology of ankylosing spondylitis. Ann Rheum Dis 1949;8:143-8.

101. Gran J T, Husby G: Ankylosing spondylitis in women. Semin Arthritis Rheum 1990;19:303-12.

102. Gran J T, Husby G, Hordvik M: Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromso Northern Norway. Ann Rheum Dis 1985;44:359-67.

103. Edmunds L, Elswood J, Calin A: New light on uveitis in ankylosing spondylitis. J Rheumatol 1991;18:50-2.

104. Brewerston D A, Nicholls A, Walters D, James D C O: Acute anterior uveitis and HL-A27. Lancet 1973;2:994-6.

105. Bulkley B H, Roberts W C: Ankylosing spondylitis and aortic regurgitation. Description of the charactristic cardiovascular lesions from a study of eight necropsy patients. Circulation 1973;48:1014-27.

106. Tucker C R, Fowles R E, Calin A, Popp R L: Aortitis in ankylosing spondylitis. Early detection of aortic root abnormalities with two-dimensiuonal echocardiography. Am J Cardiol 1982:49:680-6.

107. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Strangel W, Deicher H: Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year follow up. J Rheumatol 1988;15:1109-14.

108. Bernstein L, Brook O J: Cardiac complications in spondyloarthritis ankylopoietica. Acta Med Scand 1949;135:185-94.

109. Gladman D D, Shuckett R, Russell M L, Thorne J C, Schachter R K: Psoriatic arthritis (PSA) - an analysis of 220 patients. Q J Med 1987; 62:127-41.

110. Torre Alonso J C, Rodriguez Perez A, Arribas Castrillo J M, Ballina Garcia J, Riestra Noriega J L, Lopez Larrea C: Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. Br J Rheumatol 1991; 30:245-50.

111. Bennett R M: Psoriatic arthritis. In: McCarty D J, Koopman (eds). Arthritis and Allied Conditions. Philadelphia: La and Febiger, 1993:1079-94.

112. Lambert J R, Wright V: Psoriatic spondylitis: a clinical and radiological description of the spine in psoriatic arthritis. Q J Med 1977;46:411-25.

113. Scarpa R, Oriente P, Pucino A, Torella M, Vignone L, Riccio A, Oriente C B: Psoriatic arthritis in psoriatic patients. Br J Rheumatol 1984;23:246-50.

114. Salvarini C, La Scocco G, Marchioni P, Gremontsi T, Rossi F, Mantovani W, Battistel B, Bisighini G, Portioli I: Prevalence of psoriatic arthritis in Italian psoriatic patients. J Rheumatol 1995;22:1499-1503.

115. Russell A S, Schlaut J, Percy J S, Dassetor J B: HL-A transplantation antigens in ankylosing spondylitis and Crohn's disease. J Rheumatol 1976;1:203-9.

116. Hyla J F, Frank W A, Davis J S: Lack of association of HLA-B27 with radiographic sacroiliitis in inflammatory bowel disease. J Rheumatol 1976;3:196-200.

117. Michet C J, Mashado E B V, Ballard D J, McKenna C H: Epidemiology of Reiter's Syndrome in Rochester, Minnesota: 1950-1980. Arthritis Rheum 1988;31:428-31.

118. Keat A: Reiter's syndrome and reactive arthritis in perspective. N Eng J Med 1983;309:1601-1615.

119. Olivieri I: Undifferentiated seronegative spondyloarthropathy in females. Br J Rheumatol 1996;35:395-6.

120. Prakash S, Mehra N K, Bhargava S, Malaviya A N: HLA-B27-related "unclassifiable" spondyloarthropathies. Ann Rheum Dis 1983;42:640-3.

121. Dubost J J, Sauvvezie B: Late-onset peripheral spondylo-arthropathy. J Rheumatol 1989;16:1214-7.

122. Mody G: Rheumatoid arthritis and connective tissue disorders: sub-Saharan Africa. Brailliere's Clin Rheumatol 1995;9(1):31-44.

123. Amor B, Dougados M, Khan M A: Management of refractory ankylosing spondylitis and related spondyloarthropathies. Rheum Dis Clin North Am 1995;21:117-28.

124. Creemers M C W, Van Riel P L C M, Franssen M J A M, Van de Putte L B A, Gribnau F W J: Second-line treatment in sero-negative spondyloarthropathies. Semin Arthritis Rheum 1994; 24:71-81.

125. Black R L, O'Brien W M, Van Scott E J, Auerbach R, Eisen A Z, Bunim J J: Methotrexate therapy in psoriatic arthritis. Double-blind study on 21 patients. JAMA 1964;189:743-7

126. Willkens R F, Williams H J, Ward J R, Egger M J, Reading J C, Clements P J, Cathcart E S, Samuelson C O, Solsky M A, Kaplan S B, Guttadauria N, Halla J T, Weinstein A: Randomised double-blind, placebo-controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27:376-81.

127. Gladman D D: Psoriatic arthritis: recent advances in patho-genesis and treatment. Rheum Dis Clin North Am 1992;18:247-56.

128. Basi Ferraz M, Tugwell P, Goldsmith C H, Altra E: Meta-analysis of sulphasalazine in ankylosing spondylitis. J Rheumatol 1990;17:1482-6.

129. McConkey B: Sulphasalazine and ankylosing spondylitis - editorial. Br J Rheumatol 1990;29:2-5.

130. Peters N D, Ejstrup L: Intravenous methylprednisolone pulse therapy in ankylosing spondylitis. Scand J Rheumatol 1992;21:134-8.

131. Calin A, Elswood J: The outcome of 138 total hip replacements and 12 revisions in ankylosing spondylitis: high success rate after a mean followup of 7.5 years. J Rheumatol 1989; 16:955-8.

132. McKenna F, Hickling P, Brophy T, Taggart A, Wright V: Ankylosing spondylitis in women and men: a comparative study (Abstract). Br J Rheumatol 1986;25 (suppl):69.

133. Wordsworth B P, Mowat A G: A review of 100 patients with ankylosing spondylitis with particular reference to socio-economic effects. Br J Rheumatol 1986;25:175-80.

134. Calin A, Elswood J: The natural history of juvenile-onset ankylosing spondylitis: a 24-year retrospective case-control study. Br J Rheumatol 1988;27:91-3.

135. Section 5: Community Health Care. In: Annual Report of the Medical Officer of Health City of Cape Town 1994/1995;1:61-4.

136. Quinn T C, Welsh L, Lentz A, Crotchfelt K, Zenilman J, Newhall J, Gaydos C: Diagnosis by AMPLICOR PCR of Chlamydia trachomatis infection in urine samples from women and men attending sexually transmitted disease clinics. J Clin Microbiol 1996; 34:1401-6.

137. Gaston J S H, Deane K H O, Jecock R M, Pearce J H: Identification of 2 Chlamydia trachomatis antigens recognised by synovial fluid T-cells from patients with Chlamydia-induced reactive arthritis. J Rheumatol 1996;23:130-6.

138. Billingham M E J, Carney S, Butler R, Colston M J: A mycobacterial 65-kD heat shock protein induces antigen-specific suppression of adjuvant arthritis, but is not itself arthritogenic. J Exp Med 1990;171:339-44.

139. Lindquist S, Craig E A: The heat-shock proteins. Annu Rev Genet 1988;22:631-77.

140. Bloom B R, Murray C J: Tuberculosis: commentary on a re-emergent killer. Science 1992;257:1055-64.

141. Li S G, Quayle A J, Shen Y, Kjeldsen-Krogh J, Oftong F, Gupta R A, Natrig J B, Forre O T: Mycobacteria and Human heat shock protein - specific cytotoxic T lymphocytes in rheumatoid synovial inflammation. Arthritis Rheum 1992;35:270-81.

142. Quayle A J, Wilson K B, Li S G, Kjeldsen-Krogh J, Oftung F, Shinnick T, Sioud M, Forre O, Capra J D, Natvig J B: Peptide recognition, T-cell receptor usage and HLA restriction elements of human heat-shock protein (hsp)60 and mycobacterial 65-kDa hsp-reactive T cell clones from rheumatoid synovial fluid. Eur J Immunol 1992;22:1815-22.

143. Gaston J S H, Life P F, Jenner P J, Colston M J, Bacon P A: Recognition of a mycobacteria-specific epitope in the 65-kDa heat-shock protein by synovial fluid-derived T cell clones. J Exp Med 1990;171:831-41.

144. Pope R M, Lovis R M, Gapta R S: Activation of synovial fluid lymphocytes by 60-kD heat-shock proteins in patients with inflammatory synovitis. Arthritis Rheum 1992;35:43-8.

145. Mustafa A S, Lundin K E A, Nekieb R H, Shinnick T M, Coulson A F W, Oftong F: HLA-DR4-restricted T-cell epitopes from the mycobacterial 60 000 MW heat shock protein (hsp60) do not map to the sequence homology regions with the human hsp 60. Immunology 1996;87:421-7.

146. Section 6: Notifiable Conditions. In: Annual Report of the Medical Officer of Health City of Cape Town 1994/1995;1:65-7.