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SYSTEMIC LUPUS ERYTHEMATOSUS

THE JOHANNESBURG EXPERIENCE

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A dissertation submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg for the Degree of Master of Medicine.

Johannesburg 1986.

This thesis is my own work. No part of it has been presented at any other University. The information used in this thesis was obtained while I was employed by the University of the Witwatersrand and the Johannesburg Hospital.



DR RCA MORRISON

ABSTRACT.

This study is a predominantly retrospective analysis of patients in Johannesburg who presented with Systemic Lupus Erythematosus at 12 years of age or older. Johannesburg is situated at high altitude and has a high level of ultraviolet light irradiation, a known exacerbating factor of the disease. This study draws comparisons with reported disease characteristics of lupus patients elsewhere in the world. In addition, it examines differences in the clinical manifestations of the disease amongst the principle South African racial groups.

THIS THESIS IS DEDICATED TO MY WIFE .

ACKNOWLEDGEMENTS.

"Mind that the body of facts for this study are the result of some other mind's study of the bodily facts"- Anonymous.

Considerable thanks must go to the following people -

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CONTENTS. PAGE.

Declaration. ii

Abstract. iii

Dedication. iv

Acknowledgements. v

Contents. vi

Tables and figures. vii

Glossary of terms. 1

1. INTRODUCTION.

1.1. General background and reasons for the study. 1

1.2. Aims of the study. 3

2. SYSTEMIC LUPUS ERYTHEMATOSUS IN JOHANNESBURG.

2.1. Introduction. 4

2.2. Materials and methods. 5

2.3. Exclusions. 8

2.4. Results. 12

2.5. Discussion. 19

3. DISEASE MANIFESTATIONS IN SLE PATIENTS OF DIFFERENT RACES.

3.1. Introduction. 90

3.2. Materials and methods. 91

3.3. Exclusions. 91

3.4. Results. 91

3.5. Discussion. 105

SUMMARY. 119

BIBLIOGRAPHY. 122

TABLES AND FIGURES

TABLES:		PAGE
2.1	Difference in ratio of females to males with age.	11
2.2	General features of patients with SLE.	13
2.3	Causes of death	18*
2.4	Contributory causes of death	19*
2.5.1	Cumulative dermatological manifestations of SLE patients.	24*
2.5.2	Cumulative musculoskeletal manifestations of SLE patients.	31*
2.5.3	Cumulative cardiac manifestations of SLE patients.	34*
2.5.4	Cumulative pulmonary manifestations of SLE patients.	39*
2.5.5	Cumulative constitutional manifestations of SLE patients.	44*
2.5.6	Cumulative renal manifestations of SLE patients.	47*
2.5.7	Cumulative gastrointestinal manifestations of SLE patients.	57*
2.5.8	Cumulative neurological manifestations of SLE patients.	61*
2.5.9	Cumulative vascular and coagulation disorders of SLE patients.	68*
2.5.10	Cumulative haematological manifestations of SLE patients.	76*
2.5.11	Cumulative serological manifestations of SLE patients.	80*
3.1	Proportion of subcultures in the general population compared with proportion of patients within these subcultures.	91*
3.2	General features of SLE patients within various racial groups.	92
3.3	Differences in clinical and biochemical findings between races at diagnosis.	95
3.4	Cumulative differences in clinical and biochemical findings between races.	99
3.5	Comparison between various studies of Black SLE patients.	112

* Opposite Page

FIGURES: PAGE

2.1 Annual incidence of patients with SLE. 9

2.2 Distribution of SLE patients by hospital of origin. 10

2.3 Distribution according to age at diagnosis of SLE (by sex). 14

2.4 Distribution of patients by racial group. 15

2.5.1 Dermatological manifestations at diagnosis. 22

2.5.2 Musculoskeletal manifestations at diagnosis. 29

2.5.3 Cardiovascular manifestations at diagnosis. 32

2.5.4 Pleuropulmonary manifestations at diagnosis. 37

2.5.5 Constitutional manifestations at diagnosis. 42

2.5.6a Renal manifestations at diagnosis. 45

2.5.6b Renal biopsies at diagnosis. 45

2.5.7 Gastrointestinal manifestations at diagnosis. 55

2.5.8 Neurological manifestations at diagnosis. 59

2.5.9 Vascular and coagulation disorders at diagnosis. 66

2.5.10 Haematological manifestations at diagnosis. 74

2.5.11 Serological manifestations at diagnosis. 78

2.6 Survival analysis for SLE patients according to renal function. 86

3.1 Survival analysis for SLE patients accoding to racial group. 93

GLOSSARY OF ABBREVIATIONS USED IN THE TEXT.

adsDNA - antibodies to native (double stranded) DNA
ALT - alanine aminotransferase
ANF - antinuclear factor
aSm - antibodies to Smith antigen
AST - aspartate aminotransferase
aRNP - antibodies to ribonuclear protein
CNS - central nervous system
CVA - cerebrovascular accident
DPGN - diffuse proliferative glomerulonephritis
DVT - deep venous thrombosis
ENA - extractable nuclear antigen
ESR - erythrocyte sedimentation rate
FPGN - focal segmental proliferative glomerulonephritis
FPWR - chronically (>6 months) false positive serological test for syphilis
GI - gastrointestinal
GN - glomerulonephritis
ITP - idiopathic thrombocytopenic purpura
LA - lupus anticoagulant
LBT - lupus band test
LE - lupus erythematosus
PTT - partial thromboplastin time
RA - rheumatoid arthritis
RF - rheumatoid factor
SAH - subarachnoid haemorrhage
SLE - systemic lupus erythematosus
ssDNA - single stranded (denatured) DNA
WCC - white cell count.

1. INTRODUCTION.

1.1. General background and reasons for the study.

Since systemic lupus erythematosus is a clinical syndrome of unknown cause or causes, characterised by multisystem involvement and multiple remissions and exacerbations, it largely defies accurate classification and definition of its severity. However, there is ever-increasing evidence that the disease expression hinges on the interaction of environmental, genetic and immunological factors.

Rheumatological diseases have always incriminated environmental factors and Johannesburg's environment in particular has certain unique properties that make a study of SLE in this area worthwhile. Johannesburg has, along with certain Australian towns, the distinction of having the highest level of ultraviolet irradiation in the world. This irradiation has been considered to be a potent stimulator of the pathological exacerbations seen in SLE and hence the disease manifestations in Johannesburg might be expected to be more severe than elsewhere in the world. In addition, a study in the Johannesburg region with its large number of varied mines might show up an association between mining and SLE, as suggested by the finding of serological markers for SLE (the anti-nuclear factor) in miners in Utah [1].

All the patients in this particular study existed within the same macro-environment, and were attended by physicians with access to

sophisticated diagnostic facilities. However, they inhabited different sub-environments ranging from a sophisticated Westernised subculture to the primitive African one; the manifestations of the disease in patients with these diverse backgrounds make an interesting sub-study.

It is known that the manifestations of SLE vary markedly between racial groups [2,3] and in the Republic of South Africa there exists considerable genetic separation between the Caucasians, Blacks and Asians with the Coloureds comprising a melting pot. SLE has always been regarded as the template for immunogenetic diseases, but so far has defied the tissue typists by not associating absolutely with specific tissue types or chromosomes; this study paves the way for an extensive tissue typing exercise, particularly in the area of Class II HLA antigens (the D and DR groups, and more specifically the recently-defined sub-groups within the latter class), which may aid our understanding of the genetics of the disease. Reports relating to SLE in Africa have increased in number over the last 5 years and will be used for comparison in the discussion later.

1.2. Aims.

The overall aims of the study therefore are:-

1. To obtain an overview of the disease as it presents in patients in Johannesburg for comparison with European and American findings;

2. To examine whether the high altitude and increased levels of ultraviolet radiation might be associated with alterations in those disease manifestations usually affected by ultraviolet radiation;

3. To assess the changes in the manifestations of SLE in patients of different races, and to compare these findings with those of other African studies.

2. SYSTEMIC LUPUS ERYTHEMATOSUS IN JOHANNESBURG.

2.1. Introduction.

The clinical picture and prognosis of SLE has changed dramatically over the years, with greater physician awareness of the ramifications of the disease and with better serological aids to diagnosis. The recognition of a mild form of SLE involving mainly the skin and joints is largely responsible for altering the 5 year survival from 24% in 1944 to 91% in 1976 [4,5]; even in the SLE nephritis group the 5 year survival lies currently at 78% [6].

There is also a suggestion that the frequencies of certain established clinical manifestations have altered over the years. For instance, the classical malar or butterfly rash appears to be less frequently seen in recent years. On the other hand, it has been widely recognised that the haemolytic anaemia of SLE (in patients who are often seronegative) may antedate other symptoms by many years, and therefore it is increasingly accepted as a criterion of SLE. It is for this reason that I shall compare my findings with those of earlier, as well as more recent, overseas studies.

2.2. Materials and methods.

This study is largely retrospective, and includes all patients whose SLE was diagnosed between January 1970 and December 1984. The minimum age of patients was 12 years. The major sources of case records were the Rheumatology, Renal and Haematology Units of the Johannesburg Hospital, the Connective Tissue Disease clinic at Hillbrow Hospital, the Renal Units of the JG Strydom and Coronationville Hospitals, and the files of Dr B Goldberg, a physician in private practice. These units have the records of the majority of the SLE patients from the four hospitals. The Pulmonology Unit of the JG Strydom Hospital contributed cases, as did three private dermatologists. Dr H Tayob supplied details of private Indian patients. In addition, 35 other doctors supplied information concerning our patients.

Despite attempts to obtain a cross sectional picture of the disease in the population, certain limitations and biases did occur. The records of the Johannesburg Hospital were the most complete with respect to the period 1970 - 1979, so that the information about the long term follow-up of these predominantly White patients was more complete than at other hospitals. The patients seen at the JG Strydom Hospital were also Whites, and at the Coronationville Hospital they were Coloureds and Indians, whilst the Hillbrow Hospital treated Blacks and Indians; the patients from the private sector were mixed with the exception of Dr Tayob's patients who were predominantly Indians. In the final analysis, the number of White patients was probably equally

divided between private and hospital sectors, with renal patients in particular referred to hospital for dialysis and transplantation. The private dermatologists attend many of the milder patients. The Coloureds, on the other hand, as a population group are seen almost entirely at the Coronationville Hospital. Details of the Indian cases were derived from private physician and hospital records.

Blacks attend the Baragwanath Hospital as well as the Hillbrow Hospital but comprehensive details of SLE patients at Baragwanath Hospital were not available. However, the hospitals serve the same area so that the two patient groups are very similar. The Hillbrow Hospital was only opened in 1980, meaning that our sample contains Black patients whose disease was largely diagnosed subsequent to that date, and this may account for the increased annual incidence in later years, illustrated in Fig. 2.1. Ethnic, sociological and economic factors will be dealt with in a later chapter.

The date of "diagnosis" is the date the patient first fulfilled the modified 1982 criteria for the classification of SLE suggested by Tan et al [7]; the patient had to be domiciled in Johannesburg. The date of "presentation" is the date of the first symptom likely to be due to SLE.

The patient records were studied for the presence of certain symptoms and signs at the time of diagnosis, and relevant haematological, biochemical and serological measurements were analysed. These serological and haematological parameters were

assessed according to the normal levels of the local laboratory. The collation of these variables was greatly assisted by the use by some doctors of a printed standardized format for assessing the SLE patients at each visit. If the presence or absence of a manifestation had not been noted it was marked "Missing". Thereafter the patients were reassessed for the presence of the same clinical and laboratory parameters throughout the course of their disease, in order to formulate a cumulative frequency for the manifestation. The cumulative frequency does not include recurrent episodes of the same symptom. Certain clinical parameters were assessed for their occurrence during the first year, from the first to the fifth year, from the fifth to the tenth year, and from the tenth to the fifteenth year post diagnosis; care was taken that loss of patients to followup or death did not significantly alter the presence or abscence of these parameters in the followup periods.

However the pitfalls of any retrospective analysis are present in this study. An obvious shortcoming was our inability to compensate, firstly, for the effect of differences in attendance frequencies as a result of the differences in disease severity. Also, it has not been possible to control for the beneficial effect of therapy, nor for the excessive or inadequate therapeutic regimens which might also affect the natural course of the disease, and hence, particularly in the former case, may play a significant role in morbidity and especially late mortality.

Details of death include the major cause of death and the major precipitating factors. The data was collected by the author and

compiled by the MRC Institute for Biostatics on to the Central Computer at Tygerberg Hospital; initial analysis was performed using BMDP, a predominantly medically-orientated statistical programme; subsequent analysis was made using the mainframe IBM Computer of the Computer Centre of the University of Witwatersrand, with the SAS statistical method. For most clinical and biochemical parameter comparisons a Chisquare analysis was made. A Fisher Exact 2-tail analysis was performed on small figures, and Student T-tests were utilised where necessary. Multivariate analysis using SAS was made when more than one variable was thought to be operative.

2.3. Exclusions.

Inevitably there is overlap of SLE with associated diseases such as rheumatoid arthritis and scleroderma. For the purposes of this study patients having erosive arthritis, features of scleroderma (either in the form of progressive sclerosis or the mixed connective tissue disease syndrome) or drug-induced SLE are excluded.

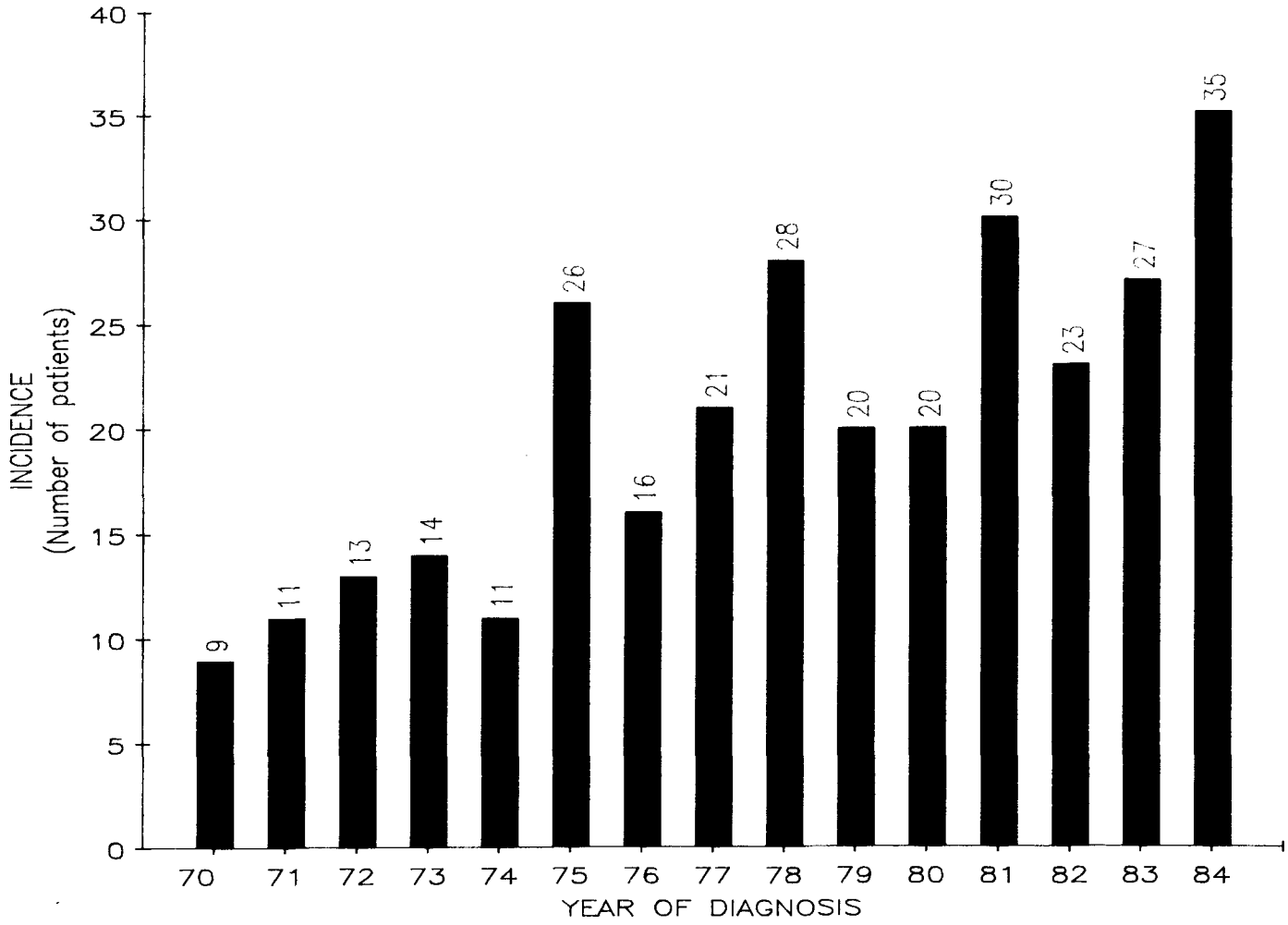


Fig 2.1 Annual incidence of patients with SLE Period 1970 – 1984

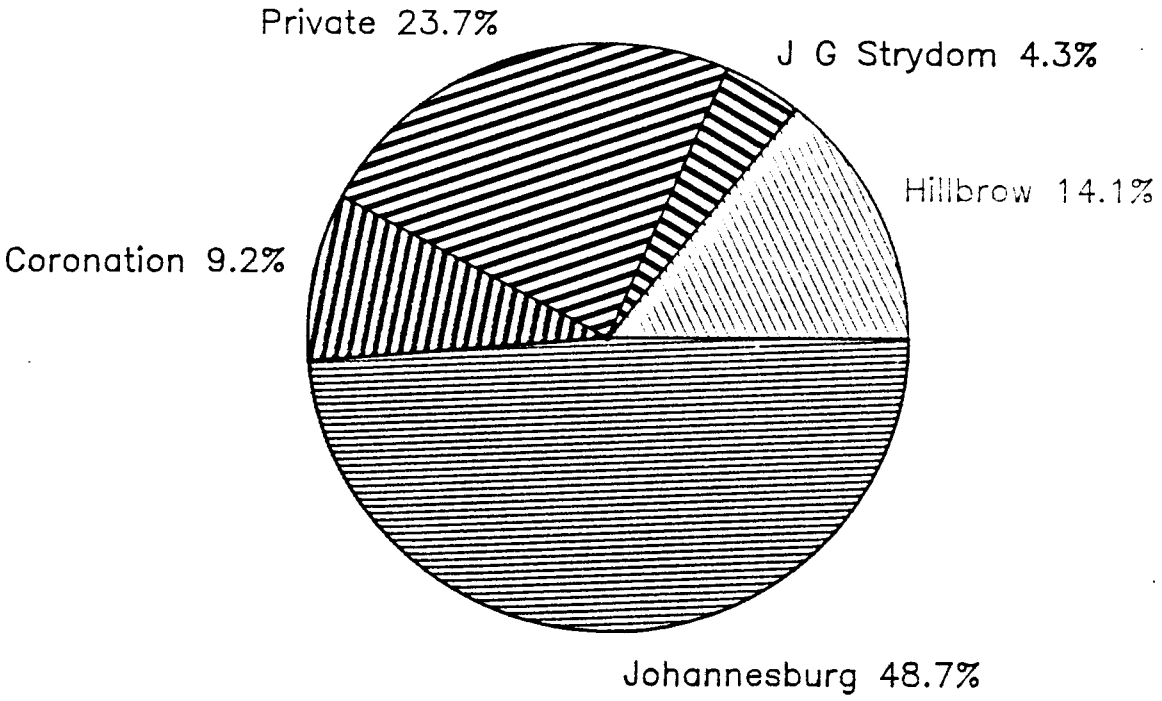


Figure 2.2 Distribution of SLE patients by hospital of origin

TABLE 2.1 DIFFERENCE IN RATIO OF FEMALES TO MALES WITH AGE (DECADES)

AGE (years)	FEMALE (number)	MALE (number)	RATIO (F:M)
10 - 19	44	4	11 : 1
20 - 29	76	11	7 : 1
30 - 39	66	10	6,6 : 1
40 - 49	30	11	2,8 : 1
50 - 59	22	8	2,7 : 1
60 - 69	11	3	3,6 : 1
70 - 79	4	2	2 : 1
80 and over	1	1	1 : 1
Total	254	50	5 : 1

2.4. Results.

2.4.1. General features.

The annual incidences using the date of diagnosis of SLE are shown in Fig. 2.1, with the increase in later years partly attributable to the opening of the Hillbrow Hospital. The introduction of ANF measurement in 1975 may explain some of the increase in diagnoses after this time. The total number of patients was 304 of whom approximately 25% were followed by private practitioners, and 75% by hospital clinics, although many patients were seen by both. Fig. 2.2 shows the breakdown of the various groups.

Table 2.1 shows the variation in sex ratio with age. The overall ratio of female to male was 5:1, but varied from 11:1 in the very young to near equality in the elderly.

Some general features of the disease are shown in Table 2.2; frequencies are compared with those of Dubois {8}. The table illustrates little difference between the two studies, except in the overall sex ratio which is lower in our experience (p= 0,008), and the frequency of a family history of rheumatoid arthritis which is higher in our patient sample (p= 0,00001). Fig. 2.3 illustrates the frequency of different ages at diagnosis for both sexes. Fig. 2.4 gives the breakdown of the proportions of different racial groups in the study; this does not reflect the incidence or prevalence of the disease. Other details relating to racial differences will be discussed in Chapter 3.

TABLE 2.2

GENERAL FEATURES OF PATIENTS WITH SLE

	Features	Morrison (304 cases)	Dubois (520 cases)
1.	Sex Ratio	5 : 1	9 : 1
2.	Age at diagnosis:-		
	range (years)	12 - 80	
	mean (months)	34	29
	median (months)	31	28
3.	Period from first symptom till diagnosis:-		
	range (months)	0 - 240	-
	mean (months)	31	24
4.	Follow up:-		
	range (months)	0 - 164	0 - 158
	mean (months)	52	-
	median (months)	42	-
5.	Family History:-		
	SLE	4.2%	5.0%
	Rheumatoid arthritis	18.0%	6.0%

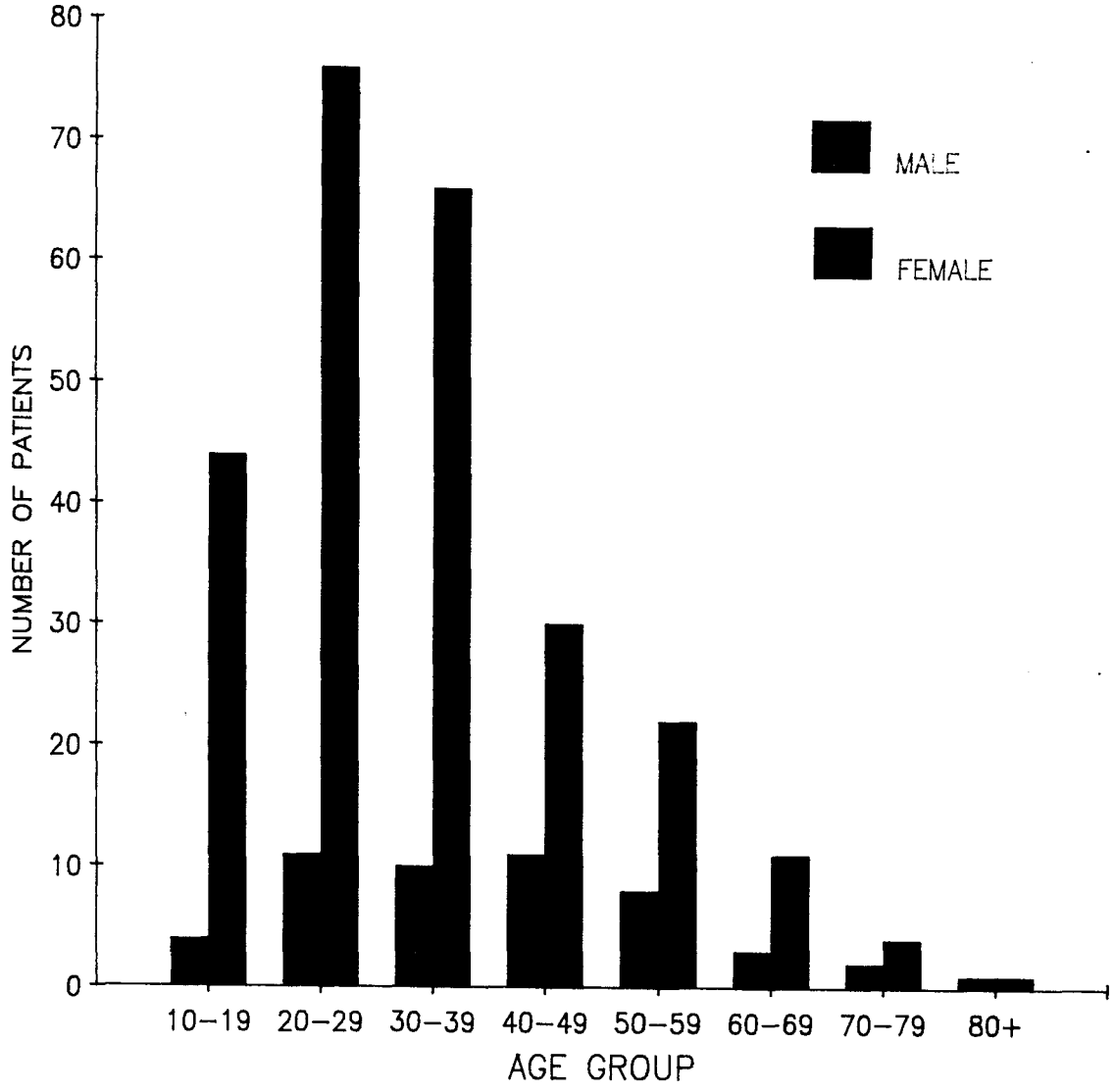


Figure 2.3 Distribution according to age at diagnosis of SLE

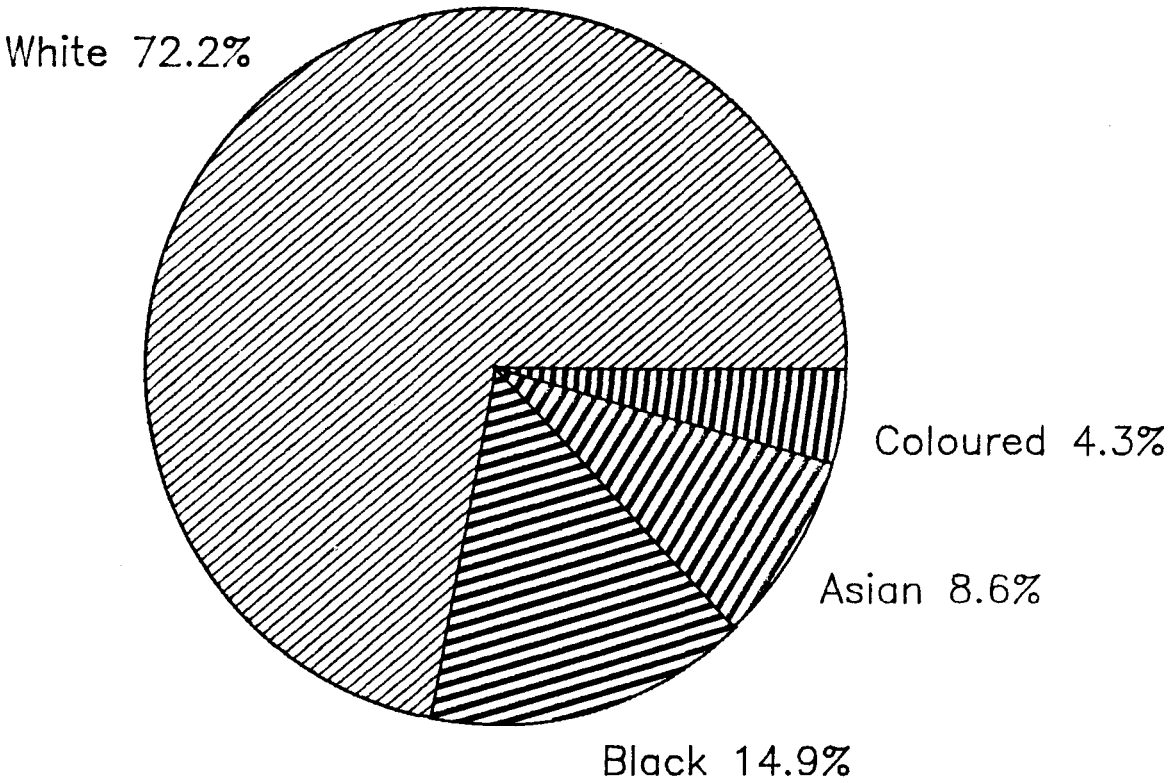


Figure 2.4 Distribution of SLE patients by racial group

2.4.2. Clinical features.

(i) On presentation:

The histograms from Fig. 2.5.1 to Fig. 2.5.11 show the frequency of various signs and symptoms of patients at the time of diagnosis, grouped by systems. In these histograms and in the subsequent tables of clinical manifestations throughout the disease, when the percentage alone is expressed, it signifies that at least 90% of the total group had the presence or absence of that manifestation documented; in other words information regarding that manifestation was missing in less than 10%. Certain manifestations were recorded in only a few patients, in which case the fraction of patients who were positive compared to the total number of patients in whom that feature was measured, was given in brackets; there is obviously overlap of features in the same patient. Dubois [8] looked at the chief complaint of the patient at diagnosis, whereas I included all features at diagnosis. Arthritis was the most common manifestation in both studies. Discoid lupus was the second most common primary manifestation in Dubois' group, but uncommon in ours (11%). Malar rash, fever and pleurisy were important features in both samples, but our patients frequently had alopecia or photosensitivity, which were uncommon primary problems in Dubois' patients.

(ii) Frequencies of manifestations over the follow-up period:

Here the total frequency of the various signs and symptoms the patients manifested within the course of their disease is compared with those reported in two large overseas studies and one South African study in Tables 2.5.1 to 2.5.11 inclusively. The largest was completed by Dubois and Tuffanelli in 1964 in Los Angeles, and comprised 58% Whites and 28% Blacks [8]. Estes and Christian

published results of research they had undertaken on 150 SLE patients in New York in 1971, of whom 47% were Black [9]. The third study, by Jessop and Meyers, emanated from Cape Town in 1973, and included 130 patients made up of 28% Whites, 66% Coloureds and 6% Blacks [37]. When compared with Dubois' study, our patients had lower frequencies of fever [56% cf 84% p= 0,00003], cerebrovascular accidents [7% cf 25% p= 0,00001], lymphadenopathy [26% cf 59% p= 0,000004], pericarditis [15% cf 30% p= 0,0002], rheumatoid factor [23% cf 57% p= 0,000003],and discoid LE [13% cf 27% p= 0,0003]. Conversely our patients had higher frequencies of photosensitivity [46% cf 33% p= 0,001], hypertension [44% cf 25% p= 0,00007], Raynauds' phenomenon [32% cf 18% p= 0,0002], alopecia [51% cf 21% p= 0,000002], mouth ulcers [36% cf 9% p= 0,000002] and the lupus anticoagulant [18% cf 0,4%], though the latter may be due to an increase in the awareness of the significance of this factor and hence a selective bias in recent years.

Although many of the differences may be explained by the difference in the criteria for the inclusion of patients into the two studies, with a bias towards milder cases in our study, it is particularly noticeable that the skin manifestations, with the exception of discoid lupus, are increased in our group. The more severe manifestations such as CVA, pericarditis and renal failure requiring dialysis are less frequent in our study. Dubois' patients were more "reactive" in that they presented more frequently with lymphadenopathy, fever, and positive rheumatoid factor. The remaining CNS, musculoskeletal and pleuritic symptoms were approximately the same in both samples.

2.4.3. Causes of death.

Of our sample, 19,3% died and the survival curves are shown in Fig. 2.6 illustrating a 5 year survival of 83% overall. Since renal disease is considered to be the most important cause of decreased survival, the corresponding curves are shown for those patients who had had a serum creatinine level > 150 umoles/l and for those who had always had normal levels. The 5 year survival rates were 68% for those with raised creatinine levels and 92% for those with normal levels ($p = <0,05$).

The "cause" of death is always difficult to define. I elected to follow the example of Estes and Christian [9], and selected the single most crucial factor that brought about death. Theoretically any patient requiring dialysis has suffered renal "death"; this group comprised 33 patients in our study [refer Table 2.5.6], but this figure was not included in the mortality figure unless the patient subsequently died. Our findings were unusual since a high proportion of deaths in our patients was directly due to pulmonary causes, with direct renal causes of death being relatively uncommon. More complete details of death are contained in sections 2.5.6, 2.5.8 and 2.5.15.

Table 2.3 outlines the most important causes of death and Table 2.4 shows the most significant contributory causes; note that more than one contributory cause can exist in any one patient.

2.5. Discussion.

2.5.1. General.

The increased incidence of diagnosis of SLE patients over the last 15 years is shown in Fig. 2.1. This increase is at least partly due to the introduction around 1975 of a better diagnostic test in the form of the antinuclear factor assay. It is also partly due to improved patient records, particularly at hospitals other than the Johannesburg hospital, with the advent of specialist clinics for SLE and better filing systems. The late increase [post 1980] is in part a result of the opening of the Hillbrow Hospital, discussed earlier. The change in the female to male ratio with age is striking; it is 11:1 in the young and 1:1 in the elderly. Also, the males exhibited only a limited variation in the frequency of diagnosis with variation in age, whereas females
showed a marked increase in diagnosis during their reproductive years (Fig. 2.3). Both of these findings suggest the possible influence of an environmental or hormonal factor.

The period from the appearance of the first symptom attributable to SLE till diagnosis was 31 months and is similar to the 2 year span in the Dubois report [8]. Of note is the fact that our study includes a patient who had symptoms for 20 years prior to diagnosis; the elderly appear to be frequently misdiagnosed as sufferers of a "general arthritic condition", senile dementia or para-neoplastic disease.

Environmental factors in a mining city such as Johannesburg could play

a role in the aetiology of SLE; in tracing patients it was remarkable how many patients had their original addresses actually at a mine or in close proximity to one. Unfortunately this aspect was not researched further but when considering the association between rheumatiod arthritis (RA) and mining [10], we noted with interest that many of our SLE patients had relatives with RA (18% cf 5,5% Dubois [5] and 5% in general population [11]).

2.5.2. Genetic factors in SLE.

We found a family history of SLE in first or second degree relatives in 4,2% of our total patient group, compared with Arnett's 7% [12] and Dubois' 2% [8]. All our cases were related as either mother to daughter, sister to sister or female to female relative. There were no males with a family history, which is considerably fewer than the 10% recorded in "sporadic" cases [12]. It has been reported that where there was a father to son history of SLE, many developed the disease pre-pubertally [14], making it possible for this group not to be represented in this study. However, the paediatric SLE patients treated by paediatric nephrologist Dr P Thomson over the past years have had no family history (Dr P Thomson's personal communication). Hughes [2] noted LE cells in 27% of female first degree relatives but in only 8% of male first degree relatives, and similar abnormalities have been reported in siblings [13].

The importance of these family associations is their possible link with the complement-deficient states which should always be looked for

in those with a family history of a collagen disease. We did not discover any complement deficiencies in our study, but this may be due to lack of investigative capacity. Family studies are often necessary, because of the considerable difficulty in defining congenital deficiences. Many so-called "inactive" SLE patients still have increased consumption of complement factors and hence manifest with low or absent levels of complement factors. However in these latter cases the CH5Ø is usually measurable; several of our patients had very low levels of CH5Ø, but neither they nor their families were subsequently investigated.

A lupus-like syndrome has been associated with the congenital deficiency of virtually every component of the complement pathway, notably C1q, C1r, C1s, C4, C2, C3, C5, C7, C8, and C1 esterase inhibitor [15,16,17,18,19]. Within the congenital complement deficiency group there appear to be marked similarities in disease manifestations even though the genetic origins of the various deficiencies are markedly different.

Genetic factors are attaining greater importance with the realisation that SLE is not a homogenous disease; closer association may now be made between clinical subsets of the disease, the HLA system and other inherited disorders particularly the congenital complement deficiency group mentioned above. There are variations in the disease in different racial groups, a subject which will be discussed in a later section.

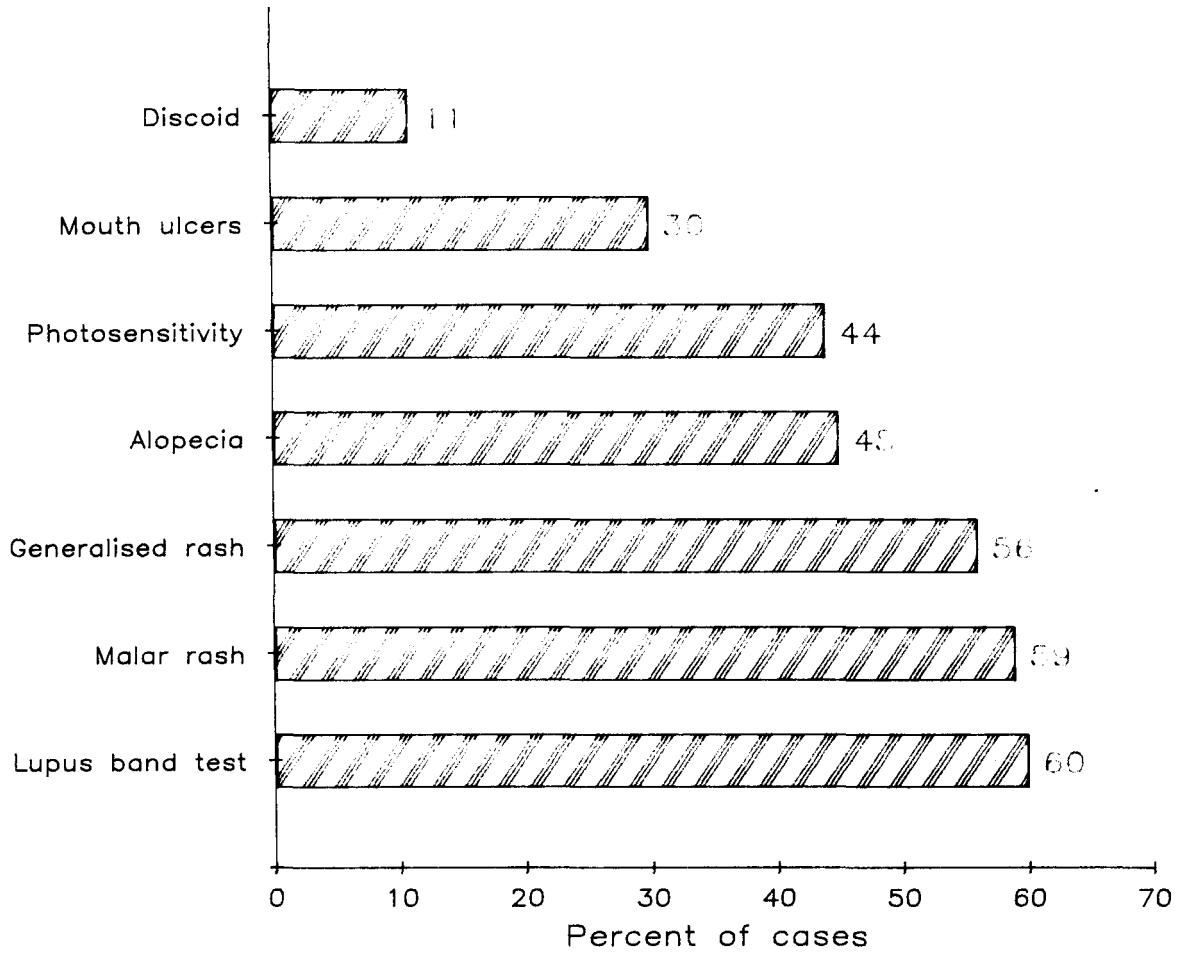


Figure 2.5.1 Dermatological manifestations at diagnosis

2.5.3. Dermatological and oral manifestations.

Dermatological manifestations are not the most common presenting signs of SLE, but are probably the most striking. Frequencies for this group of manifestations in our patients at diagnosis and throughout the disease are shown in Fig. 2.5.1 and Table 2.5.1 respectively.

Of particular relevance to SLE sufferers in Johannesburg is the symptom of photosensitivity. In our study, 8% of patients had, on presentation, an exacerbation of symptoms other than skin rash after exposure to sun (cf 6% Dubois [8]), and 44% had photosensitive skin eruptions, of which 6% were very severe and incapacitating. The cumulative frequencies vary significantly from those of other studies (46% cf 33% Dubois, p= Ø,ØØ1 [8]). Of the 14Ø patients who had photosensitivity at any time, only 7 manifested with it for the first time after diagnosis. Several patients in "remission" complained of photosensitivity. In addition, most of our cases were diagnosed in winter when there is on average 2Ø% less UV irradiation than in summer. Dubois found no significance in the month of onset. This would suggest that photosensitivity as a symptom is unrelated to disease activity and that Johannesburg may be unique in its increased prevalence of the symptom. The link between SLE and sensitivity to ultraviolet light has long been recognised, but recently certain additional physical and physiological facts have emerged.

The pathological features of sunlight arise from the UV-B region (wavelength 28Ø - 315nm of the UV spectrum) and include sunburn, photosensitivity and predisposition to skin cancer [2Ø,21]. Factors

modifying the UV component of sunlight include the time of day, season, degree of latitude, cloud cover, reflection of UV light from the ground and, finally, altitude [22]. The first three relate to the height of the sun in the sky; the higher the sun, the less ozone that must be penetrated. The ozone is singularly important in preventing wavelengths less than 295 nm from reaching the earth's surface, the significance of which is discussed below.

Johannesburg has an average of 8,6 hours of sunshine per day, compared to London's 4 - 5 hours per day [23,24]. In addition, even with moderate cloud cover, the resultant scattered UV penetration is seldom less than 10% of that of a clear day, and the light cloud cover found frequently over the Johannesburg area makes little difference to the UV exposure. An additional factor in Johannesburg is the reflection of sunlight from the ground; a lush green British lawn scatters about 3% of the UV light, whereas the barren ground of many recreational areas on the Highveld reflects approximately 20% [20].

Probably the most pertinent factor is Johannesburg's altitude of nearly 2000 meters; every additional 300 meters results in an increase in UV exposure of 4%. Even more important is the fact that the greater the altitude the greater the number of short wavelength waves which penetrate the ozone layer [25]. At Durban the shortest wavelength discernible is 300 nm but in Johannesburg levels of 290 nm are approached, and these are significantly more likely to activate SLE than wavelengths of 300 nm.

Interestingly enough, the use of UV sensitive plastic "skin" has demonstrated that the highest exposure to overhead sunlight is in the

butterfly distribution of the face, mimicking the malar rash, especially when a photosensitizing drug such as phenothiazine is used [22]. Dubois et al found that phenothiazines are important inducers of SLE and in the presence of UV light they react with DNA and possibly make it antigenic [5]. In support of this hypothesis it was found that 22% of psoriatic patients receiving UV light with Psoralen as a sensitizer (PUVA) developed a positive ANF [27].

Despite our high UV light exposure, discoid lesions were uncommon on presentation (11%); the cumulative frequency was 13% (cf 29% Dubois [5], p= Ø,ØØØ3).

We did not include "pure discoid" lupus in our study. Controversy reigns as to when discoid lupus is "pure" and when it is a subset of SLE. In one study, 62% of discoid lupus patients had abnormal blood results in the form of positive ANFs, FPWRs and lymphocytotoxic antibodies; in total 6,5% progressed to SLE, particularly those with persistence of abnormal blood results [28]. Roujeau et al demonstrated that of 7 patients with discoid LE presenting with hypocomplementaemia without clinical renal disease, 2 had definite proliferative glomerulonephritis on biopsy and another 5 had glomerular immune deposits [26].

The histology of mouth ulcers closely resembles that of discoid lupus, leading to their inclusion in the integumentary division. Of our patients 3Ø% had mouth or nose ulcers at diagnosis and 36% overall (cf 7% Estes [9], cf 9% Dubois [8] p= Ø,ØØØØØ2). The disparity between our frequencies of discoid LE and mouth ulcers and those of overseas studies suggests a difference in activating mechanisms, although it is

possible that some Johannesburg clinicians are failing to recognise discoid skin lesions.

Jonsson et al [30] reported mouth ulcers in 45%, but commented that most of these were non-painful discoid-type lesions or erythematous patches, as opposed to true ulcerations. In contrast, our patients presented with painful ulcers, and their presence appeared to denote disease activity. Jonsson found that the classical oral lesions, including ulcers, were associated with an absence of nephritis; he also found that all ulcers had immunoglobulin deposits in the basement membrane, mimicking a positive lupus band test (LBT). This is the investigation of the dermo-epidermal junction for the presence of immunoglobulins, complement and properdin deposits; these are usually demonstrated by immunofluorescent staining techniques.

Diffuse skin rashes were present in 56% of our cases at diagnosis and were markedly pleomorphic in their presentation; since rashes were not necessarily the major problem at diagnosis, it is difficult to compare our patients with those of Dubois, where 20% had skin rashes as the presenting symptom [8]. The cumulative frequency of 66% may reflect the high UV irradiation that our patients are exposed to.

The malar rash was present in 59% of cases on presentation and 66% overall (cf 57% Dubois, 39% Estes [8,9]). The corresponding cumulative figures for Jessop et al (29%) were much lower. We classified malar rash at diagnosis into three categories, similar to those used by Dubois; these were the malar erythema or blush (9%), discrete maculo-papular or discoid eruptions in the butterfly distribution (49%), and thirdly, severe chronic disfiguring discoid

lesions (1%). Our figures do not bear out the contention that the malar rash is becoming less frequent at presentation since two groups, one diagnosed between 1970 and 1974 and the second between 1980 and 1984, had similar frequencies of malar rash at diagnosis.

The frequency of alopecia in our patients at diagnosis was 45%, with a cumulative frequency that is very significantly higher than that of other studies (51% cf 21% Dubois [8], p= 0,000002).

In total 85% of all our patients manifested with skin complaints, either with malar or generalised rash, alopecia, discoid LE, photosensitivity or mouth or nose ulcers.

Of our cases who had skin biopsies at diagnosis, 31 out of 52 had positive histology and 30 out of 50 had a positive LBT; in total 39 out of the 63% tested had a positive LBT (62%). Our figures concur with those of Provost; using the same criteria we did he reports finding positive LBTs in 40-55% of SLE patients [31].

The relevance of the LBT is controversial, particularly with respect to renal disease, since there is a similarity between the immunoglobulin deposits in the skin and those in the kidney basement membrane. However this phenomenon in the skin could be a result of UV irradiation; IgG appears in the basement membrane of the epidermis 7 weeks to 4 months after sun testing, possibly as an antibody response to an antigen in the skin. For this reason care should be taken to examine non-irradiated areas [29]. Other authors, including Dahl [34], have also stressed the importance of biopsy material being taken from unexposed areas, since this increases the specificity of the

biopsy, particularly when differentiating SLE from discoid lupus.

Douglas Smith and Rothfield showed at least one component of properdin, complement or immunoglobulin deposited in the non-inflamed deltoid skin of 73% of SLE cases, but also in 36% of patients with other rheumatic diseases, giving a specificity of 64% and a predictive value for SLE of 57% [32]. Provost showed that the incidence of a positive test could be correlated with disease activity; a positive LBT was found in 91% of those with active disease, and in only 33% with dormant disease [31]. It was found to be increased as much as threefold in patients with renal disease in some studies [33,129]. A fact that appears to hold true is that for any individual SLE patient there are fewer immunoglobulin deposits without SLE activity than with active disease [33].

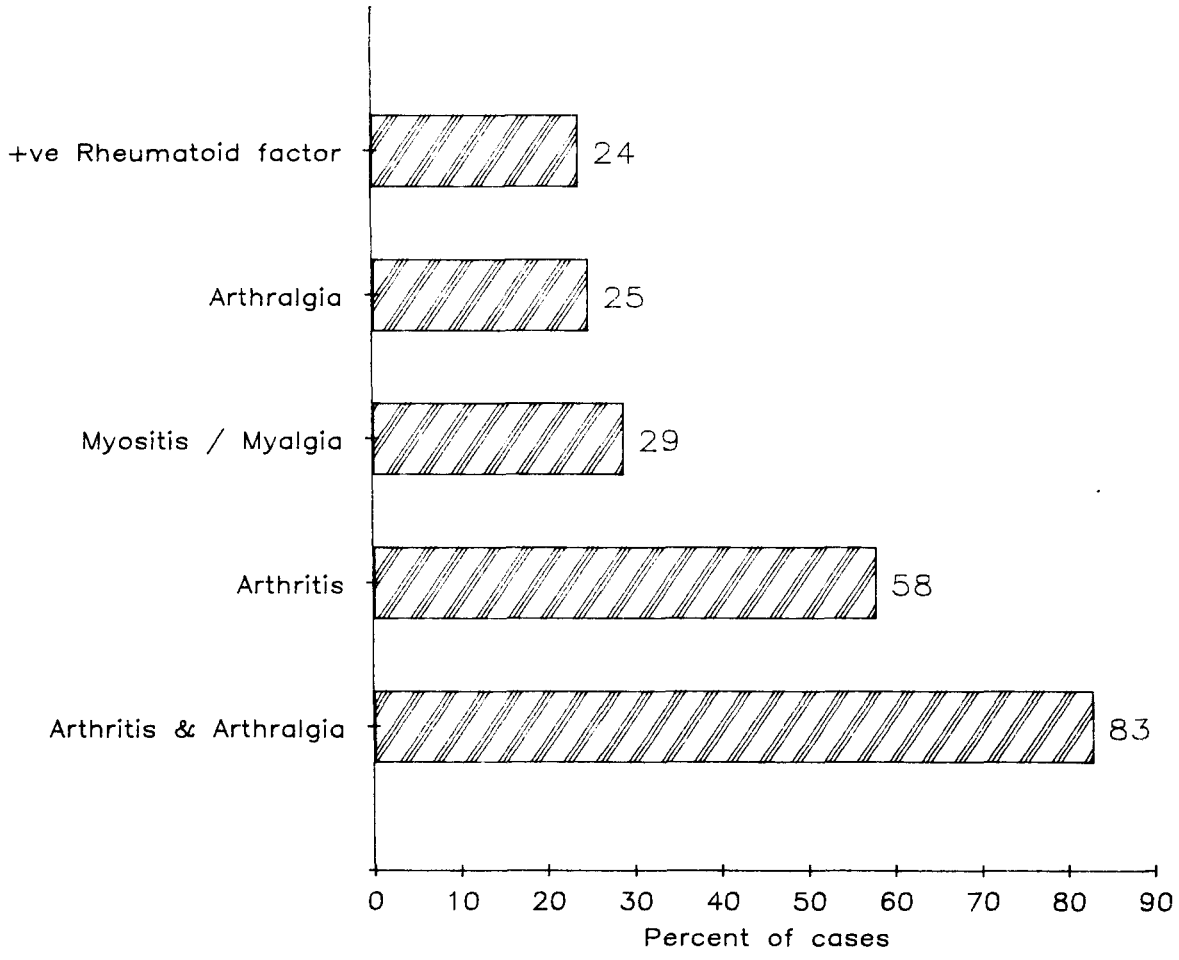


Figure 2.5.2 Musculoskeletal manifestations at diagnosis

2.5.4. Musculoskeletal manifestations.

Musculoskeletal manifestations are the most common group of clinical findings in SLE, and their frequencies at diagnosis and throughout the course of the disease are displayed in Fig. 2.5.2 and Table 2.5.2 respectively.

In our patient sample, 83% had painful joints at diagnosis; 25% had arthralgia or tenosynovitis only, 55% had swollen joints and a further 3% had incapacitating arthritis. The cumulative frequency of 86% is similar to the 92% and 98% found by Dubois [8] and Grigor [40] respectively. The rheumatoid factor (RF) was positive in 24% of our cases at diagnosis; there was a cumulative frequency of 23%, compared with Jessop's 24% [37] and Dubois' 57% [8] (p= 0,000003). I can give no reason why the South African patients appear to have a lower frequency of positive RF, unless there are differences in laboratory methods.

The arthritis of SLE is classically described as non-erosive, but tendinous rupture can lead to deformity that mimics RA; however the two diseases are different on both clinical and immunological grounds. Certain researchers feel that rheumatoid-like deformities that do not develop erosions after two years can be diagnosed as the "Jaccoud" deformities of SLE [51]. SLE may occur with RA, since the latter does occur in 3% of the general population, but the association is uncommon and presumably coincidental [35]. One of the commonest causes of pain localized to a joint in SLE is tenosynovitis, which exhibits no objective swelling or sign of inflammation; as a result many young

TABLE 2.5.2

CUMULATIVE MUSCULOSKELETAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Arthritis	62	-	-	-
Arthralgia	24	-	-	-
Combined arthritis and arthralgia	86	92	95	82
General muscular symptoms (myalgia and myositis)	38	48	-	-
Rheumatoid factor - positive	23	57	21	24
Combined muscle and joint pains	87	-	-	-

female patients with this complaint are dismissed as "neurotic".

Belonging in a subset of the disease are patients on Penicillamine treatment for RA who develop drug-induced SLE. This entity is often slow to resolve (2% of patients on Penicillamine therapy develop clinical SLE over 5 years [36]), and it is possibly associated with tissue types All + B15. In addition, juvenile RA can probably progress to clinical SLE [35].

Myositis can be a manifestation of SLE; its existence does not always denote the presence of the mixed connective tissue disease. Symptoms in our cases ranged from mild myalgia (muscle aches without muscle enzyme rise) in 15% at diagnosis, to myositis (inflammation of muscle as evidenced by pain, swelling and muscle enzyme rise) in 14%; many patients complained of muscular pain referred from tendons or joints. Muscle symptoms occurred in 38% of our patients throughout the course of their disease, compared with another study which has shown that 50% of its patients had these symptoms [38]. In 8% of the latter group, severe muscular swelling and marked weakness were the presenting symptoms, as opposed to 3% in our findings. The same researchers also found that patients with the milder form often had normal CPK and mildly increased aldolase levels, and that most of their cases of muscular involvement responded favourably to steroid therapy [38]. A study by Vilppula showed an abnormality in the EMG in 70% of his patients [39].

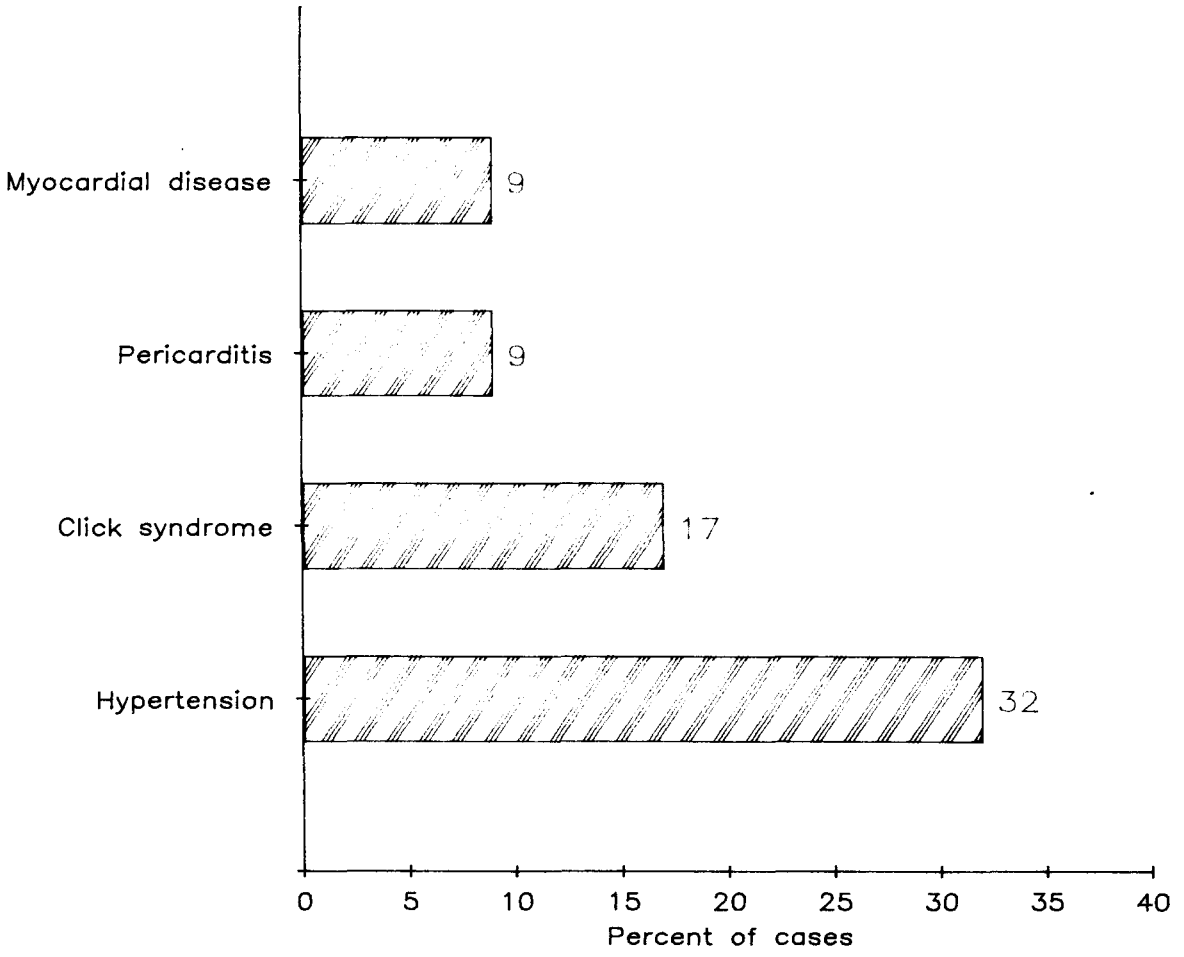


Figure 2.5.3 Cardiovascular manifestations at diagnosis

2.5.5. Cardiac manifestations.

The frequencies of cardiac manifestations at diagnosis and throughout the period studied are illustrated in Fig. 2.5.3 and Table 2.5.3 respectively. Hypertension was present in 32% of our patients at the time of diagnosis. The cumulative frequency of 44% is higher than Dubois' (25%, p= Ø,ØØØ7) or Jessop's (3Ø%) [8,37], but similar to that of Estes' study (46%) [9]. We noted a marked increase in hypertension in those few patients followed for 15 years which Bulkley also describes [41], and a late deterioration in myocardial function in SLE patients has been attributed to hypertension [42].

In our patients, 9% had clinical evidence of pericarditis on presentation, with or without symptoms, with an additional 3% having symptoms on history very suggestive of pericarditis. The cumulative frequency for pericarditis throughout the period of study was 15% (cf 3Ø% Dubois [8], p= Ø,ØØØ2), with 3% having tampanade. Estes and Christian [9] found pericarditis in 2Ø% of their patients, usually in association with pleural effusion, and pericardial tampanade in 1%; this latter frequency is the same as in our patients at diagnosis. Chang [43] found pericarditis to be the most frequent cardiac manifestation. Other workers demonstrated effusions echocardiographically in two thirds of patients with active SLE [44], many of whom did not have symptoms or signs of pericarditis.

With the advent of steroid therapy, the myocardial manifestations in SLE have changed dramatically. Libman Sack's endocarditis is usually discovered only at autopsy and the growths are smaller and their

TABLE 2.5.3

CUMULATIVE CARDIAC MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Myocardial disease (Myocardial ischaemia and myocarditis)	13	-	20	3
Pericardial disease	15	30	20	9
Click syndrome	18	-	-	-
Hypertension	44	25	46	30
Combined pericardial and myocardial disease	22	-	-	-

occurrence is less frequent than in the pre-steroid era [41,42]. In addition, certain studies have demonstrated that myocardial inflammatory processes, which used to be present universally at autopsy, occur much less frequently [43]. Recent attention has therefore focussed more on myocardial disease in the form of myocardial ischaemia and conduction abnormalities, the latter particularly in newborn infants of SLE mothers (associated with the Ro antibody - see later [154]). In this study myocardial disease manifested as either myocardial ischaemia or myocarditis, the latter being defined as a tachycardia out of keeping with the patient's fever, or an enlarged heart, or a gallop rhythm. Myocarditis was present in 1% at diagnosis, making it an uncommon finding. Dubois [8] in his work showed a total frequency of 7,8% (cf 3% in our series), and many of his patients had associated pericarditis.

Of our cases, 8% had myocardial ischaemia at diagnosis, and this high level could not be explained by the high proportion of elderly patients in our sample, since the younger patients had higher frequencies of myocardial ischaemia than the elderly. In the younger group 60% had had no previous steroid therapy. Myocardial ischaemia was described in 4% - 8% of our patients throughout the 10 years post diagnosis, but the prevalence increased dramatically to 60% in the 5 cases screened from 10 to 15 years post diagnosis; this striking rise in late incidence has also been noted by Urowitz et al [47] who attributed it to atherosclerosis. The total cumulative frequency for myocardial ischaemia throughout the study period was 10%, which is considerably higher than the 1%-2% described separately by Estes [9] and Ropes [45]. The former group felt that coronary artery disease was a coincidental finding in SLE, but our findings and recent

laboratory evidence suggest otherwise, notably that myocardial infarction in SLE patients occurs not merely sporadically or as a side effect of long-term steroids but as a manifestation of SLE per se.

Our autopsy findings in patients with myocardial ischaemia confirmed those of other studies, notably that arteritis is uncommon [43,47,48,50], and that there is either atherosclerosis or hyaline thromboembolus present [43,49]. South Africa has a scourge of coronary artery disease in young people, but autopsies performed on our 3 young patients with myocardial infarction showed no evidence of causative atheroslerosis, but rather of fresh thrombosis. In addition there is controversy about the reputed higher incidence of atherosclerosis in patients receiving steroids [50,41]. In one of these studies the risk factors of hypertension and raised serum cholesterol were increased in such a group of patients receiving steroid therapy. However they also tended to have more severe renal and CNS disease which may have potentiated the risk factors above. Mitral valve disease and pericardial adhesions were noted by these researchers to be increased in those with coronary narrowing, irrespective of steroid dose, suggesting that lupus activity plays a significant role in coronary insufficiency [50].

Recent studies highlight the causative role of the lupus anticoagulant factor in major arterial and venous thromboses. This is probably the mechanism operating in the "hyaline thromboembolus" type of coronary artery occlusion and the mechanisms will be discussed with the abnormalities of coagulation in a later section; suffice it to say that the use of steroids and the role of follow up angiography in SLE patients with myocardial ischaemia is currently undergoing careful

analysis [52].

Conduction abnormalities (excepting the neonatal form mentioned above) occasionally accompany SLE myocarditis and pericarditis, but are usually transitory and improve with treatment of the underlying condition [43,8]. Unfortunately their frequency was not measured in our study.

Clinical murmurs were found in a high proportion of cases both in our work and other series [8]. Of our patients 17% were found at diagnosis to have the posterior billowing mitral leaflet syndrome (Click syndrome); this is higher than the percentage quoted by Prof J Barlow for matched controls (5%-10%), but it approximates other estimates of prevalence in normal subjects. Barlow's syndrome may reflect a subclinical endocarditis, but there was no marked increase in the number of patients with the click syndrome when assessed throughout the period of the disease. Ropes' study included some patients with endocarditis without the presence of a murmur [45], and an acquired form of aortic stenosis has also been reported by other workers [46].

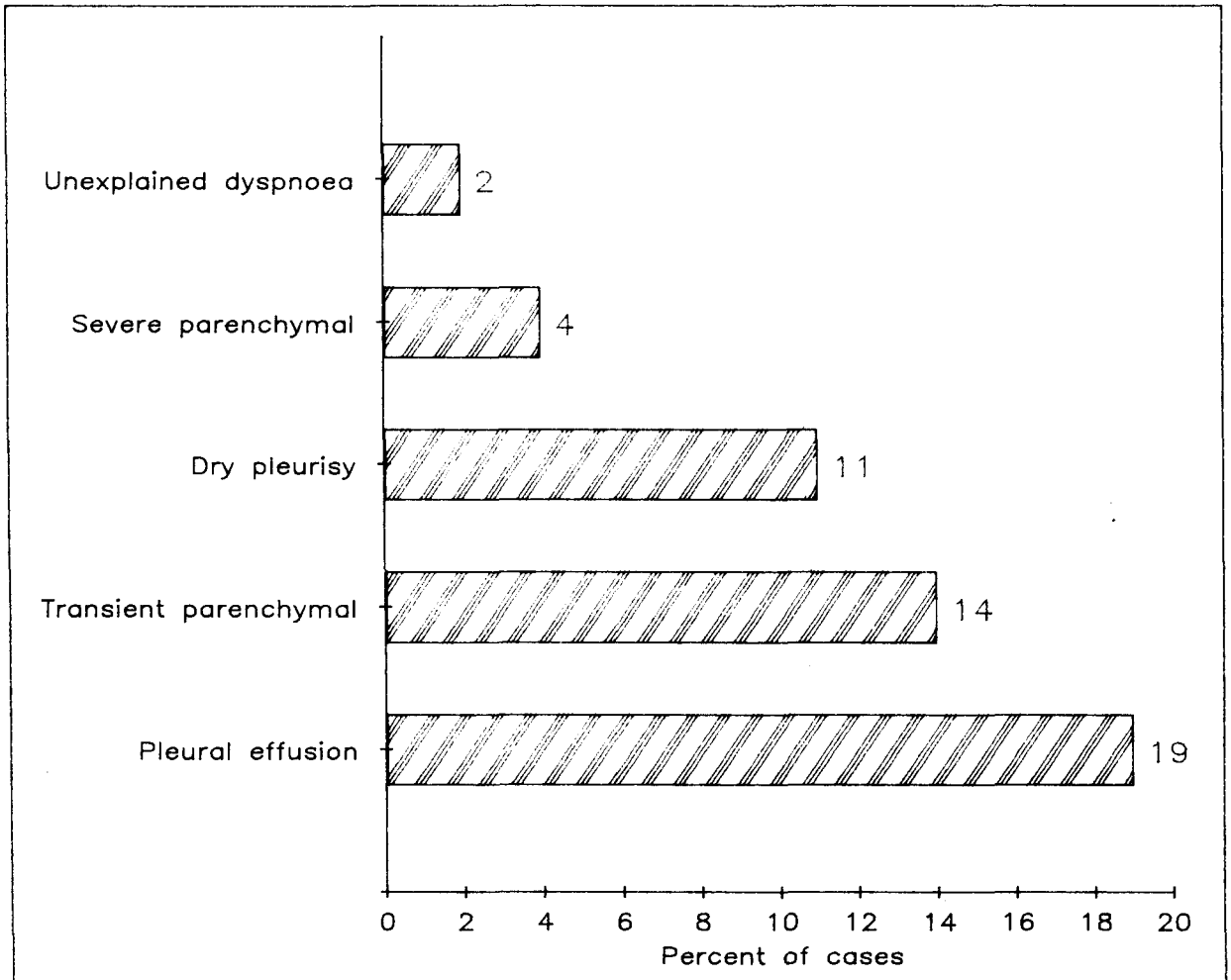


Figure 2.5.4 Pleuro–pulmonary manifestations at diagnosis

2.5.6. Pleuro-pulmonary manifestations.

SLE involvement of the lung is predominantly either parenchymal or pleural; the frequencies of the various manifestations at diagnosis and cumulatively are listed in Fig. 2.5.4 and Table 2.5.4 respectively. Many patients complain of pleuritic-type chest pain without clinical or radiological evidence of active pleural involvement; at autopsy many are found to have fibrinous adhesions, and Hughes [2] describes a syndrome of painful "dry pleurisy" which may respond to pleurectomy [53]. Pleuritic chest pain was present in 11% of our cases at diagnosis. Clinical evidence of pleurisy was found in 19% of patients at diagnosis and thereafter cumulatively in 28%; the latter figure closely resembles those found by Dubois (30%), Harvey (16%) and Estes (40%) [8,54,9]. Massive pleural effusion, involving at least three quarters of a pleural cavity, was found in 1% of our patients.

The experience of Haupt et al [58] was of pleurisy in 30% of his cases, of which only 60% were attributable to SLE, but we include in this category only those whose pleurisy on retrospective review was due to SLE. Pleuricentesis is not usually indicated, but when pulmonary embolism, congestive cardiac failure, tuberculosis or other infection is suspected, examination of the fluid for certain characteristics of SLE pleuritis may be necessary; these include low complement, normal sugar, LE cells, ANF in titres greater than 1:160 and a ratio of pleural fluid ANF to serum ANF of greater than or equal to 1:1 [56]. The latter suggests a possible immunological basis for the pleuritis of SLE.

TABLE 2.5.4

CUMULATIVE PLEUROPULMONARY MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Life threatening pulmonary involvement	6	-	-	-
Transient pulmonary infiltrate	21	-	-	-
Pleurisy	28	30	40	34
Unexplained dyspnoea	4	-	-	-
Combined pleuropulmonary manifestations	40	-	-	-

Pulmonary manifestations were more difficult to categorize; there appeared to be a group of patients in our study (14% at diagnosis) with asymptomatic radiologically-proven pulmonary infiltrates, often basal, which resolved spontaneously. These transient infiltrates are probably atelectases, and occur episodically throughout the course of the disease; the cumulative frequency for this manifestation was 21%.

Life-threatening complications such as pulmonary haemorrhage, significant infective pneumonia, diffuse infiltrates or interstitial fibrosis were uncommon at the time of diagnosis of SLE (3,5%). These manifestations had a cumulative frequency of 6%, which approximates the finding in one study (2% [9]) but is lower than another (18% [58]).

Severe pulmonary infections were a major cause of death, and although infections caused by uncommon opportunistic organisms such as nocardia have been associated with SLE [55], our experience, backed by antemortem and postmortem investigations, was that the infective agents were frequently common pathogens. These included infections with pneumococcus (4 cases), staphylococcus aureus (2 cases), and klebsiella (1 case). No opportunistic lung infections were documented in our research, but this may be partly explained by a lack of investigative capacity. The effect may also be partly environmental, since until recently pneumocystis carinii infection was uncommonly documented in Johannesburg even amongst the immunocompromised renal transplant patients [personal communication, Prof A Meyers].

Totally different to the often localised transitory pulmonary infiltrates mentioned above, are the diffuse infiltrates; these

occurred infrequently in less than 1% during any follow-up period in our group. However such an infiltrate was the direct cause of the death of one of our patients. Carette, describing the NIH experience of 8 patients over 10 years, ascribes these infiltrates to infection, congestive heart failure, uraemia, drug reactions and pneumonitis, with or without pulmonary haemorrhage. Autopsy or biopsy frequently showed intra-alveolar haemorrhage, perhaps as a result of co-existing thrombocytopenia [59]; it would be interesting to know whether there was an associated lupus anticoagulant factor present (see later). In another study in which 70% of patients had anti DNA antibodies, immunofluorescence studies revealed deposits with anti nuclear and anti-dsDNA activity along the alveolar wall [60]. These and other authors [61] postulated that these deposits could be associated with vasculitis, causing intra-alveolar haemorrhage, since immune deposits are not usually present in alveoli of SLE patients who do not have pulmonary disease. Others have, however, noted intra-alveolar haemorrhages in association with non lupus-related conditions such as infections, uraemia and heart failure [62,58].

Only 4 cases in our sample were documented as having interstitial fibrosis, and no patient manifested with primary pulmonary hypertension. The uncommon syndrome of interstitial fibrosis has been postulated to belong in a subset of SLE associated with intra-alveolar haemorrhage. This is possibly due to vasculitis, since Perez et al found 10% of patients in this subset developed primary pulmonary hypertension [57].

The combined total frequency of pleuritic and parenchymal manifestations was 40%.

Dyspnoea from unexplained causes was rare at presentation in our study (2%), but gradually increased to involve 14% after 15 years of followup. In attempting to explain this dyspnoea, overseas studies have looked at nonspecific respiratory function parameters and have found abnormalities in 80% of SLE patients, including some asymptomatic patients. These abnormalities consist of a restrictive pattern with decreased compliance, and an "alveolar block" [63]. The same authors found no association between pulmonary disease and other parameters of SLE activity. Considering the altitude, the low incidence of dyspnoea in our study is surprising; up to 30% have complained of dyspnoea in other studies of SLE [65], but this may reflect the co-existence of other disease.

Various authors report abnormal chest X-Rays in 68% of lupus patients. The related conditions include the "Shrinking lung syndrome", which is characterised by reduced mobility of the diaphragm, probably as a result of diffuse fibrosis, and aggravated by atelectases at the lung bases [65,66,58]. This syndrome is occasionally non-progressive but may also be associated with pericarditis and conduction abnormalities [66].

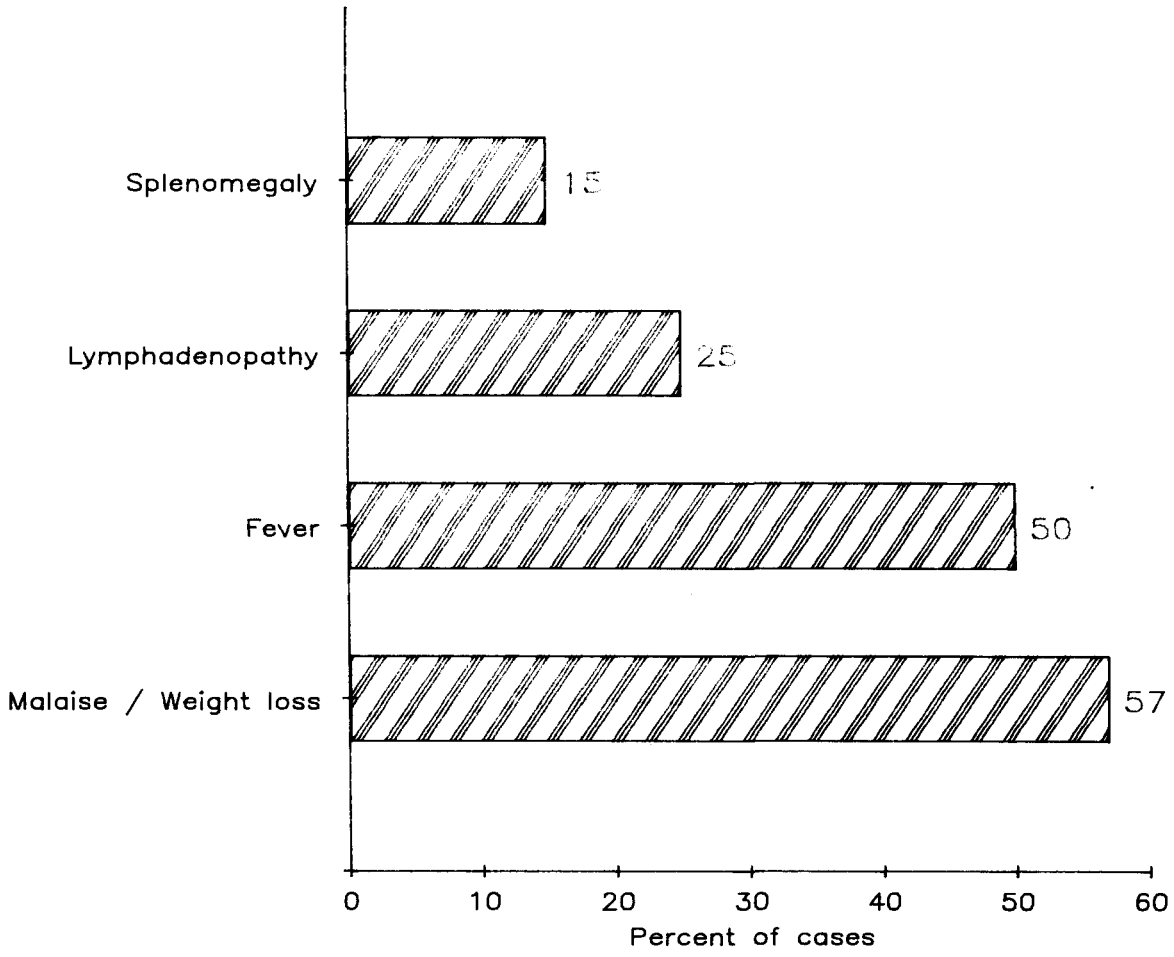


Figure 2.5.5 Constitutional manifestations at diagnosis

2.5.7. General constitutional symptoms and signs.

The frequencies of constitutional features at diagnosis and throughout the period studied are outlined in Fig. 2.5.5 and Table 2.5.5 respectively.

Weight loss and malaise were significant features at diagnosis in 57% of our patients, but massive weight loss (a loss greater than 25 lbs) only occurred in 2%. Weight loss and malaise appeared to occur in the same individuals, as only one sixth of those who presented with the symptoms did so for the first time after the date of diagnosis. In Dubois' report, 51% of the patients had symptoms of weight loss (cf our cumulative frequency of 58%), and the periods of weight loss correlated loosely with periods of fever [8]. We found that fever occurred in 50% of patients at diagnosis; 50% of the pyrexias were between 38 and 39 degrees Celsius, with 11% of the total group having temperatures in excess of 39 degress Celsius at diagnosis. The cumulative total of 56% (cf 84% Dubois [8], p= 0,00003) includes all patients who at some time manifested with fever. The fever in another study was ascribed to active SLE in 60%, to infection in 23% and to other causes in 17%; the presence of leukocytosis, neutrophilia, rigors and the absence of anti dsDNA antibodies reliably distinguished infection from SLE [64].

Lymphadenopathy occurred in 25% at diagnosis, and 16% of the total group had nodes which were sufficiently large for lymphoma to be included in their differential diagnosis. Many patients had, in fact, undergone node biopsy but the histology usually reflected

TABLE 2.5.5.

CUMULATIVE CONSTITUTIONAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Malaise/weight loss	58	51	-	-
Fever	56	84	-	-
Lymphadenopathy	26	59	36	29
Splenomegaly	20	9	18	16
Combined manifestations	80	-	-	-

nonspecific lymphadenitis as no distinct pathological features, apart from occasional plasma cell nests, were noted. The frequency of splenomegaly was 15% at diagnosis, and cumulative totals were 26% and 20% for lympadenopathy and splenic enlargement respectively. This frequency of lymphadenopathy is considerably lower than that found by Dubois (59% [5], p= 0,000004) or Estes (36% [9]), whilst that of splenomegaly approximates other studies (9% Dubois, 15% Harvey, 15% Larson, 18% Estes [8,54,67,9]).

In total, 80% of patients presented with one of the above 5 constitutional manifestations at some stage in their disease.

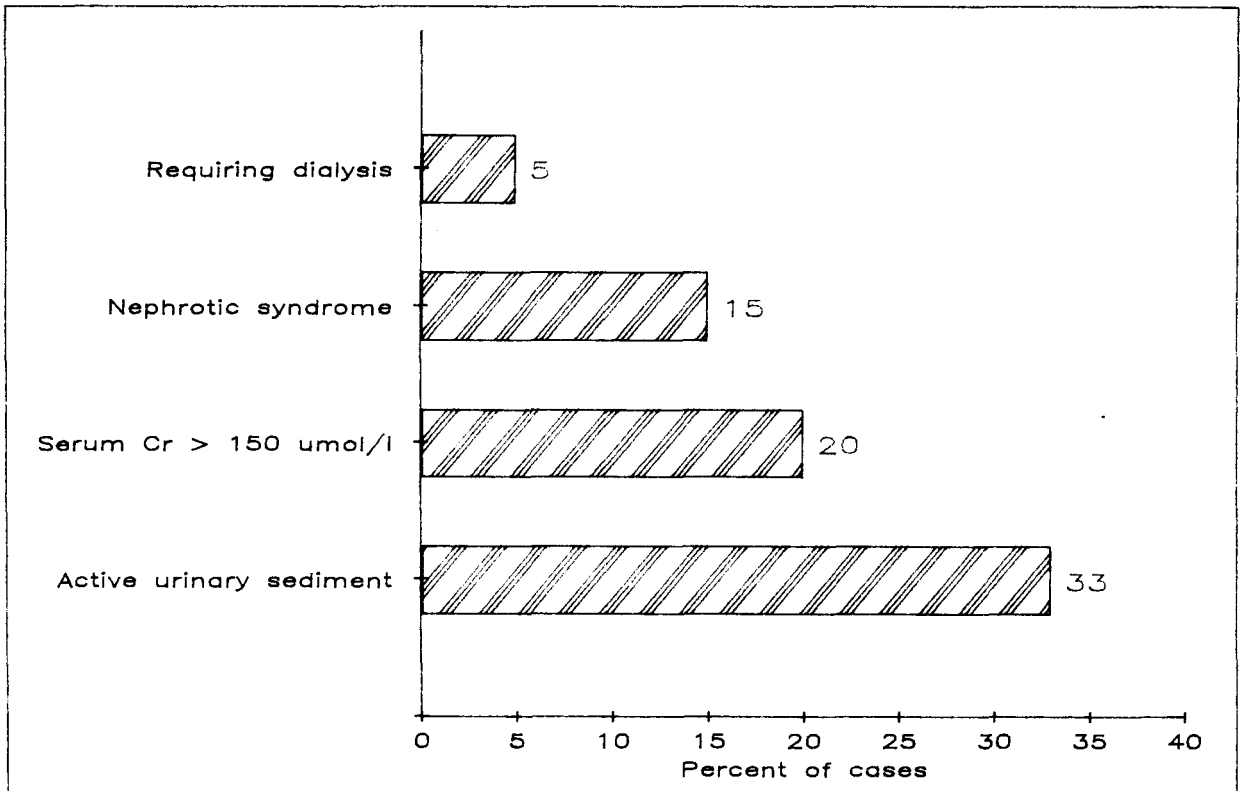


Figure 2.5.6a Renal manifestations at diagnosis

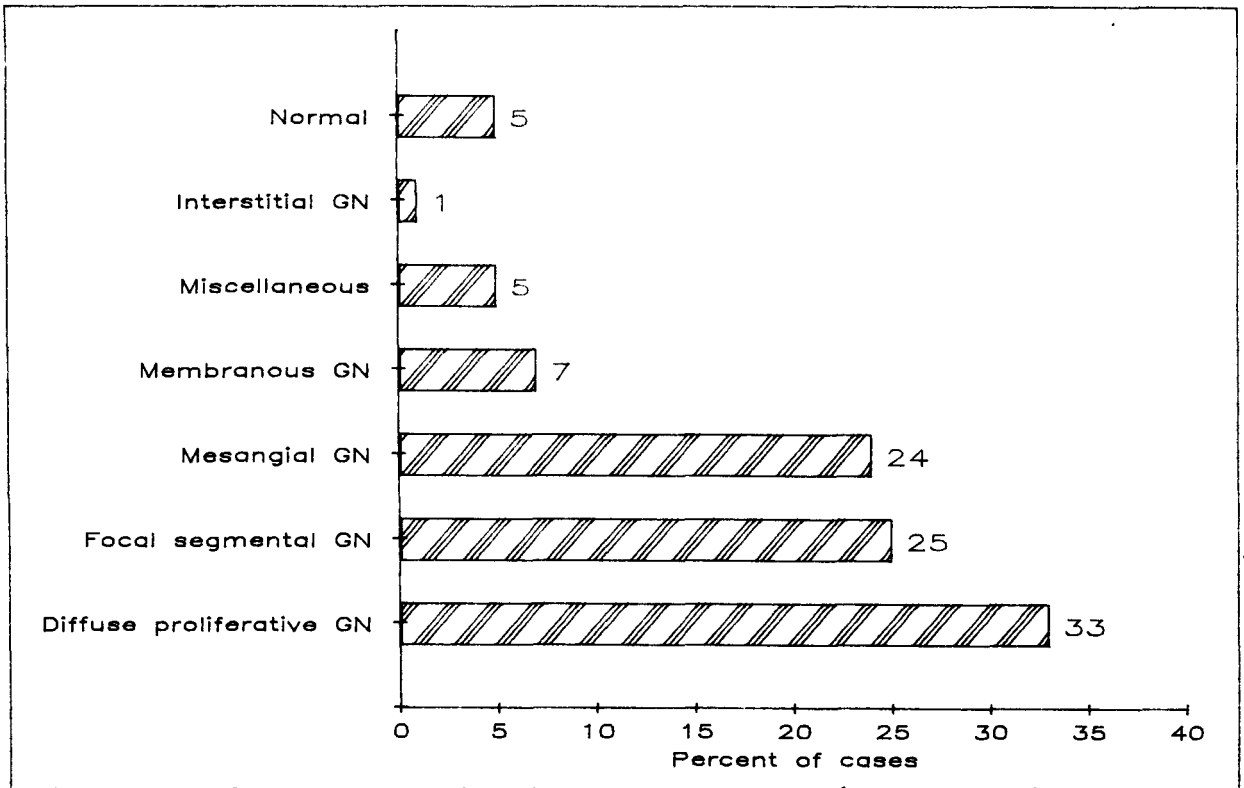


Figure 2.5.6b Renal biopsies at diagnosis (103 cases)

2.5.8. Renal manifestations.

Since renal function has been believed by many to be the single most important factor in determining the outcome for patients with SLE, there has been increasing interest in identifying prognostication factors.

We therefore examined established parameters of renal involvement, not only with respect to frequency, but also in the light of currently available knowledge of activity and prognostication indicators. Although many urinary abnormalities, such as the presence in the urine of tissue-like macromolecules [68], fibrin degradation products [69], F(ab)2 fragments and free light chains [70], are associated with renal lupus activity and progression of damage, we only studied proteinuria, active urinary sediment, raised serum creatinine levels (>150 umoles/l), and renal biopsy and immunofluorescence as indicators of outcome. The relationship between raised adsDNA, low complement components and nephritis will be discussed later under the section dealing with serological investigations. In addition, the vast source of comparative renal literature would enable one to make an in-depth analysis of many factors pertaining to renal disease; however the prescribed length of this report requires me to limit such an analysis.

The frequencies of the renal manifestations at diagnosis and cumulatively are illustrated in Fig. 2.5.6a and Table 2.5.6 respectively.

TABLE 2.5.6

CUMULATIVE RENAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
End-stage failure - dialysis	11	18	-	-
Serum creatinine > 150 µmol/dl	34	-	-	-
Proteinuria in nephrotic range	21	23	26	30
Urinary casts	36	-	-	-
Creatinine clearance <75 ml/min	67	-	-	-
Combined				
- creatinine clearance <75 ml/min)				
- proteinuria >0,5 gm/l)	67	-	-	-
- urinary casts)				
Renal biopsy - (Total 168)				
- normal	7	-	-	-
- interstitial GN	1	-	-	-
- miscellaneous	5	-	-	-
- membranous GN	7	-	-	-
- focal segmental GN	22	-	-	-
- mesangial GN	24	-	-	-
- diffuse proliferative GN	34	-	-	-

The simplest method of assessing renal activity in SLE is to look for the presence of an active urinary sediment of granular renal tubular casts and haematuria. Of our patients, 33% had granular casts at diagnosis; since this proportion dropped to 17% within the first year (taking into account deaths from renal and other causes), much of this lupus activity in the kidney must be reversible. In fact Wallace and Dubois [6] showed no correlation between active urinary sediment at diagnosis (in 38% of their cases) and deterioration of renal function, although they did find that persistence of this sign denoted a poor prognosis. They also demonstrated an improved survival rate amongst those patients whose urinary sediment, proteinuria, blood pressure and serum albumen normalised within the first year (90% 15 year survival). The cumulative frequency was 36%, with 76% of these patients manifesting with an active sediment at diagnosis. Unfortunately there are no comparative cumulative figures in other studies for the frequency of urinary casts alone. The presence of urinary casts correlated with a reduction in only the short term survival of patients; 5 year survival rates were 76% and 86% for those with and without casts respectively.

Abnormal serum creatinine levels and creatinine clearance rates did not show the improvement during the first year following diagnosis seen with urinary casts; in fact there was a slight, non significant increase in the total number of patients with raised serum creatinine levels (>150 umoles/l) at the end of 1 year. Of our patients 20% and 34% had a serum creatinine >150 umoles/l at diagnosis or at some stage in their illness respectively. Other researchers showed that patients who had a serum creatinine >130

umoles/l at the time of their first renal biopsy had an associated increased risk of dialysis at 1 and 3 years post biopsy. In those who initially displayed a normal serum creatinine level but subsequently required dialysis, the mean time from the first sustained abnormal creatinine measurement to dialysis was 4,5 months [72], although this very rapid deterioration was not seen in our patients. Our work demonstrates the marked difference in the 5 year survival rates between those whose renal function was always normal (93%) and those who at any time had a serum creatinine level >150 umoles/l (67%, p= <0,05).

The frequency of those patients with a creatinine clearance of <75 mls/min was 65% at diagnosis and 67% throughout the disease period.

Abnormal proteinuria of greater than 0,5 gms/24 hours was present in 33% of cases at diagnosis, with a nephrotic level of >3,5 gms/24 hours in 15%. Wallace and Dubois [6] noted that the presence of the nephrotic syndrome at the onset of nephritis (but not later) was a poor prognostic sign, but we found no alteration in the 5 year survival rates of those with the nephrotic syndrome at diagnosis or at any other stage in their illness. In total, 21% of our patients presented with the nephrotic syndrome (66% of these presented at diagnosis); 58% of patients had proteinuria >0,5 gms/24 hrs at some time during the course of their disease. Dubois and Estes report the existence of the nephrotic syndrome in 23% and 26% of their patients respectively, and Ropes reports albuminuria in 94% of his patients [8,9,45].

In total, 67% of all our patients had some renal abnormality, as

indicated by the presence of proteinuria >Ø,5 gms/l, urinary casts or a creatinine clearance <75 mls/min.

The renal biopsies of our patients were graded according to the WHO classification [171], notably normal, mesangial GN, focal segmental proliferative GN (FPGN), diffuse proliferative GN (DPGN), membranous GN, and interstitial nephritis. We included a miscellaneous category comprising non lupus-related histologies, such as acute tubular necrosis. Light and electron microscopy, as well as immunofluorescence were used for the assessment.

We found that of the 1Ø3 renal biopsies performed at diagnosis for clinical suspicion of nephritis 5% were normal and 24% showed mesangial GN (refer Fig. 2.5.6b). Many individual patients underwent changes in their renal histological type from one assessment to the next. No patient who in our experience had a normal biopsy at diagnosis progressed to end-stage renal failure. Out of the total of 168 biopsies performed during the period studied, 7% were normal and 24% showed mesangial GN; FPGN was present in 22%.

FPGN and DPGN may be associated with impaired glomerular function and proteinuria, but particularly with scarring, which is a very poor prognostic sign [74]. In our work, 25% of all biopsies at diagnosis showed FPGN. Some individuals showed a fairly remarkable change in their renal histology with time; 4 patients converted from FPGN to mesangial GN, 3 progressed to DPGN, and 2 changed to membranous GN. FPGN has been found by some to be the most common form of histology in the mild cases of SLE, with the

best prognosis for renal function [9,6,75]. Magil [75] found more CNS involvement in patients with FPGN than in those with DPGN, although this was not significant in our study. FPGN probably follows the same renal course as DPGN depending on how closely one applies the criteria for histological type.

The histological diagnosis of DPGN was made in 33% of biopsies at diagnosis, and in 34% of all biopsies throughout the study. However the relevance of a diagnosis of DPGN on biopsy is emphasised by our finding that 52% of the patients who joined a dialysis programme or who underwent transplantation had had DPGN documented at some time in their illness, in contrast to the group who did not progress to chronic renal failure of whom only 15% had had DPGN (p= Ø,ØØØ2). This appears to confirm the report of Estes [9], who found that DPGN held the poorest prognosis and was resistant to therapy. Magil et al [71] reported that an increase in the serum creatinine level in the presence of DPGN denoted a poor prognosis.

Membrano-proliferative GN, a subgroup of DPGN, comprised 47% of the latter group in our sample. Baldwin showed that all his patients with membrano-proliferative GN had haematuria, compared to only half of those with membranous or focal GN, and very few of those with mesangial GN; he also showed that patients with membrano-proliferative GN had a poor prognosis (50% 5 year survival [76]).

Membranous GN in SLE is reputed usually to occur several years after the diagnosis of SLE, often with proteinuria. This was not

the case in our series, with frequencies of membranous GN in 7%, 8,5% and 4,5% of all biopsies at diagnosis, during the first year, and from 1 to 5 years respectively. Estes [9] found that membranous GN was the least common of all histologies, but was often nephrotic and denoted a poor prognosis. Membranous GN was present in 7% of all biopsies taken in our study period.

The interstitial form of nephritis was present in only 2 kidneys out of the 168 biopsied in our sample, and can be associated with anti tubular basement membrane antibodies [77]; it can cause salt wasting, hyperkalaemia, tubular acidosis and even renal failure.

The role of the WHO histological classification in prognostication has been challenged by Fries [79], Whiting O'Keefe [80] and Wallace [6], all of whom noted no difference in outcome whether FPGN, DPGN or membranous GN was present. Others noted that, irrespective of histological type, a severely abnormal biopsy on light microscopy was associated with a greater risk of dialysis in the 5 years post biopsy, but that at least 25% of those requiring dialysis at 5 years had previously had an only mildly abnormal biopsy [72]. One of our patients who had seemingly fulminant DPGN made a complete recovery both clinically and histologically, confirming other such reports [73].

Recently new parameters have been put forward as prognostic factors, and in the light of these new developments all our histological sections are currently being reappraised. Certain factors, possibly important in the pathogenesis of the more severe forms of renal injury, have emerged, but discussion of these is

unfortunately largely beyond the scope of this review. Austin et al [81] found that 3 clinical features were strongly associated with renal failure, notably age below 24 years, male gender and elevated serum creatinine level; also patients with diffuse proliferative or membrano-proliferative GN were at a modest but significantly increased risk. In addition, the use by Austin and others [82] of a glomerular cellular activity rating and a chronicity index (such as glomerular sclerosis, fibrous crescents, interstitial fibrosis and tubular atrophy) increased the predictability of the outcome considerably. Austin also pointed out the importance of tubular, interstitial and vascular changes. In prognostication it is probably wisest to use clinical parameters, current histopathological features and these recently-described severity and chronicity indices to predict the feasibility of treatment.

Of all our patients, 11% required dialysis. In Kimberley's study of nephritis patients following biopsy, 25% of the group who required dialysis did so within one year of the biopsy, and 50% within 3 years. They were differentiated from the non-dialysis group by the presence of abnormal urinalysis, proteinuria, adsDNA antibodies, decreased complement levels and hypertension, and more of the dialysis group were receiving immunosuppressive therapy [72]. In our sample, those patients with urinary casts and serum creatinine levels >150 umoles/l were more likely to require dialysis than those without.

The mean survival period of those patients who had undergone dialysis and subsequently died was 44 months from diagnosis (range

Ø - 16Ø months), compared with a survival period in those who died without ever undergoing dialysis of 39 months (range Ø - 138 months).

This, together with other evidence, might suggest that the long term outlook for SLE patients in end-stage renal failure is not as grim as previously considered [78]. We found that many patients' SLE symptoms decreased following haemodialysis, and almost all were able to reduce their immunosuppressive drugs [72]. Wallace [6] agreed with the above but noted that life-threatening episodes were common with the onset of nephritis. In other studies rehabilitation was excellent, and recovery from renal failure was not unheard of (3 cases in our experience); one researcher reports that 25% of his renal failure patients were able to discontinue the dialysis programme, although 8% only transiently [72]. Transplantation is well tolerated, making the outlook for SLE patients with end-stage renal failure comparable to that of patients with end-stage renal failure from other causes. In Kimberley's study, of the 45% on dialysis who died within a 9 year follow up period, 23% had active SLE within 3 months of the first dialysis and 22% had inactive SLE [72].

Of all deaths, 65% occurred in patients who had had a serum creatinine >15Ø umoles/l at some stage in their disease. Of those needing dialysis, 52% died (4 lost to follow-up), compared to 16% of those not needing dialysis (p= <Ø,ØØØ1). The survival curve (from diagnosis date) for patients who had a serum creatinine level >15Ø umoles/l at any time is shown in Fig. 2.6 and it illustrates a 5 year survival of 68% (mean survival = 1ØØ months),

compared with the 5 year survival of 92% in those with normal renal function (mean survival = 150 months).

In our patients who had been in renal failure and subsequently died, the direct causes of death were septicaemia (5), pulmonary disease (3), myocardial infarct (2), renal disease (4) and CNS involvement (1). Contributory factors included renal disease (11), pulmonary disease (4), CNS involvement (3), cardiac failure (3), septicaemia (2), DIC (1) and endocarditis (1), with more than one contributory cause existing in some patients.

Boyce et al showed death in SLE patients with renal disease occurred primarily in those receiving high doses of steroids [78] and that often the cause of death was "relatively " unrelated to their renal disease. In the same study, of the patients with nephritis, diagnosed from 1971 to 1980, 32% died from renal disease, 26% from infection, 6% from CNS involvement, 9% from cardiovascular disease, 2% from pulmonary disease, 4% from GI vasculitis and 21% from other causes. Supporting our finding that infection is a major cause of death in the nephritis group, Fish et al reported that infection caused half of all deaths in children with SLE (80% of the total group had nephritis [84]). In Wallace's group the frequency of death due to infection rose from 25% during the period 1961 - 1970 to 30% during the period 1971 - 1980 [6]. Karsh found that the major causes of death in patients with nephritis were renal failure (40%), cardiovascular events (25%) and infection (16%) [85].

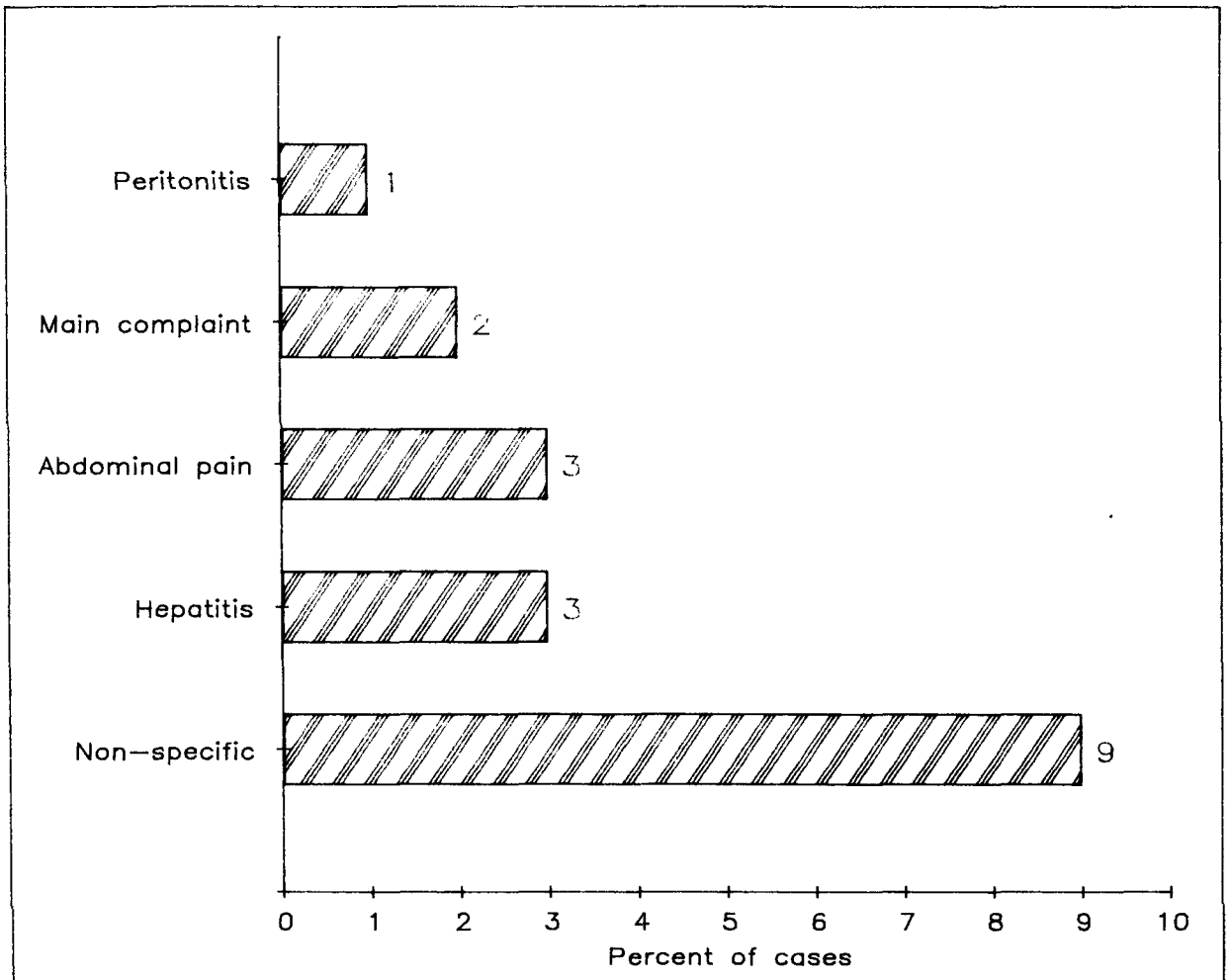


Figure 2.5.7 Gastrointestinal manifestations at diagnosis

2.5.9. Gastrointestinal manifestations.

Gastrointestinal symptoms and hepatitis are uncommon manifestations of SLE, but attain great importance because of their misdiagnosis. In our experience patients with these symptoms suffered extensive investigations and protracted delay prior to the diagnosis of their SLE. The frequency of these manifestations in our patients at diagnosis and cumulatively can be found in Fig. 2.5.7 and Table 2.5.7 respectively.

The four patients whose main complaints at diagnosis were gastrointestinal presented with symptoms of abdominal pain and distention (4/4), diarrhoea (4/4), malabsorption (2/4), and pancreatitis with hepatitis (1/4). The malabsorption in both of our cases was initially diagnosed as a gluten enteropathy and this potential error has been documented previously in 4 cases [87]. One of our cases had a biopsy-proven ulcerative colitis.

Throughout the course of the disease 6% of our patients complained of abdominal pain (cf 20% in other work [86]), and peritonitis occurred in 1% of cases (cf 16% Estes [9]). The milder form of abdominal pain and the enteritis can be a result of intestinal ischaemia, due to vasculitis or thrombosis of the mesenteric vessels [87]; in a study of autopsy specimens, 57% of patients with lupus manifesting with enteritis had arterial vasculitis, as opposed to 25% of those without. Many other gastrointestinal symptoms are probably due to medication, and 10% of our entire patient group complained of miscellaneous GI symptoms during the

TABLE 2.5.7

CUMULATIVE GASTROINTESTINAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Peritonitis	1	-	16	-
Abdominal pain	6	19	-	7
Gastrointestinal symptoms	10	7	-	-
Major GI symptoms	2	0,4	-	-
Hepatitis	5	-	-	-

follow-up period; these figures approximate Dubois' (7% [8]).

Patients were classified as suffering from severe hepatitis if they had a serum ALT or AST >200 units (normal <40 units), or if they had marked derangement of hepatic function, or if there was histological evidence of severe hepatitis. It was found in 2% of the group throughout the study period (5 cases), of which 2 cases were definitely drug- or alcohol-related. Of the remaining 3 cases, 1 developed a chronic active hepatitis picture with disappearance of her SLE manifestations. Less severe hepatitis, with less significant enzyme rise or functional derangement, occurred in an additional 3%. Hepatitis was previously reported in 4 cases of SLE in the Johannesburg area [88], and these include 3 of our patients, with the fourth excluded from this trial because of sampling criteria. Some of the hepatitis seen in SLE patients has been attributed by Hoffman and others to drugs, with as many as 55% of one group of patients having elevated enzymes; however in 25% of their cases no cause other than SLE was found [87]. Estes [9] found that hepatitis was rarely associated with renal disease.

Pancreatitis occurred uncommonly in our sample; only 2 patients were affected and both of them died, confirming the experience elsewhere that pancreatitis is fatal in most cases [91]. Reynolds found pancreatitis to be present in 8% of his SLE patients [89], a far more significant proportion than in our experience.

The pancreatitis of SLE is a clinician's nightmare. Although vasculitis was documented by Dubois in fulminant pancreatitis

prior to the use of steroids, there is no doubt that steroids per se are a potential cause, particularly in children [5,9]. Often the patient is critically ill, has frequently had steroids prior to the onset of pancreatitis and may have suffered some abdominal insult in the past; one of our patients had developed peritonitis following a renal biopsy four months prior to the onset of pancreatitis. For this reason the concern is whether the pancreatitis is vasculitic or iatrogenic in origin [89]. Another worrying feature is that pancreatitis is often only mildly symptomatic and may present in the absence of other signs of SLE activity [91].

Pancreatitis has been reported to account for as much as 37% of acute abdominal pain in one group of SLE patients [90], and in another group of 55 lupus patients suffering from abdominal pain, clinical pancreatitis and hyperamylasemia were discovered in 20 of them (48% [86]). The latter authors found evidence of active lupus; they also postulated that the steroids may cause decreased clearance of the immune complexes and that this can lead to vasculitis.

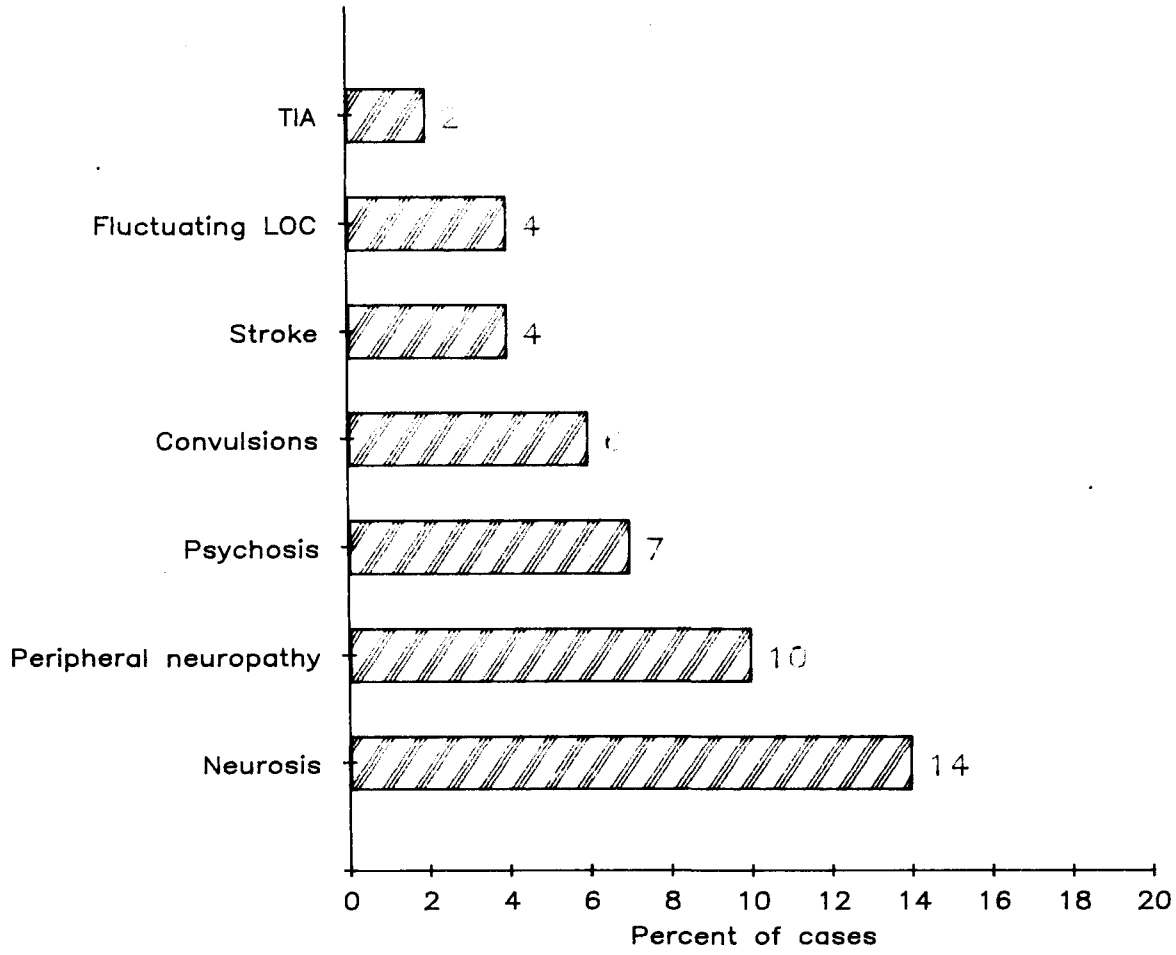


Figure 2.5.8 Central nervous system manifestations at diagnosis

2.5.1Ø. Central nervous system manifestations.

In no other system is there greater difficulty in defining SLE involvement than in the CNS, particularly in the sphere of psychoneurosis and organic mental syndromes. The inevitable interactions between premorbid personality and pathology, SLE activity and iatrogenic disease make it sometimes impossible to define the effect of each, especially since there is a general lack of diagnostic criteria and an absence of definitive laboratory tests in CNS lupus. In addition, since the improvement in survival of patients with renal involvement, CNS causes of severe morbidity and mortality have taken on a more significant role, the details of which will be discussed later.

Neurological manifestations are outlined in Fig. 2.5.8 and Table 2.5.8. Psychiatric manifestations ranging from mild neurosis to frank psychosis were found in a total of 3Ø% of patients over the whole study period (cf 59% Estes, [9]). Episodes of severe psychosis, suicidal tendencies and depression were found in 7% at diagnosis. Throughout the study 11% of patients presented with these symptoms (cf 22% Estes [9]).

Moderate depression and anxiety neurosis occurred in 14% of our patients at diagnosis and in 19% overall. Liang et al have commented that these milder symptoms often include hypochondriasis, hysteria and somatic concern [92]. There is also a reactive element resulting from altered family relationships with loss of social contact and poor body image because of the

TABLE 2.5.8

CUMULATIVE NEUROLOGICAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Transient ischaemic attacks	3	-	-	-
Cerebrovascular accident	7	25	5	-
Fluctuation of levels of conciousness or intellect	10	-	21	-
Fits	11	14	26*	9
Psychosis/suicidal tendencies	11	12	22	5
Peripheral neuropathy	14	12	7	-
Anxiety/depression-mild	9	-	5	-
Combined CNS manifestations	48	-	-	-

* INCLUDED 9% with renal disease

actual existence of SLE and apparently unrelated to lupus activity [92]; fewer RA patients than mildly- affected SLE patients fear death (Ø% cf 23%). It has been postulated that the majority of the milder symptoms are non-organic [93], so that the physician's acumen is vital here. In Estes' findings 5% had these milder symptoms [9], but figures as high as 41% have been reported [93]. Baker concluded in his review that significant psychosis was not merely a result of the lupus activating an abnormal premorbid personality, nor was it a stress response; the psychosis was rather a direct CNS manifestation of SLE. This syndrome was reported to be totally reversible and responsive to somatic therapy [95].

There is a comprehensive review of the pathogenesis of CNS lupus by Zvaifler and Bluestein, who suggest that the pathology in the CNS of SLE patients is dependent on both the existence of antibodies against brain tissue and the disruption of the normal blood brain barrier [99].

Another source of contention is the "steroid effect" on the CNS of lupus patients; some researchers feel SLE patients may be more susceptible to the steroid psychosis [9], while others believe that the importance of the steroid psychosis is exaggerated [94]. This factor was not controlled in our research.

In the CNS there is an increased frequency of infection, and since this infection is frequently atypical, it may occasionally be the root cause of the CNS aberration; it is therefore generally felt that lupus involvement of the CNS should be a diagnosis of

exclusion because of the relative difficulty of treatment compared with that of the infective causes [96].

Headaches, which often appeared to be vascular in origin, occurred in 14% overall in our study.

"Organic mental syndromes", here defined as changes in levels of consciousness extending to coma, also frequently have diverse potential causes. In our study, 3% of our patients presented with a period of coma attributable to SLE within weeks of diagnosis, and 6% presented with coma overall. Fluctuating levels of consciousness, not including post-ictal confusion, also occurred in 1% at diagnosis, with a cumulative frequency of 4%. The total frequency of these "organic mental syndromes" in our research was 10% (cf 21% Estes, 18% Grigor [9,40]).

Non-lupus related causes are more easily defined in the case of fits than in the case of coma or changing levels of consciousness, and fits can occur as a result of uraemia, cerebral infection or metabolic disturbances. They can be grand mal, focal, or petit mal and 6% of our patients had definite fits due to SLE at diagnosis, with an additional 3% that were either equivocal or due to other causes. We did not notice any late increase in the frequency of fitting episodes as has been described elsewhere, and there was a cumulative frequency of 11% (cf 20% Delaney, 9% Jessop [94,37]). Other workers have noted that fits may precede other SLE manifestations [9], and that 25% develop subsequent recurrent fits or epilepsy [94].

In our series, focal lesions, usually presenting as CVAs, occurred in 4% at diagnosis, with a total of 7% manifesting throughout the study period (cf 10-15% Delaney [94], 25% Dubois [8] p= 0,00001). There appeared to be a late increase in transient ischaemic attack (TIA) from 1% at diagnosis to 10% at 10 years, but there was no associated increase in definitive CVAs. Of considerable importance is the fact that the majority of our patients who suffered a CVA were not renal patients, unlike the CVA patients in Estes' research [9]. Some of the focal lesions occurred in patients in whom the lupus anticoagulant (LA) was present; Hughes and others have described the same association and this topic will be discussed with disorders of coagulation [97,98]. The possibility exists that the late increase in TIAs is due to a steroid side effect of increased atheromatous degeneration of the carotid vessels, and is similar to the late increase in the frequency of myocardial ischaemia seen in our patients.

Sub arachnoid haemorrhage (SAH) occurred in 2 patients; another study has shown an increased incidence of SAH amongst lupus patients, but in that study there was no autopsy evidence of vasculitis [8].

As already mentioned, infection can play a major role and one patient in our study died of a Listeria Monocytogenes meningitis.

Chorea manifested in 2 patients, and in agreement with Zvaifler's findings, in one of our patients the movement disorder preceded other manifestations of SLE by more than 2 years [99].

We found the SLE-related peripheral neuropathy an interesting disease. In total, 10% of our patients presented at, or shortly after diagnosis with peripheral neuropathy (cf 10-15% Delaney [94]). This varied from a mild sensory loss limited to the digits (4%) to a major syndrome (2%), including 2 patients with a Guillain Barre-like syndrome and one case of an acute myelopathy resembling a demyelinating disease; this type of myelopathy has been described in other research, where it occurred in the absence of other SLE manifestations and was associated with a high mortality [94]. The remaining neuropathies were predominantly sensory, involving approximately a quarter of each limb. Six of our Black patients were given steroids for severe manifestations of SLE; they were also taking isoniazid prophylactically (with low dose pyridoxine supplements) to prevent reactivation of their tuberculosis, which is endemic in this population. They all manifested, within an average period of 4 weeks, with varying degrees of a predominantly sensory peripheral neuropathy, and all improved rapidly when the isoniazid therapy was discontinued and pyridoxine supplemented in larger doses. This was possibly a result of the toxic side effects of isoniazid in slow acetylators; the latter trait has been found in more than 60% of Blacks [100,101,102], but the acetylator status of the local Blacks is unknown. The cumulative frequency of all types was 14% overall, which is similar to the 7% documented by Estes and Christian [9]. We must concur with their finding that the neuropathy was predominantly sensory in nature, that some of these neuropathies progressed slowly, and that others diminished gradually over 18 months. In the final analysis, 48% of all our patients had suffered from at least one of the following CNS manifestations:

CVA, fluctuation of consciousness, seizure, peripheral neuropathy or psychiatric disease.

Cheatum et al noted that nervous system involvement was the most important cause of death in non renal patients, and that, at death, 100% of these patients had some CNS abnormality [83]; however, the latter is not valid in our experience, although organic CNS disease and suicide together do constitute the greatest cause of death (25%).

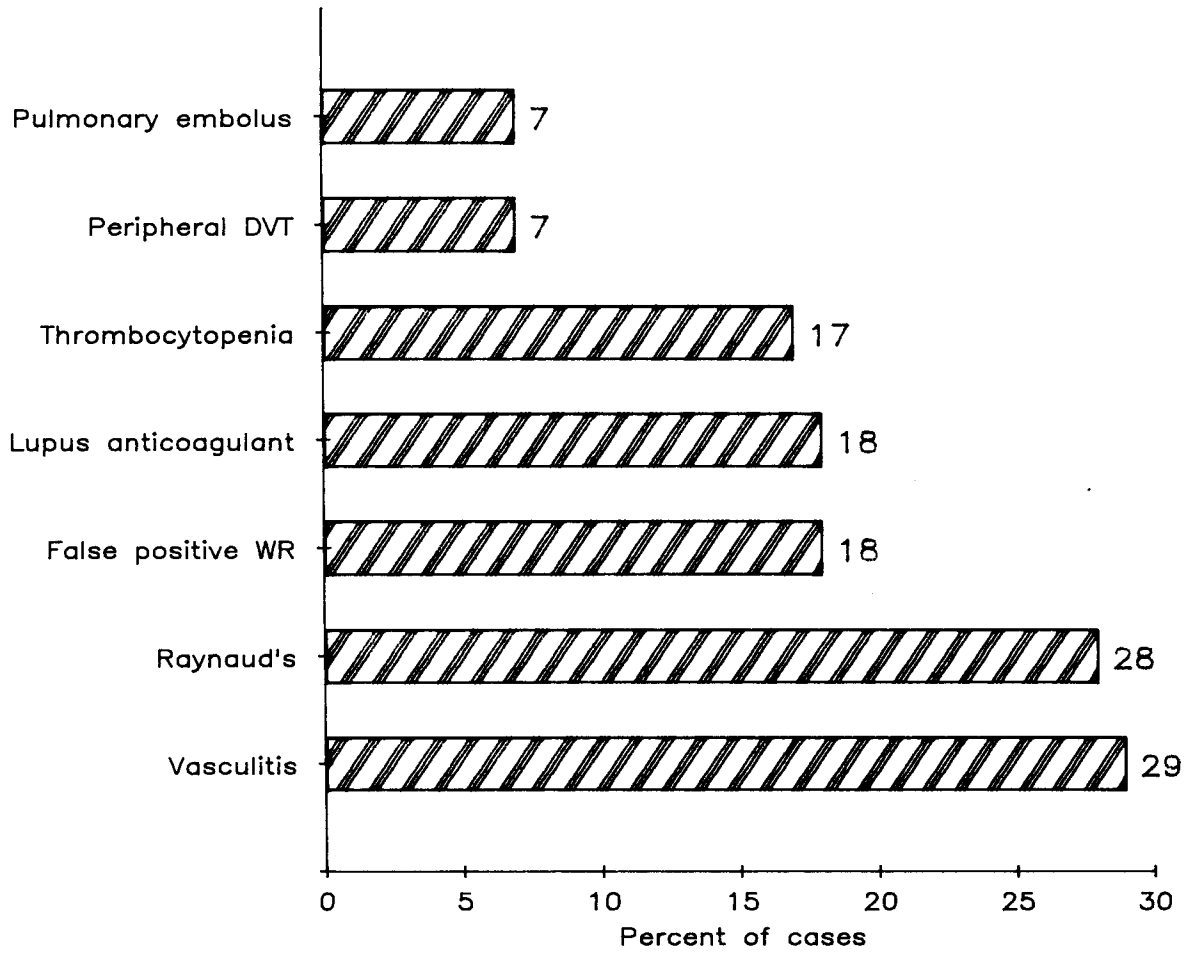


Figure 2.5.9 Vascular and coagulation disorders at diagnosis

2.5.11. Vascular manifestations and disorders of coagulation.

The frequencies of the manifestations dealt with in this section are illustrated in Fig. 2.5.9 and Table 2.5.9 respectively. Although the Raynaud's phenomenon may not be associated with the digital vasculitis and necrotic gangrenous ulcers seen in SLE, the three entities are grouped together here for convenience. In our series Raynaud's phenomenon occurred in 28% of patients at diagnosis, and in 2% it was severe and incapacitating. Raynaud's phenomenon was present at diagnosis in 90% of the total number of patients who ever manifested with it; we also found it in patients who were otherwise in clinical remission. The cumulative total frequency was 32% (cf 18% Dubois [8] p= 0,0002, and 21% Estes [9]), with 3% severely affected.

Raynaud's phenomenon has been associated in other research with an increase in certain clinical parameters including arthritis, rash and photosensitivity, and with a reduction in severe renal disease [103]. In our search for common aetiological factors we found no association between the Raynaud's phenomenon and CVA.

The vasculitic lesions ranged from sub-ungual and peri-ungual haemorrhages to gangrenous ulcers and systemic vasculitis. Finger tip vasculitis occurred in 24% of patients at diagnosis whereas the severe form was present in only 5%. The cumulative frequencies were 30% and 5% for the mild and severe forms respectively. Vasculitis has previously been associated by other researchers with raised adsDNA and ANF antibodies, and with a

TABLE 2.5.9

CUMULATIVE VASCULAR AND COAGULATION DISORDERS OF SLE PATIENTS

(PERCENTAGE UNLESS EXPRESSED AS A FRACTION)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Ileofemoral thrombosis)) Pulmonary embolus))	11	-	-	-
Deep venous thrombosis)	8	-	-	-
Vasculitis	35	-	21	14
Raynaud's phenomenon	32	18	21	24
Lupus anticoagulant	18 (14/77)	0,4	-	-
False positive WR	20 (37/182)	11	24	-
Thrombocytopenia < 100,000/cu mm	18	7	19	-

lower incidence of renal disease [104]. Histological examination of blood vessel walls of SLE patients with vasculitis often reveals immunoglobulin, complement and fibrinogen deposits; unlike the increased fibrinogen consumption found in active SLE and nephritis, in cutaneous vasculitis there is decreased fibrinolytic action with a possible failure of the release of the plasminogen activator [104].

There does not appear to be any form of progression or association between cutaneous vasculitis and thrombosis of major arteries and veins; cutaneous vasculitis is not held to be a poor prognostic sign, unlike the lesions of medium-sized arteries which can lead to death if cerebral vessels are involved [105]. In the same series the authors reported a difference in the clinical manifestations of patients with different histopathological types of the medium-sized arteries; those with fibrinoid degeneration and thrombosis of blood vessels died of uraemia, whereas those with sclerosis died of infection. The latter type occurred infrequently in females and more of those patients with sclerosis suffered from photosensitivity and had LE cells in their blood [105].

There is a link between arterial or venous thrombosis and antibodies to the phospholipid, procoagulant [106], an association first noted in SLE patients by Feinstein and Rapoport in 1972; they called the antibody the lupus anti-coagulant (LA) [108].

In our study, 6 patients out of the 34 whose levels were measured (18%) at diagnosis had the LA. Other authors [110] have found the

LA in 5%-10% of SLE patients (cf 18% of our patients throughout their disease, although this might reflect a bias in our series towards patients with clotting abnormalities).

The LA can occur in the absence of SLE, particularly in pregnant patients who may or may not have a positive ANF [97]. In a study of male patients with a positive LA, only 12% had SLE and a further 12% were ANF positive; few had a FPWR [117]. The LA is sometimes present in patients with neoplastic disease, in those receiving phenothiazine therapy and in seemingly healthy individuals; 60% of positive LAs occur in patients with auto-immune diseases including Dego's disease and Behcet's disease [97].

The LA is an immediately-acting coagulation inhibitor, mediated through its action on the Platelet Factor III (the phospholipid procoagulant); after it's release from the platelets the Platelet Factor III is involved in the interaction of several clotting factors, and the LA presumably binds to the phospholipid, preventing the binding of Factor X and prothrombin to it, and hence halting the prothrombin activation. The LA therefore causes a prolonged partial thromboplastin time (PPT), and when serum from patients with the lupus anti coagulant is added to normal plasma the same effect is achieved [107]; this forms the basis for the laboratory tests for the LA. This coagulation defect cannot be corrected by the addition of normal plasma but is corrected by increasing the serum lipid concentration, presumably because some of the LA binds to the lipid [111].

The LA may be associated with thrombocytopenia, possibly through antibody-mediated cytotoxicity. However the presence of the LA causes bleeding only when there are low levels of platelets, and rarely where there is an absolute lack of prothrombin [108]. In our work thrombocytopenia was associated with the LA in 35% of cases (p= <0,04 - small numbers). More often the LA is associated with thrombosis, and the clinical importance of the LA was illustrated by Gladman et al in 1980, when they found 17 out of 180 patients with SLE had 21 episodes of deep vein thrombosis (DVT) over 7 years; 9% of these had associated pulmonary emboli (often misdiagnosed as pleuritis) and an additional 5 out of the 17 patients died as a result [109].

In our study, at diagnosis, 11 out of 170 patients (7%) had a DVT and 7% had life-threatening thrombosis (either ileofemoral thrombosis or pulmonary embolus); during the entire period studied 11% of our patients manifested with this latter severe thrombosis and 8% with DVT. Of the cases with DVT or pulmonary embolus, 27% had a positive LA (not significant) and there was increased mortality in patients with DVT or pulmonary embolus. One report demonstrates that 25%-60% of patients with LA had thrombosis (cf 21% in our study, but this may be due to sampling error); 50% of the former group had low platelets [110].

An explanation for this clotting tendency is that the LA causes inhibition of prostacyclin production and activity by binding to phospholipid membranes and interfering with the release of arachidonic acid [111]; this explains the rationale for using aspirin in the treatment of this condition.

Apart from venous thrombosis, the LA has been recently associated with cerebral infarction, TIA and thrombocytopenia [112]. In our experience of patients who suffered a CVA, in whom the LA was measured, 50% were found to be LA positive (p= <Ø,Ø35 - small numbers). Although there may be other causes for cerebral thrombosis in SLE such as bacterial endocarditis and local cerebritis, the LA appears to be of increasing aetiological importance. It appears that the degree of prolongation of the PTT is also important; when the PTT is increased two times above normal, there is a risk of an associated arterial thrombosis, whereas when it is increased 1,8 times above normal, there is a risk of an associated venous thrombosis [98]. These researchers also showed that 4% of young patients with cerebral infarcts had positive LAs.

Hughes reports a possible association between pulmonary hypertension and the LA, as well as a link between other large vessel thromboses (often loosely-labelled vasculitides) and the LA [97]; the latter include limb arterial thrombosis [115] and splanchnic artery thrombosis with bowel gangrene [116].

There is also an association between the LA and multiple recurrent miscarriages and stillbirths [118]. We found 50% of SLE patients with a history of 3 or more abortions were LA positive (p= Ø,Ø35 - small numbers). The frequency of the LA in nonaborters was 15%. Another study reports that 33% of those with the LA had more than one abortion [119].

The association between the LA and a chronically (> 6 months) false positive serological test for syphilis. The FPWR has previously been documented; the Wasserman reaction measures antibodies to bovine cardiolipin, and the general concensus of opinion is that both the LA and the WR tests assess antibodies to phospholipid [120] and that cardiolipin antibodies may crossreact with, or be part of, antiDNA antibodies.

Of our patients who were positive for the LA, 42% also had a FPWR (p= <0,03); contrary to this, a small study of male patients with the LA showed that the frequency of the FPWR was not increased [117]. In our study a frequency of 18% positivity for FPWR was present at diagnosis.
Two patients had a positive fluorescent treponemal antibody test at low titres but did not show the characteristic beaded pattern described in SLE patients. There was no increase in the cumulative frequency of FPWR in those who had a strong family history of SLE; in addition there was no significant association between the LA or FPWR and the perinatal morbidity of infants born to LA- or FPWR-positive mothers. The presence of the LA or FPWR did not correlate with the sex of a patient, or the existence of vasculitic lesions or Raynaud's phenomena.

Other anticoagulants besides the LA have been described in lupus patients; Rouget et al reports a familial occurrence of a circulating anti-thrombinase anticoagulant [122], which did not require a cofactor and which inhibited Factors XI, XIa, XII, plasma prekallikrein and high molecular weight kininogen. Poon has described an antibody against plasma thromboplastin antecedent

[123]. Other abnormalities include the presence in the blood of SLE patients, of inhibitors to Factors VIII and IX, resulting in bleeding, and inhibitors to Factors XI, XIa and XII resulting in clotting [125]. An acquired form of antithrombin III deficiency has also been described [124].

The thrombocytopenia of SLE is not often severe and only 6% of our patients manifested at diagnosis with platelet counts of less than 30 000 per cumm (cf 5% Hughes [125]), whereas levels of less than 100 000 per cumm occurred in 17% at diagnosis. Amongst our patients 18% had a platelet count less than 100 000 per cumm at some stage in their disease (cf 7% Dubois, 19% Estes [8,9].

Presumably antiplatelet antibodies play an aetiological role in the thrombocytopenia, but the precise mechanism is unclear since these antibodies are present in 80% of lupus patients without thrombocytopenia; it is possible that these antibodies induce the platelet release reaction [126]. The strong association between thrombocytopenia and clotting disturbances of lupus necessitates its inclusion in this section.

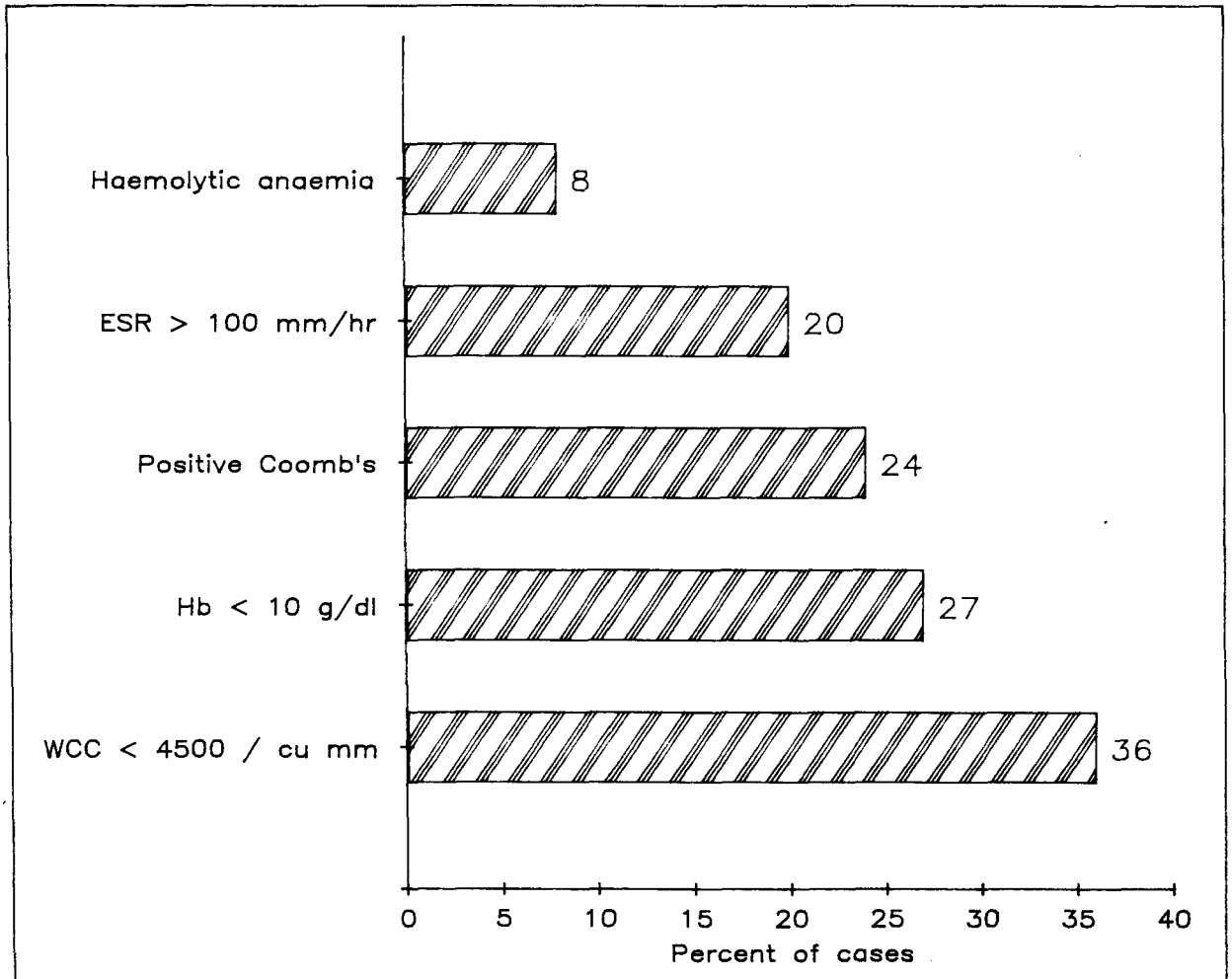


Figure 2.5.10 Haematological manifestations at diagnosis

2.5.12. Haematological manifestations.

The haematological abnormalities caused by SLE are seldom life-threatening. The frequencies of these manifestations in SLE patients at diagnosis and throughout their disease can be seen in Fig. 2.5.1Ø and Table 2.5.1Ø respectively. Of our patients, 27% had a haemoglobin less than 1Ø gms/dl at diagnosis; severe anaemia with a haemoglobin of less than 5 gms/dl occurred in 2%. In total 34% of patients presented throughout the study period with a haemoglobin less than 1Ø gms/dl.

As already mentioned, many patients with features of haemolysis or idiopathic thrombocytopenic purpura (ITP) are seronegative, or have low titres of ANF, and may not manifest with other symptoms of SLE for many years, if at all [8]. Significant haemolytic anaemia occurred in 8% of our cases at diagnosis and 1Ø% overall (cf 6% Dubois, 12% Grigor, 1Ø% Jessop [8,4Ø,37]). The Coombs' test was positive in 38 out of 162 of our SLE cases in whom it was measured (23% cf 27% Estes [9]), and others have found that SLE is the commonest cause of a positive Coombs' test [127]. A positive Coombs' test was found in 2Ø of the 3Ø patients with haemolytic anaemia in whom it was measured (66% p= Ø,ØØØ1). One of our patients presented with a picture of microangiopathic haemolytic anaemia.

Leukopenia, with a white cell count (WCC) of less than 4ØØØ/cumm, is one of the criteria for the diagnosis of SLE. In our Black patients we set the low limit of normal at 35ØØ cells/cumm since

TABLE 2.5.10

CUMULATIVE HAEMATOLOGICAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE - UNLESS EXPRESSED AS A FRACTION)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop et al
Haemoglobin < 10 g/dl	34	-	-	-
Leukopenia < 4,500 cells/cumm	38	43	66	22
Positive Coombs test	24 (38/162)	-	25	-
Haemolytic anaemia	10	6	14	10
ESR > 100 mm/hr	22	-	-	-
Combined (see text)	58	-	-	-

this is the limit drawn in other population studies of Blacks (local laboratory standards). Leukopenia was found in 30% of our patients at diagnosis and 32% manifested with it throughout the study period. The corresponding figures for a WCC less than 4500/cumm were 36% and 38% respectively; the latter figure is lower than that of other studies (cf 66% Estes, 46% Grigor, [9,40]), but is higher than that of the Cape Town study (22% [37]). Levels below 2000/cumm at diagnosis were uncommon (4%) and this leukopenia appears valuable in differentiating the vasculitis of SLE from other causes which usually occur in conjunction with high white cell counts.

Leukopenia probably results from the effects of lymphocytotoxic antibodies, which are present in as many as 75% of SLE patients in some series, and which are often complement-binding; they may or may not reflect general SLE activity [128]. These antibodies may also be associated with other haematological, dermatological and neurological manifestations of the disease [8] but occur rarely with congenital complement deficiencies and vasculitis [128]. Other causes of low WCC in SLE patients include decreased amounts of granulocyte or monocyte progenitor cells in the bone marrow [128], neutrophil aggregation by activated complement, and immune complexes that preferentially deplete helper T cells [130].

A total of 58% of our patients presented at some time with one or more of the following haematological manifestations: anaemia, haemolysis, thrombocytopenia and leukopenia.

The erythrocyte sedimentation rate (ESR) was raised above 100

mm/hr in 20% of our cases at diagnosis; it is an unreliable guide to disease activity and may be normal in patients with active disease [5], particularly in those with cerebral SLE [125].

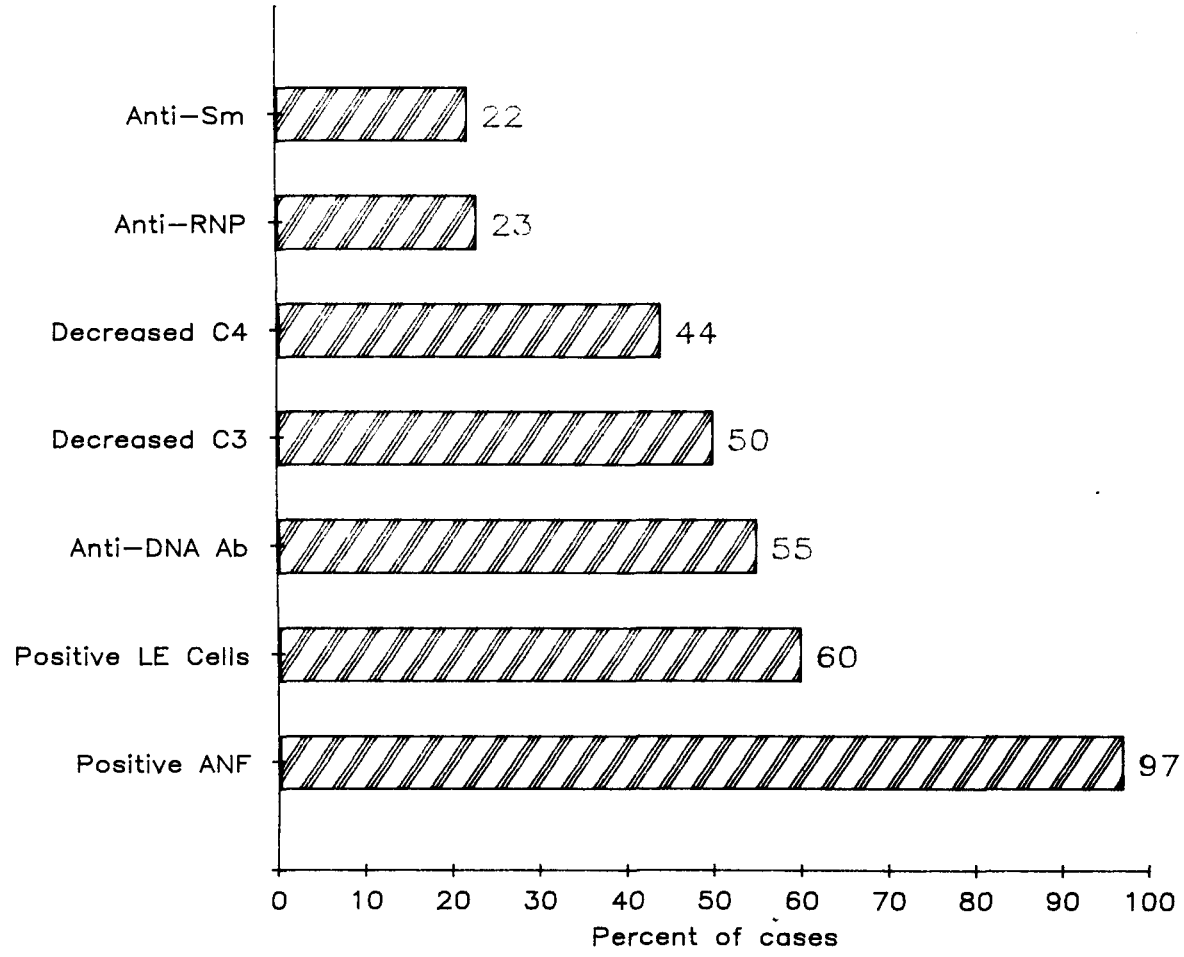


Figure 2.5.11 Serological manifestations at diagnosis

2.5.13. Acquired complement deficiencies as a measure of disease activity.

The role of congenital abnormalities of the complement cascade in the aetiology and manifestations of SLE has been briefly discussed above; a more extensive review is beyond the scope of this study.

The proposed mechanisms of activation of SLE imply initiation of the complement cascade and its consumption, and it is therefore natural to assume a relationship between depressed levels of individual complement components and activity. However, due to differing rates of production of complement components in different patients, absolute levels of complement have been unreliable predictors of consumption; in addition decreased synthesis of C3 has been described in SLE [132], and hence reduced levels in this circumstance do not necessarily reflect disease activity. There has therefore been a swing towards the use of qualitative assessments of complement function, such as the measurement of circulating activated complement components or their breakdown products. However, during the period studied, practitioners only utilised C3 and C4 levels to gauge disease activity.

Details of abnormalities in complement levels in SLE patients at diagnosis and throughout their disease can be seen in Fig. 2.5.11 and Table 2.5.11 respectively. At diagnosis, in the presence of active disease, 50% of our patients had depressed levels of C3 (cf

TABLE 2.5.11

CUMULATIVE SEROLOGICAL MANIFESTATIONS OF SLE PATIENTS

(PERCENTAGE - UNLESS EXPRESSED AS A FRACTION)

Signs & Symptoms	Morrison	Dubois	Estes et al	Jessop at al
Positive LE cells	59 (98/167)	76	78	91
Positive ANF	98	-	87	-
Anti Sm antibodies	20 (41/202)	-	-	-
Anti RNP antibodies	22 (44/202)	-	-	-
Anti dsDNA antibodies	56 (158/281)	-	-	-
Decreased C4	52	-	-	-

38% Weinstein [133]) and a similar percentage of our patients had reduced C4. Depressed levels of both C3 and C4 were present cumulatively in 52%. Of greater relevance is a drop in C4 prior to exacerbation; some researchers have found that a decrease in C4 correlates with extrarenal exacerbation in 25% of patients, and with renal exacerbation in 67%-80% of patients [134].

2.5.14. Antibodies to nuclear components in SLE.

Serological reactions directed against components of the nucleus have long been the hallmark of the connective tissue diseases and of SLE in particular. The discovery of the LE cell reaction greatly aided the definition of lupus, and the introduction of the ANF furthered this.

The frequencies for the presence of the various anti-nuclear component antibodies at diagnosis and throughout the disease are contained in Fig. 2.5.11 and Table 2.5.11 respectively. LE cells were found in 60% of 167 of our patients at diagnosis and 59% cumulatively (cf 78% Estes, 91% Jessop [9,37]). The ANF frequency shows 97% positivity at diagnosis. The number of those patients with a low titre of ANF (below 1:80) increased threefold from diagnosis to the assessment at 5 years (42 patients). One of the possible reasons for this change in frequency may be the progression by some patients to end-stage renal failure with time (18 out of the 42 patients above), which has been found in some work to be associated with a drop in ANF titres [135].

Neither the presence of LE cells nor a positive ANF titre are diagnostic for SLE, occurring as they do in a multitude of pathological conditions, as well as in 5% of normal individuals [136] and 10% of pregnant women [137]. In addition, high titres do not necessarily denote increased lupus activity, but the switch from IgM ANF to IgG ANF may do so [148].

As already mentioned, many of the SLE cases associated with congenital complement deficiency are seronegative for ANF, and according to various studies these seronegative patients appear to have a characteristic disease profile associated with the presence of the Ro/SSA antibodies (these are non-histone antibodies found more frequently in Sjogren's syndrome, but also present in 30% of SLE patients [114]), annular erythema [139], and congenital heart block in the infants of lupus mothers (possibly due to transplacental passage of Ro antibodies) [140]. Seronegative patients also have more vasculitis, mouth ulcers, alopecia, rheumatoid factor positivity, photosensitivity, Sjogren's syndrome, and thrombocytopenia, with a lower proportion of patients having positive lupus band tests, nephritis and CNS disease [139,140,141]. Of these patients 10% are reputed to become seropositive within 4 years [142]. In some "seronegative" patients, the ANF is complexed to the rheumatoid factor and these sera become positive after in vitro treatment with penicillamine [143], thereby making the distinction between this group and the penicillamine drug-induced lupus unclear.

Like the ANF and the LE cell tests, the measurement of antibodies to double stranded DNA (adsDNA) is a diagnostic criterion of SLE, but in addition the presence of adsDNA in significant titres is considered to denote active disease [144], . Antibodies to dsDNA are more specific for SLE than is the ANF but are also found in normal individuals in very low titres; however lymphocytes from SLE patients produce adsDNA spontaneously in vitro, whereas normal lymphocytes do not [145].

In our experience 55% of patients presented at diagnosis with adsDNA, compared with 70%-75% in Reichlin's work [144]. There are many reports confirming the link between adsDNA and disease activity, particularly in association with decreased levels of complement. In fact the presence of both adsDNA and low serum complement levels is considered to be diagnostic of SLE by some [133]. However no association has been shown between adsDNA and survival [2,146], and our 5 year survival figures did not illustrate any significant difference between those with and those without adsDNA (80% and 86% respectively). The cumulative frequency for the presence of adsDNA was 56%.

Holman and Fries report a positive association between the presence of adsDNA and the existence of certain lupus subsets, particularly those of renal involvement (75% adsDNA positive), CNS involvement, more severe arthritis, more pleuritis and haematological abnormalities [79]. It is possible that those patients with active SLE without adsDNA also comprise a group with their own specific pattern of disease manifestations [147]. Miniter et al however, have shown no association between adsDNA and the clinical manifestations of low platelets or psychosis [172]; some negative associations have been reported, with Raynaud's phenomenon being less common in patients with adsDNA [147].

The qualitative binding of complement by the adsDNA may be important, particularly in differentiating why some patients with adsDNA develop nephritis while others do not, but as yet this matter remains unresolved [149]. As a generalisation, it has been

claimed that in the absence of more sophisticated qualitative tests (as above), adsDNA monitors disease in general, whereas low C3 indicates renal activity in particular. Antibody reactions against other forms of DNA, including single stranded or denatured DNA (ssDNA), have also been found by others in the sera of SLE patients [144].

There is another group of antibodies found in SLE and related diseases, and these are directed against non-DNA nuclear antigens, the latter being derived by saline extraction; these antigens are hence termed extractable nuclear antigens (ENA). Antibodies to only 2 forms of these antigens were measured regularly in our study and then only in the later years; these are the ribonuclear protein (RNP) and Smith (Sm) antigens.

In our study 22% and 20% of patients presented throughout their illness with anti-RNP (aRNP) and anti-Sm (aSm) antibodies respectively (cf 23% and 7% respectively Hughes, 30% and 20% respectively Clotet, [114,150]). Anti-RNP antibodies occurred in 23% at diagnosis as did anti-Sm antibodies in 22%.

The associations with the ENA antibodies are controversial, and they probably lack prognostic influence [151] since various researchers have shown that neither the presence nor absence of aSm or aRNP determined whether a patient had SLE or an overlap syndrome, and they could not be used to predict the clinical severity or the manifestations [152]. However, other researchers do not agree; they have found positive associations between aRNP in high titres and Raynaud's phenomenon, mixed connective tissue

disease (not included in this study), pulmonary manifestations [153], and tenosynovitis of the hands [150]. They have also reported positive associations with a higher frequency of normal complement levels as well as with a decreased frequency of Coombs' positivity, adsDNA, renal disease, and of the LA [150].

The aSm is almost specific for SLE, with RA patients only very occasionally being aSm positive [114]. The associations of the aSm with certain clinical features remain unresolved since one claim of a link between aSm and encephalopathy in 71% of SLE patients has probably been refuted on technical grounds, due to the presence of contaminating antigens [155]. These authors and others report associations between the existence of aSm and lower white cell counts [155], more cutaneous vasculitis and Raynauds' phenomenon, more cardiac and pulmonary manifestations when adsDNA is also present [156], more renal disease, and higher titres of adsDNA. There have also been reports that patients with aSm may belong to a group manifesting a milder form of the disease [157]. However, Barada et al demonstrated that an increase in the titre of aSm predicted a flare-up of disease activity in 50% of cases and correlated with an exacerbation in 60% [155].

Antibodies to other cellular antigens have been noted, but with the exception of the anti Ro antibody seen in association with the congenital heart block of children born to SLE mothers, none are relevant to this study.

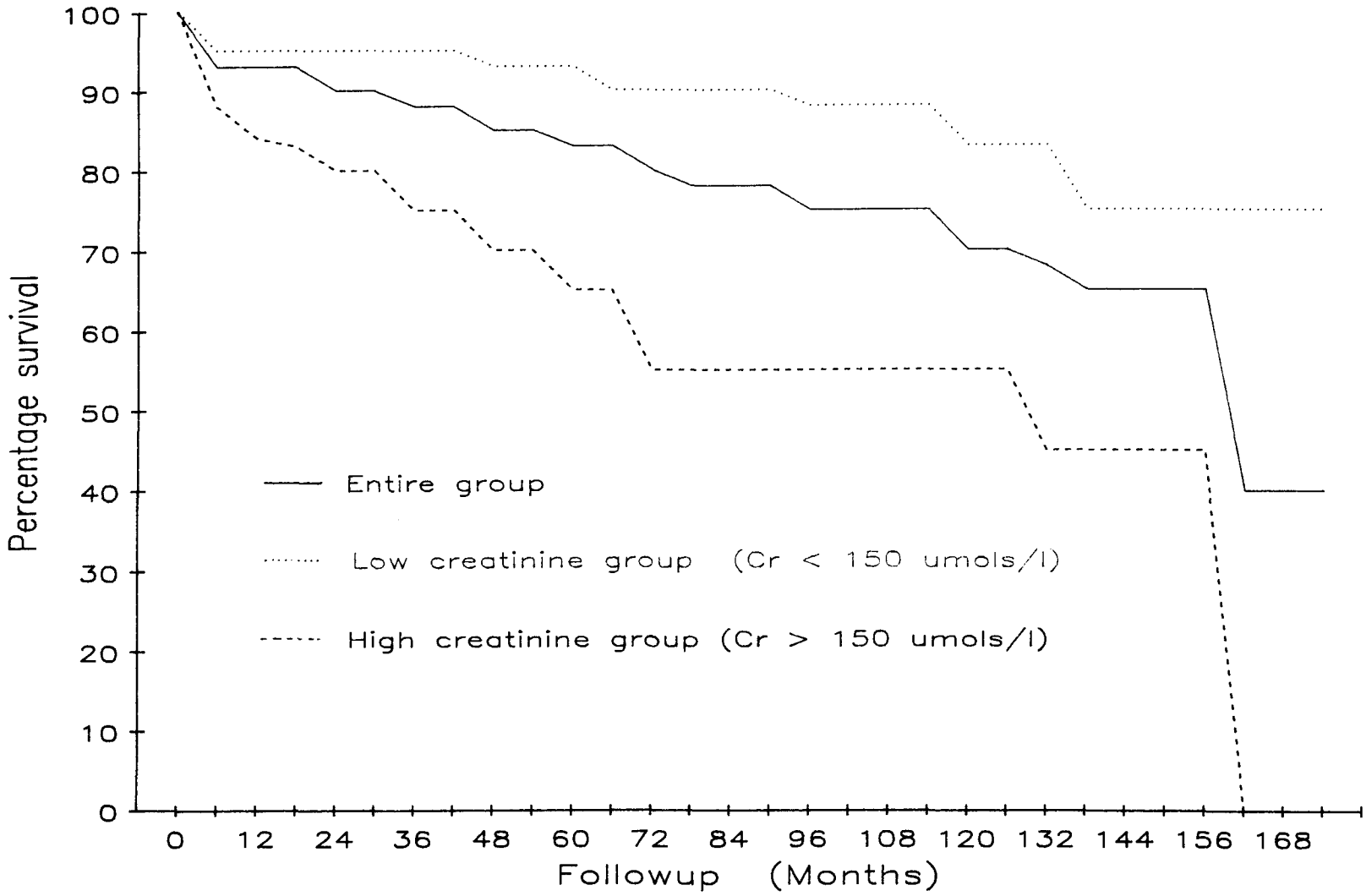


Figure 2.6 Survival analysis for SLE patients according to renal function

2.5.15. Causes of death.

The primary causes of death are outlined in Table 2.3, with contributory causes listed in Table 2.4.

With changing management trends and improvement in life-support systems, including dialysis, the causes of death have obviously changed in recent years. I have therefore attempted to compare our findings with those of more recent studies.

The pulmonary causes of mortality have been discussed in Chapter 2.5.6; pulmonary pathology was the most frequent direct cause of death in our patients with SLE and constituted 21% of the primary causes. The Cape Town group (Jessop [37]) found pulmonary involvement to be infrequently fatal amongst lupus sufferers, as did Estes et al [9]. Dubois, when reviewing changes in therapeutic regimens from 1930 to 1971, illustrated a moderately constant frequency for bronchopneumonia as a cause in 10%-14% of all deaths [5]. Nine patients died of pneumonia, and the two other deaths arising directly from pulmonary disease in our group resulted from diffuse lung disease; one patient (a non smoker) had severe emphysema, and the other died from a severe pulmonary infiltrate of unknown aetiology. The increased frequency of pulmonary causes of death may be associated with Johannesburg's high altitude.

Central nervous system causes were directly accountable for 9 deaths out of 52 (17%), and this figure is similar to those

reported by Dubois (13% [5]) and by Estes (1Ø% [9]). Jessop noted that CNS pathology was the second most common cause of death [37]. We found that CVA and subarachnoid haemorrhage were important causes of death, as did Estes [9]. Meningitis caused by an opportunistic organism (Listeria) and unexplained coma resulted in the deaths of 1 and 2 patients respectively.

Dubois [5] suggested that malignancy is an increasingly frequent cause of death, but we only had 1 such a death in a patient with a cerebral tumour.

Sepsis was responsible for the same number of deaths as CNS pathology was; 17% of the deaths of our patients resulted from sepsis, and this is similar to the 14% quoted in Estes' work. The Cape Town group found sepsis to be the third most common cause of death [37].

Myocardial infarction was responsible for the deaths of 3 patients in our series; autopsies failed to reveal atherosclerosis but did show fresh thrombosis. The frequency of death from myocardial infarction in our study (6%) agrees with those of Dubois (4% [5]) and Estes (4% [9]). One patient died of chronic constrictive pericarditis, 1 of myocarditis with fatal arrythmia, and 1 of fulminating sterile endocarditis, with destruction of valves and coronary arterial embolisation, noted at autopsy; the latter patient had only received minimal steroid therapy prior to death.

Significant renal disease was present in 15 of the 52 patients who died (29% cf 5Ø% Estes [9]). It was the direct cause of death in

only 4 cases (8%) and this is considerably lower than the figures of Dubois (20%) and Estes (31%), who, with Jessop, considered renal failure to be the most frequent cause of death. In the remaining 11 patients renal failure was merely a contributory factor, as their renal function was stable at the time of death.

Miscellaneous causes of death were cardiac failure of nonspecific aetiology (8% cf 4% Dubois [5]), suicide (8% cf 1% Dubois [5]), and hepatic encephalopathy, due to post-alcoholic cirrhosis (1 case). One Black lupus patient who died shortly after admission to hospital showed features of Addison's disease,although superimposed sepsis could not be excluded. Another patient died following a fulminant coagulopathy.

The frequencies of the contributory causes of death in our patients mirror those of other studies [9]: renal failure and sepsis were the most common contributory factors, followed by pulmonary, coagulation and CNS pathologies. Cardiac failure, endocarditis and pancreatitis also contributed to a small number of deaths.

3. Disease manifestations in SLE patients of different races.

3.1. Introduction.

Apart from the variations in disease manifestations that can be attributed to sexual differences, there is no factor that appears to modify SLE more than the racial one. The frequencies of various tissue types differ vastly between racial groups, and if one were to look at the different tissue types of SLE patients in the different races, one might find that the task of identifying a predisposing chromosomal configuration is much simpler. This is particularly true in Southern Africa, where there is "coexistence" of peoples from three different continents, notably Africa, Asia and Europe; in addition, for religious, social, cultural and political reasons there has been little admixture in the last four decades. This distinction is not absolute when considering SLE, since environmental factors in the different population groups also play a role; these factors include socio-economic status and hygiene, diet, environmental contamination, mean age, degree of intermarriage within families, delay in seeking medical help for "cosmetic" problems, homeopathic and witchdoctor practices, and emphasis on follow up, according to the degree of understanding of the nature of the disease. Most of these factors weigh heavily against the Black and the Coloured groups of patients, so that it was with interest that we compared them; it must however be pointed out that marked heterogeneity does exist within individual races.

TABLE 3.1

PROPORTION OF SUB-CULTURES IN THE GENERAL POPULATION COMPARED WITH PROPORTION OF PATIENTS WITHIN THESE SUB-CULTURES

RACE	SUB-CULTURE	PROPORTION IN POPULATION (%)	PROPORTION PATIENTS (%)
WHITES	AFRIKANER	54	41
	ANGLO SAXON	29	34 *
	JEWISH	12	14 *
	PORTUGUESE	2	)
	ITALIAN	1	) 11
	GREEK	0,5	)
	OTHER	1,5	)
INDIANS	MUSLIM	50	54
	HINDU	40	23
	TAMIL	10	23
BLACKS	ZULU	20	37
	SOUTH SOTHO	16	16
	TSWANA	14	34
	XHOSA	13	-
	NORTH SOTHO	13	13
	OTHER	24	-

* THERE MAY BE CONSIDERABLE ADMIXTURE HERE.

3.2. Materials and methods.

The sampling, data collection and analysis methods, as well as the clinical and biochemical criteria, were the same as those used in Chapter 2.

3.3. Exclusions- as in Chapter 2.

3.4. Results.

Table 3.1 shows the proportions of the different "sub-cultures" within the races constituting the population from which this study sample is drawn; they are compared with the proportions of SLE patients derived from each group.

The frequencies of the general features of the SLE patients from the various racial groups are contained in Table 3.2, and indicate that there is a higher proportion of females to males who develop SLE amongst the Blacks than in the other racial groups. The Whites tend to have a more protracted period till diagnosis, which possibly reflects the increased proportion of elderly patients with the disease; however one would expect a corresponding delay in the Black patients as they have an equal proportion of elderly lupus sufferers. As already discussed, considerable problems have been experienced in the followup of Black patients, so that their followup is on the whole much shorter than the followup of the other races; this is partly because the Hillbrow Hospital, which supplied the patient records from which our Black sample was

TABLE 3.2 GENERAL FEATURES OF SLE PATIENTS WITHIN THE VARIOUS RACIAL GROUPS

FEATURE	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Proportion of total group (%)	72	15	4	8	
Sex ratio - Male : Female	1 : 4,5	1 : 8	1 : 5,5	1 : 5,5	
Period till diagnosis -					
Mean (months)	35	24	15	19	
Range (months)	0 - 240	0 - 144	0 - 100	0 - 144	
Period of follow-up -					
Mean (months)	59	24	54	57	
Range (months)	0 - 168	0 - 100	11 - 120	1 - 133	
Proportion less than 20 yrs (%)	24	13	50	31	BC p = 0,05*
Proportion equal to or greater than 50 years (%)	17	16	0	4	
Proportion where pregnancy aggravated SLE (%)	41	14	-	-	
Recurrent miscarriages (%)	9	3	0	0	
Successful pregnancies (%)	61	82	50	60	BW p = 0,02
Neonatal morbidity (%)	20	18	-	Complication in 3 out of 4 pregnancies	
Family history of RA/SLE (%)	23	4	20	43	BI p = <0,05
Death (%)	19	24	8	23	WB p = 0,03
Cause of death (% unless stated)	Septicaemia (20) Pulmonary (17)	Pulmonary (3 cases) Septicaemia (2 ")	Pulmonary (1 case)	CNS (3 cases) Pulmonary (1 case)	

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TABLE 3.2 - CONTINUED : GENERAL FEATURES OF SLE PATIENTS WITHIN THE VARIOUS RACIAL GROUPS

FEATURE	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Cause of death (% unless stated) - continued	CNS, Suicide, Renal (11% each) Myocardial infarct (9)	CNS (1 case) Constrictive Pericarditis (1 case)		Cardiac failure (1 case)	
Contributory causes (% unless stated)	Renal (25) Pulmonary (18) Septicaemia (14)	CNS (21) Septicaemia (14) DIC (14) Renal (14)	Cardiac failure (1 case)	Septicaemia (1 case) Renal (1 case)	
5 Year survival rate (%)	85	57	90	80	WB p = <0,05

* SIGNIFICANCE SUSPECT DUE TO SMALL NUMBERS

LEGEND :
- WB = significance between White and Black patients
- WC = significance between White and Coloured patients
- WI = significance between White and Indian patients
- BC = significance between Black and Coloured patients
- BI = significance between Black and Indian patients
- CI = significance between Coloured and Indian patients

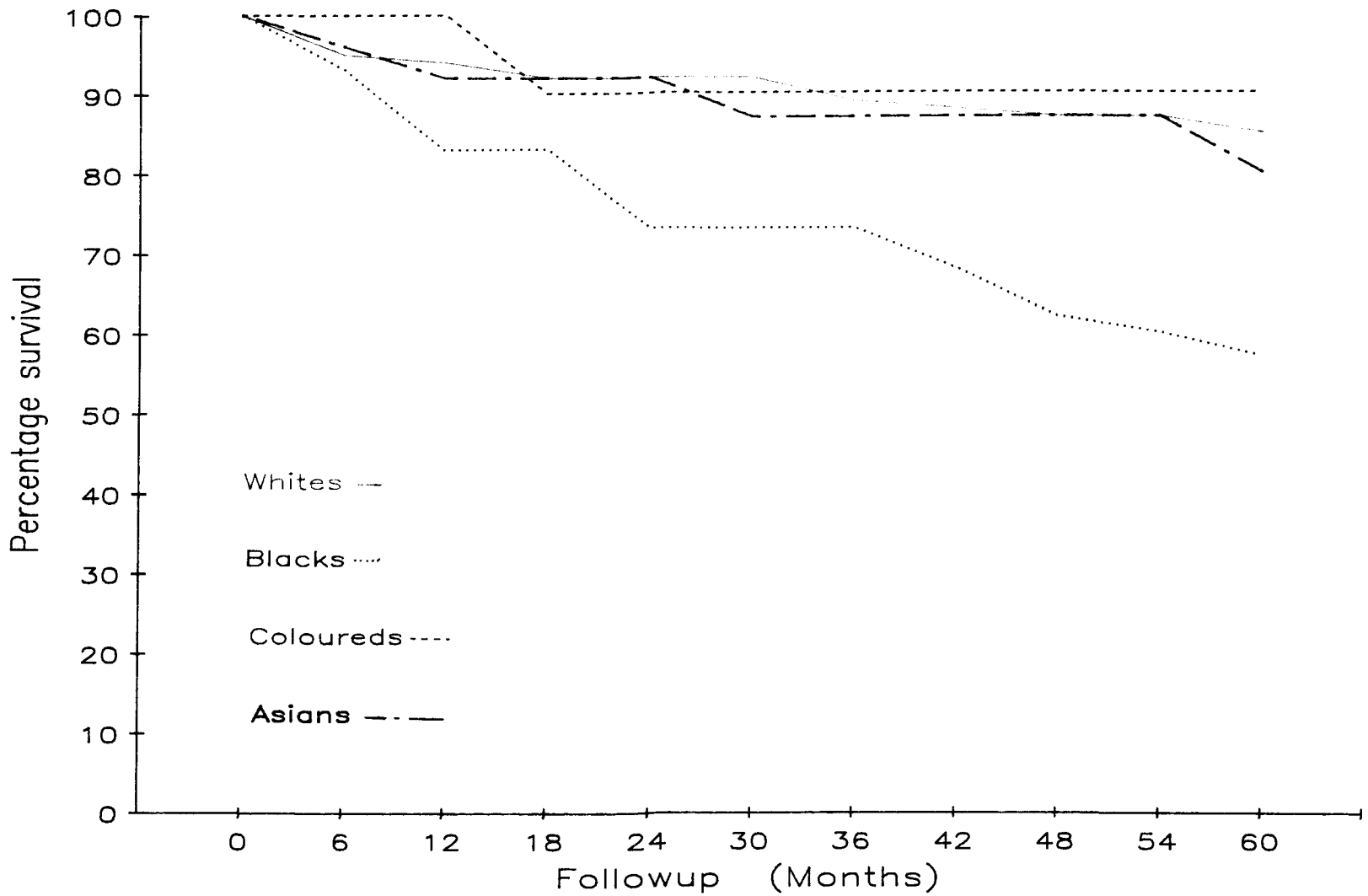


Figure 3.1 Survival analysis for SLE patients according to racial group

drawn, was only opened recently. With respect to age differences, it is noticeable that 50% of the Coloureds developed lupus before 20 years of age, compared with only 13% of the Blacks (p= Ø,Ø5); on the other hand, more Black patients and more White patients tended to present with the disease at 50 years or more.

Looking at the relationship between pregnancy and the disease state, it is noticeable that in 41% of White patients their SLE activity was aggravated by pregnancy compared with only 14% of the Blacks; figures were too small in the Coloured and Indian populations for comment. There is no significant difference between the races in the number of recurrent miscarriages, but successful pregnancies are more common in Blacks compared to Whites (p= Ø,Ø2); this may reflect the tendency towards large families amongst the Blacks. As regards neonatal mortality and morbidity, the infants of 3 out of the 4 Indian patients with lupus who fell pregnant subsequent to their diagnosis had perinatal problems.

The Indians also showed a high frequency of a family history of rheumatological diseases (43% cf 4% in Blacks, p= Ø,Ø5), although this may reflect the greater insight into the disease of the Indians. The predominant causes of death in the two largest groups, notably the Whites and Blacks, were pulmonary pathology and sepsis, whereas a high proportion of Indian patients died from CNS causes (small numbers). Although the follow up of the Black patients is poor, their 5 year survival rate of 57% is significantly worse than that of the Coloureds of 90%, using the Breslow comparative analysis (p= <Ø,Ø5)(refer Fig. 3.1).

TABLE 3.3 THE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES AT DIAGNOSIS (PERCENTAGE)

	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
General :					
Constitutional symptoms	55	68	75	36	
Fever	47	60	31	64	
Lymphadenopathy	12	23	31	22	
Splenomegaly	15	15	8	17	
Musculoskeletal :					
Arthritis and Arthralgia	80	91	84	77	
Muscle pain	28	59	0	21	WB p = 0,0009 CB p = 0,0009 IB p = 0,0009
Dermatological :					
Malar rash	62	51	38	52	
Generalized rash	44	33	17	38	
Alopecia	44	43	50	57	
Photosensitivity	52	33	8	22	WC p = 0,006 WI p = 0,04
Discoid LE	11	23	8	0	
Mouth ulcers	31	50	0	16	
Cardiological :					
Myocardial disease	7	5	8	8	
Pericardial disease	10	15	0	4	
Hypertension	33	33	31	25	
Pulmonological :					
Pulmonary infiltrate	18	17	0	19	
Pleurisy	21	21	0	15	

LEGEND : WB = significance between White and Black patients
WC = significance between White and Coloured patients
WI = significance between White and Indian patients
BC = significance between Black and Coloured patients
BI = significance between Black and Indian patients
CI = significance between Coloured and Indian patients

* SIGNIFICANCE SUSPECT DUE TO SMALL NUMBERS

TABLE 3.3 THE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES AT DIAGNOSIS (PERCENTAGE) CONTINUED :

	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Neurological :					
Transient ischaemic attack and Cerebro-vascular accident	8	5	0	4	
Coma	5	5	0	4	
Fits	8	10	8	20	
Psychiatric disease	23	14	0	25	
Peripheral neuropathy	8	31	0	4	BI p = 0,03 WB p = 0,005
Gastrointestinal :					
Peritonitis	2	0	0	0	
Gastrointestinal symptoms (as presenting symptom)	1	3	0	4	
Peripheral vascular :					
Ileofemoral thrombosis Pulmonary embolus and Deep venous thrombosis	14	12	0	14	
Vasculitis	20	27	75	28	WC p = 0,04 *
Raynauds phenomenon	25	29	33	36	
Renal :					
End stage failure-dialysis	5	9	0	0	
Proteinuria in nephrotic range	17	8	18	17	
Decreased creatinine clearance	53	82	63	67	WB p = 0,005

TABLE 3.3 THE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES AT DIAGNOSIS (PERCENTAGE) CONTINUED :

	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Haematological :					
Hb <10 grams /dl	23	30	23	61	WI p = 0,0002 BI p = 0,03
WCC <3,5 x 10^3 cells/cumm	25	30	25	18	
Platelets <100,000/cumm	16	10	15	36	WI p = 0,05 BI p = 0,04 *
Haemolytic anaemia	13	7	15	13	
ESR >100 mm/hour	13	40	36	29	WB p = 0,0002
Serological :					
Lupus anti-coagulant	22	9	-	-	
Biological false positive WR	14	30	0	29	
Positive LE cells	58	50	75	73	
Positive ANF	95	98	100	100	
Anti Sm antibodies	15	30	17	46	WI p = 0,03 *
Anti RNP antibodies	14	40	33	25	WB p = 0,009
Anti dsDNA antibodies	50	49	100	82	BI p = 0,02 BC p = 0,007 WI p = 0,009 WC p = 0,004
Positive Rheumatoid factor	28	24	0	11	
Decreased C3	32	31	75	59	BC p = 0,03 WC p = 0,007 WI p = 0,03
Decreased C4	44	26	64	53	
Positive Coombs test	27	16	30	27	
Positive skin immuno-fluorescence	58	66	-	-	

Table 3.3 outlines the clinical and biochemical manifestations present in the different race groups at diagnosis. The frequencies of arthritis, Raynaud's phenomenon, generalised and malar rashes, alopecia, hypertension, myocardial infarct, gastrointestinal manifestations, fever, lymphadenopathy, splenomegaly, and the central nervous manifestations of coma and fluctuation in level of conciousness were not markedly different between racial groups. In addition, the prevalence of haemolytic anaemia, leukopenia, LE cells, ANF, FPWR and positive Coomb's and lupus band tests was similar regardless of race. Discoid LE, pleural and pulmonary manifestations, constitutional symptoms, and psychiatric manifestations showed small but non significant differences in frequency.

Those manifestations which differed markedly were myalgia and myositis (59% in Blacks cf Ø%, 28%, 21% in Coloureds, Whites and Indians respectively, p= Ø,ØØ9 for all), photosensitivity (52% in Whites cf 8% in Coloureds, p= Ø,ØØ6; cf 22% in Indians, p= Ø,Ø4), and vasculitis (75% in Coloureds cf 20% in Whites, p= Ø,Ø4 - small numbers).

Peripheral neuropathy was significantly more prevalent in the Blacks (31% cf 4% in Indians, p= Ø,Ø3; cf 8% in Whites, p= Ø,ØØ5 - possible reasons for this have been discussed in Chapter 2). Generally the Blacks had more significant renal involvement (82% had decreased creatinine clearance, cf 53% in Whites, p= Ø,ØØ5, and 9% required dialysis cf Ø% in both Coloureds and Indians). The Blacks did, however, tend to have slightly less nephrotic

TABLE 3.4 CUMULATIVE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES

FEATURE	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
General :					
Constitutional symptoms	60	68	55	29	BI p = 0,008 WI p = 0,007
Fever	54	61	38	69	
Lymphadenopathy	12	29	31	23	WB p = 0,02
Splenomegaly	21	19	8	20	
Musculoskeletal :					
Arthritis and Arthralgia	85	91	85	85	
Muscle pain	37	60	8	32	WB p = 0,02 BC p = 0,004
Dermatological :					
Malar rash	72	54	46	54	WB p = 0,04
Generalized rash	52	33	23	35	WB p = 0,03
Alopecia	53	42	58	54	
Photosensitivity	53	32	8	27	WC p = 0,004 WI p = 0,05
Discoid LE	12	23	15	10	
Mouth ulcers	31	21	0	15	WC p = 0,05
Cardiological :					
Myocardial disease	10	8	8	17	
Pericardial disease	15	17	8	4	
Hypertension	43	35	62	62	
Pulmonological :					
Pulmonary infiltrate	28	24	15	31	
Pleurisy	30	27	8	19	

* SIGNIFICANCE SUSPECT DUE TO SMALL NUMBERS

LEGEND : WB = significance between White and Black patients
WC = significance between White and Coloured patients
WI = significance between White and Indian patients
BC = significance between Black and Coloured patients
BI = significance between Black and Indian patients
CI = significance between Coloured and Indian patients

TABLE 3.4 CUMULATIVE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES (CONTINUED) :

	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Neurological :					
Transient ischaemic attacks and Cerebro-vascular accident	11	5	15	12	
Coma	11	5	8	8	
Fits	13	12	31	23	
Psychiatric disease	34	15	0	35	WC p = 0,02 CI p = <0,05 WB p = 0,025
Peripheral neuropathy	13	31	0	4	WB p = 0,01 BI p = 0,03
Gastrointestinal :					
Gastrointestinal symptoms	1	3	0	4	
Peripheral vascular :					
Ileofemoral thrombosis, Pulmonary embolus and Deep venous thrombosis	19	12	33	33	
Vasculitis	23	24	36	31	
Raynauds phenomenon	30	29	42	40	
Renal :					
End stage failure-dialysis	11	14	8	8	
Proteinuria in nephrotic range	21	15	33	31	
Active urinary sediment	34	30	46	54	
Decreased creatinine clearance	59	83	66	100	WB p = 0,02 WI p = <0,004

TABLE 3.4 CUMULATIVE DIFFERENCES IN CLINICAL AND BIOCHEMICAL FINDINGS BETWEEN RACES (CONTINUED):

	WHITE	BLACK	COLOURED	INDIAN	SIGNIFICANCE
Haematological :					
Hb <10 grams/dl	29	36	54	62	WI p = 0,002
WCC <3,5 x 10^3 cells/cumm	26	29	31	15	
Platelets <100,000 /cumm	15	12	30	32	
Haemolytic anaemia	14	10	23	12	
ESR >100 mm/hour	18	42	33	33	WB p = 0,001
Serological :					
Lupus anti-coagulant	21	-	-	7	
Biological false positive WR	18	30	10	28	
Positive LE cells	59	54	50	67	
Positive ANF	97	100	100	100	
Anti Sm antibodies	15	34	17	39	WI p = 0,03 WB p = 0,02
Anti RNP antibodies	17	44	17	28	WB p = 0,002
Anti dsDNA antibodies	52	48	100	86	WI p = 0,002 WC p = 0,003 BC p = 0,004 BI p = 0,004
Positive Rheumatoid factor	27	22	0	14	
Decreased C3	39	33	77	67	WC p = 0,03 WI p = 0,02 BC p = 0,02 BI p = 0,03
Decreased C4	54	31	62	58	WB p = 0,04
Positive Coombs test	24	13	36	25	
Positive skin immuno-fluorescence	58	55	80 (4/5)	3/3	

syndrome (8% cf 18% in other races).

The Indians tended to have more haematological abnormalities in the form of anaemia (61% cf 23% in Whites, p= Ø,ØØØ2; cf 30% in Blacks, p= Ø,Ø3), and thrombocytopenia (36% cf 16% in Whites, p= Ø,Ø5; cf 1Ø% in Blacks, p= Ø,Ø4 - small numbers).

The Whites had fewer serological abnormalities in the form of ESR >1ØØ mm/hour (13% cf 4Ø% in Blacks, p= Ø,ØØØ2), adsDNA (5Ø% cf 1ØØ% in Coloureds, p= Ø,ØØ4; cf 82% in Indians, p= Ø,ØØ9), anti RNP antibodies (14% cf 4Ø% in Blacks, p= Ø,ØØ9) and anti Sm antibodies (15% cf 46% in Indians, p= Ø,Ø3 - small numbers); the aSm frequency was also low in the Coloureds (17%). In addition, the Blacks had a low frequency of adsDNA (49% cf 82% in Indians, p= Ø,Ø2; cf 1ØØ% in Coloureds, p= Ø,ØØ7).

The Coloureds, on the other hand, were found to have a higher frequency of low C3 (75% cf 31% in Blacks, p= Ø,Ø3; cf 32% in Whites, p= Ø,ØØ7 - small numbers) and low C4 (64% cf 26% in Blacks - non-significant). The Indians also had a high frequency of decreased C3 (59% cf 32% Whites, p= Ø,Ø3).

The cumulative frequencies of the various clinical manifestations for the different races are shown in Table 3.4 and these frequencies mirror quite closely those at presentation, although more of the racial differences reached significance when calculated over the entire period studied. Of particular note in this respect are the frequencies of myalgia and muscle symptoms (6Ø% in Blacks cf 8% in Coloureds, p= Ø,ØØ4; cf 37% in Whites, p=

Ø,Ø2), mouth ulcers (Ø% in Coloureds cf 31% in Whites, p= Ø,Ø5), malar rash (54% in Blacks cf 72% in Whites, p= Ø,Ø4), generalised rash (52% in Whites cf 33% in Blacks, p= Ø,Ø3) and photosensitivity (53% in Whites cf 8% in Coloureds, p= Ø,ØØ4; cf 27% in Indians, p= <Ø,Ø5). Pleurisy and fever were also less frequent in Coloureds but did not reach significance; neither did the lower incidences of venous thrombosis in Blacks and Whites (12% and 19% respectively cf 33% in Coloureds and Indians).

However, lymphadenopathy was significantly less common in White patients (12% cf 29% in Blacks, p= Ø,Ø2), and constitutional symptoms were least frequent in the Indians (29% cf 68% in Blacks, p= Ø,ØØ8; cf 6Ø% in Whites, p= Ø,ØØ7). There was significantly less psychiatric disease (psychosis and neurosis) amongst the Coloureds (Ø% cf 34% in Whites, p= Ø,Ø2; cf 35% in Indians, p= <Ø,Ø5). The Blacks also had less psychiatric illness when compared with the Whites (15% cf 34%, p= Ø,Ø25). Black patients suffered from peripheral neuropathy more frequently than patients of any other group (31% cf 4% in Indians, p= Ø,Ø3; cf 13% in Whites, p= Ø,Ø1). The Indians once again had a higher incidence of anaemia (62% cf 29% in Whites, p= Ø,ØØ2).

Regarding renal abnormalities, the Whites had significantly less abnormality in renal function, as measured by a decreased creatinine clearance rate, than patients of the other races (59% cf 1ØØ% in Indians, p= <Ø,ØØ4; cf 83% in Blacks, p= Ø,Ø2).

Cumulative frequencies of serological abnormalities were once again lower for the White patients, and this applies particularly

to a raised ESR (18% cf 42% in Blacks, p= Ø,ØØ1), and the presence of adsDNA (52% cf 1ØØ% in Coloureds, p= Ø,ØØ3; cf 86% in Indians, p= Ø,ØØ2). However the Blacks had the lowest frequency of positive adsDNA (48% cf Coloureds and Indians p= Ø,ØØ4). Anti RNP antibodies were significantly increased in the Blacks (44% cf 17% Whites, p= Ø,ØØ2). Anti Sm antibodies were less prevalent in the Whites (15% cf 34% in Blacks, p= Ø,Ø2; cf 39% in Indians, p= Ø,Ø3). Throughout the course of the disease the Coloureds also had low frequencies of these two antibodies. The Coloureds exhibited a high frequency of decreased C3 (77% cf 33% in Blacks, p= Ø,Ø2; cf 39% in Whites, p= Ø,Ø3) and of decreased C4. The Indians also had a high frequency of low C3 (67% cf Whites p= Ø,Ø2, cf Blacks p= Ø,Ø3). The Blacks had a lower frequency of decreased C4 (31% cf 54% in Whites, p= Ø,Ø4).

3.5. Discussion.

A few important considerations arise from the introduction of the racial variable. Let us first look at the normal distribution of subcultures within the four races studied here; most of the figures quoted are from the 1980 Governmental census [23] and deal specifically with the population of Johannesburg and the surrounding area. The proportions for the various groups and subcultures of the total population of Johannesburg are shown in Table 3.1.

The Whites or Caucasions are a heterogeneous race. The Afrikaners make up the majority of the White population (54%), and their forefathers were probably 40% Dutch, 40% German, 8% French and 5% English. The largely English-speaking group (29%), the Jewish community (12%), most of whom originate from Lithuania, and the Mediterranean group comprising Portuguese (2%), Italians (1%) and Greeks (0.5%), make up the remainder of the White group in the Johannesburg area. Much smaller numbers of Spanish, German, French, Scandinavian and Central European immigrants also reside in the area. The Whites living in the Johannesburg area number approximately 550 000, but although they comprise only 32% of the total population they constitute the largest group of patients in our study.

The second population group comprises approximately 59% of the total population of Johannesburg, and is made up of the Blacks or South African Bantu-speaking Negroes. This group is derived from

many different sub cultures and in the Johannesburg area they are as follows: the Zulus, derived from the North Nguni, comprise 20%; the South Sotho Blacks, originally from Lesotho, make up 16%; the Tswana from the Western Transvaal and Botswana area comprise 14%; the Xhosa who are also Nguni, but termed the South Nguni since they originally came from the Transkei or Ciskei area, comprise 13%; the North Sotho Blacks from the Northern Transvaal at 13% make up the last major sub culture. Social behaviour patterns differ from group to group; for instance the Nguni tribe prohibits intermarriage, whereas the Northern and Southern Sotho people with the Tswanas regard certain related marriages as preferential. The Blacks in the Johannesburg area number approximately 1 025 000.

The third group studied is the Indians, who are especially interesting since they tenaciously maintain the culture of their place of origin on the mainland of India. The Indians of Johannesburg can be divided into 3 major groups on the basis of a social caste system; these are the Muslims, the Hindus and the Tamils [158]. Lifestyles and marriages tend to be restricted to the caste group into which the individual is born; marriage between different castes is a recent social phenomenon and will not affect the patients of this study. Approximately 50% of the Indian population are Muslims; they practice the Islamic religion, are predominantly Gujarati-speaking, and tend to be the wealthy and influential leaders in the community. Muslim parents until recently encouraged marriage between cousins, with up to 35% of marriages being consanguinous (Dr T Jenkins, private communication); apart from the prohibition of pork products, the diet is non-vegetarian.

The second group, the Hindus share the physical features of the Muslims; they are, however, vegetarian and consanguinous marriages are strictly forbidden. They probably comprise 40% of the Indian community of Johannesburg.

The third group, the Tamils, are the smallest group in the area, largely because until recently their immigration was legally restricted. They are often the labourers in the caste system; they also tend to be dark and stocky, and they have coarser facial features than the Hindus or Muslims. In 1972 they comprised roughly 5% of the Johannesburg Indian population, but this figure is now probably closer to 10% [158]. The total Indian community numbers 53 135 and makes up approximately 3% of the Johannesburg population.

The final group included in the study is the Coloureds. This group is the racial melting pot; their ancestors include Whites, Hottentots, and Malays with the recent introduction of intermarriage with the South African Blacks. It is noteworthy that there are fewer Cape Malays amongst the Transvaal Coloureds than there are amongst the Cape Coloureds (Prof T Jenkins - private communication). The Coloureds are exposed to many environmental factors which are operative in the Black community; poverty, alcoholism and tuberculosis are moderately common plagues within these groups. However, the Coloureds tend to prefer a more westernised diet than do the Blacks, although this is changing with increases in their "westernisation". The Coloureds number 105 000 and comprise approximately 6% of the resident population

of Johannesburg.

The overseas literature tends to focus on Black-White differences, with occasional comparative studies which include Polynesians, Puerto Ricans, Iraqis and Orientals [3,159,160,161,162,163,164,165,168].

One of the most striking differences in SLE between Blacks and Whites is seen in the different sex ratios mentioned earlier; the Black female to male ratio was much higher than the White female to male ratio. Black patients do not develop the disease at a younger age, and in fact their age spread is very similar to that of Whites; this is contrary to other reports of the Blacks presenting with the disease a decade earlier than Whites [165]. Therefore the high female to male ratio in Blacks cannot be attributed to age differences. Black women suffering from SLE also have a significantly decreased 5 year survival rate. It would be easy to surmise that a higher level of circulating oestrogens or an increase in their sensitivity to that hormone in Black women might account for their increased frequency and severity of SLE; however, one fact weighing slightly against this is that in our experience hyperoestrogenic states such as pregnancy do not cause greater exacerbation of SLE in Blacks than they do in any other race group. Blacks do have a high proportion of women developing SLE at an older age, and in this respect onset of the disease in some Blacks appears to be associated with the menopause (unpublished data).

The shorter followup period in Blacks is probably related to

socio-economic factors and the limited records at the Hillbrow Hospital rather than to disease severity, and the lower incidence of family history may also be a result of ignorance about the disease.

Comparing clinical manifestations in Whites and Blacks, the latter group were found to have significantly more muscle symptoms (p= Ø,ØØØ9), peripheral neuropathy (p= Ø,Ø5), diminished creatinine clearance (p= Ø,ØØ5), raised ESR (p= Ø,ØØØ2), and anti RNP antibodies (p= Ø,ØØ9) at diagnosis. Cumulative frequencies calculated throughout the course of their disease showed that Black patients had a significant increase in the frequency of muscle symptoms, lymphadenopathy, below normal creatinine clearance, ESR >1ØØml/hr, and anti RNP and anti Sm antibodies when compared with Whites. During the followup years, Blacks had a higher proportion of diffuse proliferative GN but this was not significant. These increases reach greater significance when the markedly different followup periods are taken into account.

The Blacks had significantly lower frequencies of malar rash and generalised rashes, possibly because their pigmentation hinders the diagnosis of rashes. They also had less psychiatric disease and lower frequencies of decreased C4 levels. The relevance of these findings is doubtful in view of the shorter followup of the Blacks.

Nearly one half of the deaths in Black patients were directly related to pulmonary causes compared with only 1 out of 6 Whites. CNS disease was the most important contributory cause of death in

Blacks, as opposed to renal disease in the Whites; the 5 year survival was significantly worse in Blacks than it was in Whites (p= <Ø,Ø5).

Several reports have alluded to racial differences in the prevalence of SLE, particularly Siegel's work, which showed a 3:1 ratio of Blacks to Whites affected with the disease in New York [165], and Hughes' study in Jamaica, where 1 in every 25Ø females was reported to have SLE [164]. The second striking racial difference which has been described is the 3 times increased mortality amongst the Blacks of New York City, with even greater differences in Jefferson County, Alabama [165]. Our study cannot comment on South African prevalence or incidence, although one Cape Town study gives incidence levels in the female population admitted to hospital of 2, 4 and 5 per 1ØØØ for White, Black and Coloured women respectively [37]. The Blacks in our study do have the worst survival rate (57% 5 year survival rate); this may be environmental, in which case we have no means of correcting for it statistically. There was also no greater delay prior in diagnosis amongst the Blacks than there was in any other race. However the high Black mortality found in the New York study had apparently been corrected for poor housing, overcrowding and migration factors. Our study of the Blacks becomes more relevant when compared with other studies of Blacks, and particularly studies of African Blacks.

Two such pieces of SLE research have originated from Southern Africa; the larger deals predominantly with Coloureds (86 patients) and Whites (36 patients), and will be discussed later

[37]. The other study by Seedat involves Blacks (13 patients) and Indians (17 patients), but does not compare the clinical manifestations of these races [163]. The Black and Indian patients in this study tended to have higher frequencies than our patients of joint pains, positive rheumatoid factors, LE cells, and fever, with lower frequencies of malar rash, mouth ulcers, pleurisy, neurological manifestations, nephrotic syndrome and leukopenia. However the frequencies in Seedat's work resemble those of our Black and Indian patients more than they resemble those of our Whites, finding as he did a high female to male ratio and a high proportion of patients with severe renal involvement.

I have briefly outlined the manifestations of the Black patients from various studies with special reference to the country in which the population was based. These details are supplied in Table 3.5, but one must bear in mind that statistics concerning Black lupus sufferers in Africa are limited.

When compared with Hughes' study of West Indians [164], our Black patients had higher frequencies of Raynaud's phenomenon, photosensitivity, discoid lesions and malar rash. The malar rash was present in approximately the same number of patients in our sample as in Kanyerezi's study in Uganda (see Table 3,5), a country of similarly high altitude [3]. Our Black patients had lower frequencies than the West Indians of alopecia, adsDNA, and FPWR.

Previous reports suggest that SLE is uncommon in Africa and that when their disease is diagnosed the patients tend to have a severe

TABLE 3.5 COMPARISON BETWEEN VARIOUS STUDIES OF BLACK SLE PATIENTS (AS A PERCENTAGE OF THE TOTAL BLACK PATIENT GROUP IN EACH STUDY)

FEATURE	MORRISON	WILSON (REF. 164)	SIEGEL (REF. 165)	GINZLER (REF. 167)	KANYEREZI (REF. 3)	SOMORIN (REF.168)
PLACE OF ORIGIN	SOUTH AFRICA	JAMAICA	USA	USA	UGANDA	NIGERIA
MEAN AGE - YEARS	30	31	-	32	30	34
MALE TO FEMALE RATIO	1 : 8	1 : 11	-	1 : 9	1 : 4	0 : 5
FAMILY HISTORY	4	9	-	-	5	-
RAYNAUDS PHENOMENON	29	14	-	-	-	-
ALOPECIA	42	70	-	-	33	80
MALAR RASH	54	32	0	-	66	-
DISCOID LE	23	14	-	-	-	-
POLYARTHRITIS	91	89	-	-	86	40
PHOTOSENSITIVITY	32	12	-	-	-	-
PLEURISY	27	32	6	-	10	-
PULMONARY	24	-	-	-	19	20
HYPERTENSION	35	-	-	-	40	-
PERICARDITIS	17	-	5	-	10	60
PREDOMINANT RENAL HISTOLOGY	DPGN	DPGN/FPGN	-	-	-	-
ABNORMAL URINALYSIS	30	-	-	-	66	20
NEPHROTIC SYNDROME	15	2	-	-	-	40
HAEMOLYTIC ANAEMIA	10	11	-	-	-	-
PSYCHIATRIC DISEASE	15	19	)	)	35	20
COMA	5	2	0)	19)	10	-
FITS	12	3	0	-	5	-
PERIPHERAL NEUROPATHY	31	3	-	-	5	-
STROKE	5	3	-	-	-	-
adsDNA	48	82	-	-	-	-

TABLE 3.5 COMPARISON BETWEEN VARIOUS STUDIES OF BLACK SLE PATIENTS (AS A PERCENTAGE OF THE TOTAL BLACK PATIENT GROUP IN EACH STUDY) CONTINUED

FEATURE	MORRISON	WILSON (REF. 164)	SIEGEL (REF. 165)	GINZLER (REF. 167)	KANYEREZI (REF. 3)	SOMORIN (REF.168)
aRNP	44	38	-	-	-	-
FPWR	30	12	-	-	-	40
HIGHEST MORTALITY	BLACK FEMALE	-	-	BLACK MIDDLE-AGED FEMALE	-	-
5 YEAR SURVIVAL	57	-	-	73	-	-
MAJOR CAUSE OF DEATH	PULMONARY SEPTICEMIA				CNS RENAL	RENAL

form of the disease, with frequent renal involvement [3,168,37]. This may be a diagnostic error in that the milder cases are being missed. However, in most respects the frequencies of the clinical manifestations of the patients in the Ugandan group tally more closely with those of our Black patients than do those of the Jamaican patients; this is particularly true for the cutaneous and pulmonary manifestations [164].

Somorin [168], in trying to explain this low incidence, pointed out that the chloroquine used as longterm antimalarial prophylaxis in the area of his study may have suppressed the milder cases of SLE [168]; malaria is not endemic to Johannesburg and so this would not apply to our Black population; it would seem that a different disease environment exists in this country.

A notable finding amongst the Blacks in our series was the very high frequency of peripheral neuropathy, but as already discussed this was considered to be due to the prophylactic treatment of these patients with INH whilst they were receiving steroid therapy; Seedat et al [163] however found no drug-related SLE in patients on longterm INH therapy for tuberculosis.

When looking at the manifestations of SLE in our Caucasian patients, it appears that they are serologically less active from their lower levels of anti Sm and anti RNP antibodies (also the Coloureds), and adsDNA antibodies (also the Blacks); amongst Whites a markedly elevated ESR or a lowered C3 level is less frequent (a phenomenon shared with the Blacks). There are not however fewer White patients with low C4 levels, unlike the case

of the Blacks. In keeping with this general picture of "hyporeactivity", the Whites also suffer from less lymphadenopathy; similarly abnormal creatinine clearance rates are less common in Whites. However, they have more cutaneous manifestations of lupus in the form of photosensitivity, malar rash and mouth ulcers, possibly due to lack of protective pigment in their skin. Whites also have more psychiatric illness (a trait shared with the Indians).

It is noticeable that few overseas studies give figures for Whites alone, the most similar study being that by Hart and Grigor, of New Zealand patients [159]. The manifestations of our patients tally closely with theirs, except in the cutaneous manifestations, where our patients have higher frequencies of mouth ulcers, photosensitivity and alopecia; our patients also have more psychosis. On the other hand our group have less serositis (pleurisy and pericarditis). Similar differences are noted when comparing our findings with those of Harvey from the USA, whose sample comprised 84% Whites [54].

One study indicates a lower incidence of positive ANF and higher levels of C4 in Whites [147].

SLE in the Indians also shows clinical differences when compared with the disease in other groups. They had a very high frequency of family histories of either rheumatoid arthritis or SLE, possibly due to the high proportion of consanguinous marriages and marriages within castes, which is often between families from the same area of origin in India (Dr A.A. Wadee - personal

communication). A local study is in progress to assess the degree of homogeneity of tissue types within the Indian community.

Indian patients tended to have their disease diagnosed earlier than White patients (mean period to diagnosis 19 months cf 35 months) and the presentation age was younger, with only 4% presenting older than 50 years (cf 17% in Whites); this is not due to population differences, because the graph of population age is very similar for the Whites and Indians after 10 years of age [170]. Seedat's work in Durban suggested that SLE was more common amongst the Indians than amongst the Blacks, but we have no data to substantiate this [163].

The major cause of death in the Indians was CNS pathology (3 cases out of 5), whereas in Whites this was an uncommon cause (11%). Anaemia was more common in Indians (p= 0,002 when compared with Whites, p= 0,03 when compared with Blacks or Coloureds), as was thrombocytopenia; the anaemia is shared with the Coloureds (of borderline significance when compared with Whites). Indian patients had higher frequencies of abnormal creatinine clearance rates (cf Whites p= 0,002). Indian patients also presented in greater numbers with adsDNA (cf Whites p= 0,002), low C3 and anti Sm antibodies (cf Whites p= 0,03); regarding the anti Sm antibody and its association with "encephalopathy" or CNS SLE, it is interesting to note that of all the CNS manifestations, only seizures were more prevalent in Indians than in Whites, although CNS causes were the major cause of death in Indians.

Indians appeared to have a high frequency of patients in whom SLE

was either precipitated or aggravated by the pregnant or post partum states; on the other hand, weight loss and malaise were significantly less frequent (cf Whites p= Ø,ØØ7, cf Blacks p= Ø,ØØ8), as was the finding of DPGN on histology (unpublished data). The Indians had the lowest frequency of individuals requiring dialysis, which is unusual considering the high proportion with abnormal creatinine clearance rates. This is contrary to Seedat's findings, as we have already noted, because the features of Seedat's group of Black and Indian patients more closely resemble those of our Black and Indian patients than those of our White patients; unfortunately, the Durban study does not give the breakdown of manifestations for Blacks and Indians [163].

Before entering a discussion about the Coloureds, it must be noted that regrettably only a small sample of Coloured patients was studied.

If one placed the Blacks and Whites on either end of a disease continuum, one might expect that the Coloureds, because of their gene admixture, would exhibit disease patterns placing them somewhere near the midpoint. This however, is not the case; they have the best survival rates of all the racial groups despite the fact that many possible potentiating factors are shared with the other groups (see Materials and Methods in Chapter 1). It is hard to imagine that their Hottentot blood, which must surely have been greatly diluted over the last 3ØØ years, could donate immunity for SLE to this section of the community. Our findings do not tally with those of the Cape Town research which showed that the highest prevalence of SLE was amongst the Cape Coloureds (approximately 1

in 25Ø in the Coloured peoples), and that they suffered from an especially aggressive form of lupus, which was attributed to the Malaysian background of the group [37,166]. However many Transvaal Coloureds have not inherited the marked physical features of the Malay Cape Coloureds and there appear to be few Malay Coloureds in the Transvaal.

Coloureds have a shorter period from the appearance of the first symptom to diagnosis (mean period 15 months cf 35 months for Whites). A higher proportion of Coloured SLE patients presented before 2Ø years of age (5Ø% cf 13% in Blacks, p= Ø,Ø3) which is usually a poor prognostic sign. No patients presented after 5Ø years; this age group is usually associated with a milder form of the disease.

The 5 year survival rate of the Coloureds was 9Ø% (cf Cape Town group 65%, p= <Ø,Ø5 [37]), comparable with the best in the world. Our group had a decreased frequency of muscle pain (cf Blacks p= Ø,ØØ4), cutaneous manifestations such as mouth ulcers (cf Whites p= Ø,Ø5) and photosensitivity (cf Whites p= Ø,Ø2), and psychiatric disease (cf Whites p= Ø,Ø2); the incidences of serositis, generalised rashes, malar rashes and peripheral neuropathy were decreased, but not significantly so.

Coloured patients have an increased frequency of lymphadenopathy, vasculitis, haemolytic anaemia and positive Coombs' test (all non significant), as well as increased serological manifestations of "activity", notably adsDNA (cf Whites and Blacks p= Ø,ØØ4), and low C3 (cf Whites and Blacks p= Ø,Ø3). Of interest is the finding

of a "normal" proportion of positive ANFs (3,9%) in the general asymptomatic Coloured population [169].

Compared with the Cape Town group, which comprised 66% Coloureds (the remainder were predominantly Whites) our Coloureds show marked differences in the frequencies of certain manifestations. The cutaneous manifestations of malar rash, alopecia, superficial vasculitis and Raynauds' phenomenon are much less prevalent in the Cape Coloureds; the degree of musculoskeletal involvement, the frequency of haematological manifestations including haemolytic anaemia and leukopenia, and the number of patients with lymphadenopathy and splenomegaly is the same for both groups. Fits are less frequent amongst the Cape Coloureds, but psychiatric illness occurs as commonly in their group as in ours. Pleurisy was more prevalent in the Cape group, but pericarditis occurred with equal frequency. The nephrotic syndrome was equally common, but renal failure was the principle cause of death in their group, with no patients dying from pulmonary causes.

SUMMARY

In this study we demonstrated differences in clinical manifestations between our entire patient group and those of various overseas series, as well as racial differences within our patient population.

Generally our patients had a lower female to male ratio than those in overseas studies, possibly due to the high proportion of elderly patients in our series; our patients had a higher frequency of relatives having rheumatoid arthritis. Skin manifestiations, with the notable exception of discoid LE, were considerably more common in patients in Johannesburg than elsewhere, as well as being more common in the individual racial groups when compared with corresponding racial groups in the rest of the world. It is noticeable that frequencies of these skin manifestations similar to ours are noted in Uganda, another country of high altitude and high levels of ultraviolet irradiation. Hence it could be speculated that increased ultraviolet light irradiation was responsible for the increased frequency of these skin manifestations, but not of others. Certain features were less common to our group than Dubois' group, but the frequencies of these features in our patients approximated those of the patients in Estes' series.

I looked at various features of renal pathology associated with good or bad prognosis. These included the presence of urinary casts, diffuse proliferative glomerulonephritis, and serum creatinine levels greater than 150 umoles per litre, all of which

I found to be positively associated with a poor short term prognosis.

Our patients had a higher frequency of death from pulmonary causes, except for those patients with severe renal disease in whom pulmonary causes of death were infrequent.

The survival figures of the whole group were comparable with those from elsewhere in the world and we confirmed the poorer prognosis of patients with renal impairment.

When the individual racial groups were compared, the Whites had significantly more cutaneous manifestations, less serositis, less deterioration in renal function, and they had less serological indication of disease activity. Psychiatric illness was more common in whites.

The Blacks had the worst prognosis, more severe renal involvement with the exception of the nephrotic sydrome, more muscle symptoms, and more peripheral neuropathy, although the latter may have been caused iactrogenically. The Blacks, who generally presented at an older age (as did the Whites), had a higher female to male ratio. They had depressed levels of complement less frequently in spite of having a more severe form of the disease. Our blacks tended to have more skin manifestations than Blacks elsewhere (except in Uganda).

The Indians had more relatives with a history of rheumatoid arthritis, and higher frequencies of haematological disturbances.

The combination of adsDNA and depressed complement levels, normally considered to be a poor prognostic sign, was more frequent in the Indian group; however they did not have the worst prognosis, approximating that of the Whites. The Indians had fewer constitutional symptoms.

The Coloureds manifested at a younger age with lupus, and they suffered from less psychiatric disease; they were found more frequently to have depressed levels of C3 and C4, and generally to have lower frequencies of the antibodies to the extractable nuclear antigens. Coloured SLE patients had the best prognosis of all the racial groups.

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