SYSTEMIC LUPUS ERYTHEMATOSUS—AN ANALYTIC STUDY OF EIGHTY CASES IN SINGAPORE

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and

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INTRODUCTION

Since the first description of Lupus Erythematosus phenomenon in 1948 (Hargraves *et al*, 1948), Systemic Lupus Erythematosus (SLE) has been universally reported. Numerous literatures of this disease continue to appear, but reports from Singapore are few and systemic analyses of large series have not been published.

The purpose of this paper is to present the clinical manifestations, laboratory findings, long-term treatment, clinical course and prognosis of eighty S.L.E. patients found over a 15½-year period in our department at Singapore. Major differences observed in the present study as compared to some other western series are also discussed.

METHODS AND MATERIALS

Between January 1955 to June 1970 inclusive, 80 patients diagnosed as suffering from Systemic Lupus Erythematosus (SLE) in Medical Unit II, Outram Road General Hospital, Singapore, were included in this study.

The criteria for diagnosis were based on a positive L.E. cell preparation in 55 cases (68·8%), positive renal or/and skin histology with a compatible clinical picture in 16 cases (20%), and on a classical picture of multisystem disease with supportive immunological findings in 9 cases (11·2%).

All relevant data (e.g. age, sex, race, occupation etc.) of the patients were obtained on the first visit. Detailed history taken from each patient included the initial presenting symptoms, precipitating factors if any, numbers of pregnancies and abortions, exposure to drugs or/and physical agents, past illnesses, social and family histories. The clinical and laboratory findings of each case were recorded at the initial and subsequent visits. Most laboratory investigations were carried out in all patients, but special tests were only carried out whenever indicated—(e.g. Carotid angiogram or E.E.G. in central nervous system involvement.) At various stages of the disease, renal function tests and renal biopsy were performed to assess the degree of renal damage.

All cases were treated with systemic corticosteroid (oral or parental) and the dosage varied according to the disease activity and the patient's body weight. Side-effects of steroids as well as other drugs used in the treatment were noted and in severely affected cases or patients developing resistant to steroid after some period of time, an immunosuppressive drug such as Cyclophosphamide (oral and parental route) was administered.

All were closely followed up in our outpatient, and their clinical status and course, as well as all the various laboratory tests were periodically checked. In case of a death, formal autopsy was requested and the cause of death ascertained.

RESULTS

Of the 80 cases found in Medical Unit II, Outram Road General Hospital, over the 15½-year period, the majority (65%) were found during the last 5 years, a three-fold increase over a similar period between 1960 through 1965, and a six-fold increase between 1955 through 1960 (Fig. 1). As shown in Table 1, the majority were Chinese, females (8:1), in the second and third decades. The cumulative incidence of systemic involvement is summarized in Fig. 2, and that of the laboratory findings is illustrated in Fig. 3.

Fig. 4 demonstrates the difference in major systemic involvements between a western series (Dubois and Tuffanelli, 1964) and the present series.

The details of each system involved are tabulated in Table II. Figs. 5(a) and (b) show the typical renal histology of renal involvement in S.L.E.—the focal glomerulonephritis and the membranous glomerulonephritis respectively. Fig. 6 illustrates the positive antinuclear antibody factor using indirect immunofluorescence and rat's liver as a substrate.

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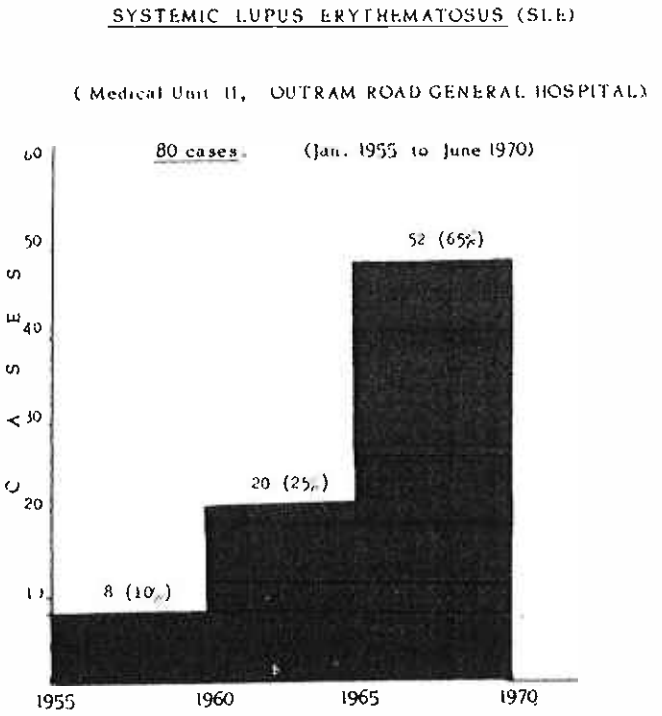
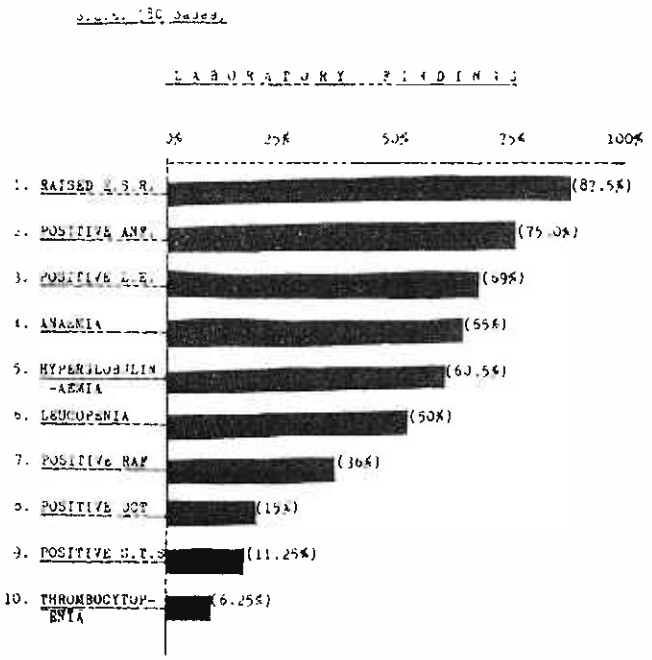


Fig. 1.



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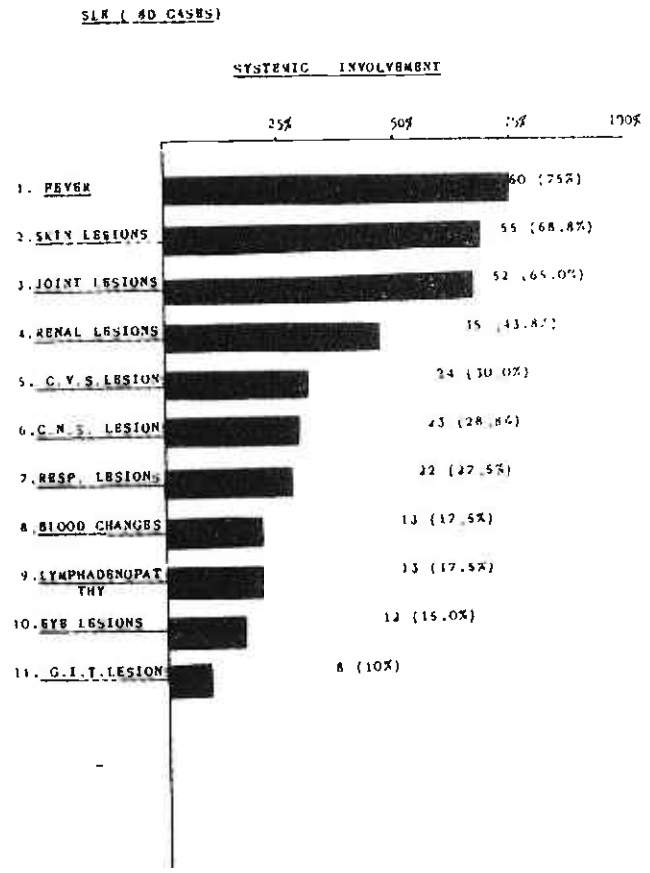

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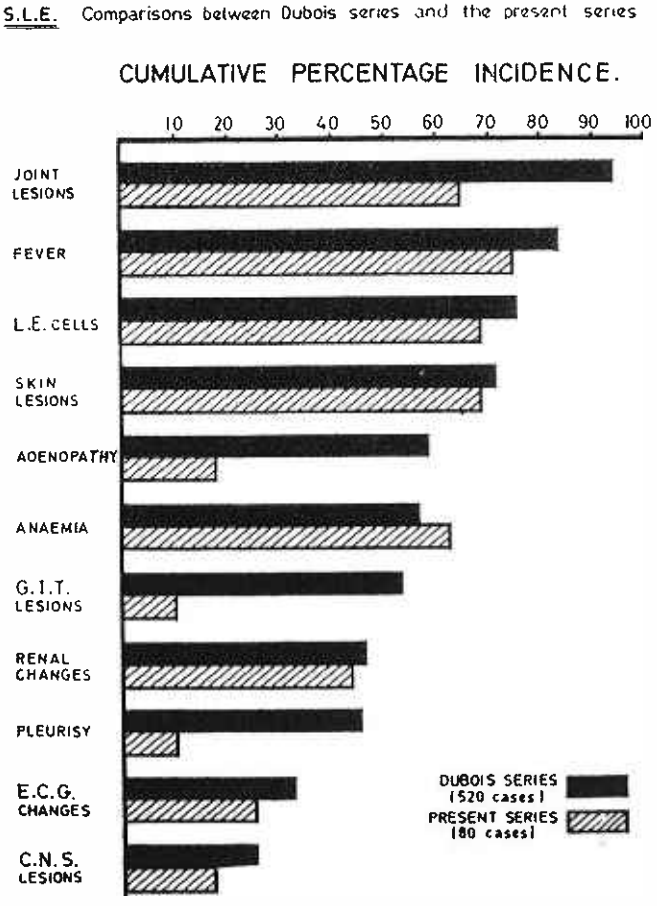


Fig. 4.

TABLE I
RACE, SEX AND AGE DISTRIBUTIONS
(S.L.E. 80 CASES)

Race:	
Chinese	70 (87·5%)
Indians	6 (7·5%)
Malays	4 (5·0%)
Sex:	
Females	71 (87·75%)
Males	9 (11·25%)
Age of Onset (Years)	
10 to 19	32 (40·0%)
20 to 29	26 (32·5%)
30 to 39	13 (16·25%)
40 to 49	7 (8·75%)
50 to 59	2 (2·50%)

TABLE II
SYSTEMIC LUPUS ERYTHEMATOSUS
(80 CASES)

Signs and Symptoms	Cases	Percentage
1. **Fever**	60	75·0
(*a*) As initial symptom	32	40·0
(*b*) With other conditions	28	35·0
2. **Skin Lesions**		
(*a*) All types	55	68·75
(*b*) "Butterfly rash"	52	65·0
(*c*) Alopecia	32	40·0
(*d*) Photosensitive rash	26	32·5
(*e*) Mucous membrane lesions	4	5·0
(*f*) Psoriasiform lesions	4	5·0
3. **Joint Involvement**		
(*a*) Arthralgia and arthritis	52	65·0
(*b*) Misdiagnosed as rheumatoid arthritis	32	40·0
(*c*) Rheumatoid arthritis deformity	12	15·0
(*d*) Subcutaneous nodules	3	3·75
4. **Renal Involvement**		
(*a*) All types including albuminuria	35	43·75
(*b*) Nephrotic syndrome	18	22·5
(*c*) Urinary infection	16	20·0
(*d*) Ureamia	7	9·0
(*e*) Renal biopsies (autopsies)	43	54·0
(i) Focal glomerulonephritis	27	63·0
(ii) Membranous ('Wire-Looped')	11	25·4
(iii) Minimal change	3	7·0
(iv) Normal	2	4·5

TABLE II *(Continued)*

Signs and Symptoms	Cases	Percentage
5. **Cardiovascular Involvement**		
(*a*) All types	24	30·0
(*b*) E.C.G. changes	20	25·0
(*c*) Hypertension	17	21·25
(*d*) Cardiomegaly	13	16·0
(*e*) Cardiac murmurs	10	12·5
(*f*) Cardiac failure	4	5·0
(*g*) Ischemic heart disease	2	2·5
(*h*) Pericarditis	2	2·5
(*i*) Arrhythmias	2	2·5
(*j*) Libman-Sachs valvulitis	1	1·25
6. **Neurological Involvement**	23	28·75
(*a*) Psychological disturbance (Anxiety, depression, psychosis)	17	21·25
(*b*) Central nervous system lesions (Convulsion, thrombosis, chorea)	12	15·0
(*c*) Peripheral nervous system involvement (Cord lesions, neuropathies etc.)	6	7·5
(*d*) Muscular involvement (Myalgia, myositis, myopathy)	9	10·25
(*e*) Aseptic bony necrosis	3	3·75
7. **Respiratory Involvement**		
(*a*) All types	22	27·5
(*b*) Pleurisy	8	10·0
(*c*) Pneumonitis	8	10·0
(*d*) Pleural effusion	4	5·0
(*e*) Associated P.T.B.	4	5·0
8. **Lymphadenopathy**	13	17·5
9. **Ocular Involvement**		
(Cytoid bodies 5; Retinal haemorrhage 3; Optic atropy 2; Conjunctivitis)	12	15·0
10. **Gastrointestinal Involvement**		
(*a*) All types (Vomiting, diarrhoea, gastritis, colitis)	8	10·0
(*b*) Hepatomegaly	20	25·0
(*c*) Splenomegaly	8	10·0

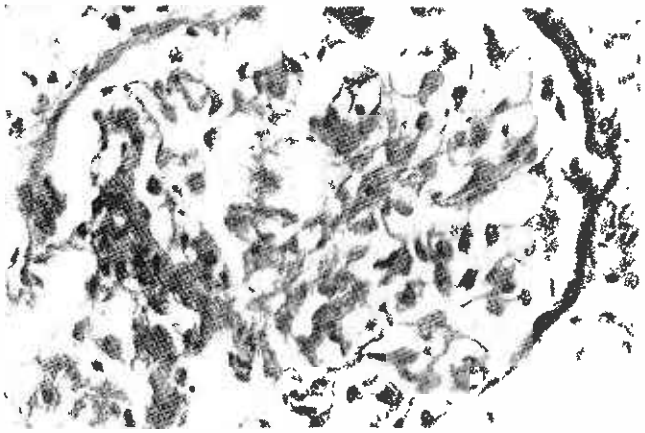
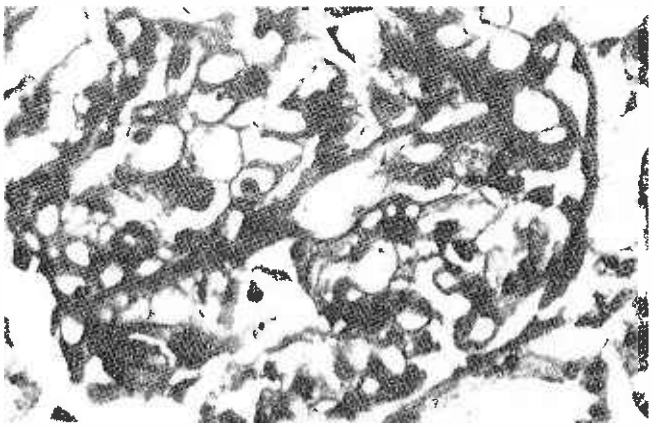


Fig. 5(a).



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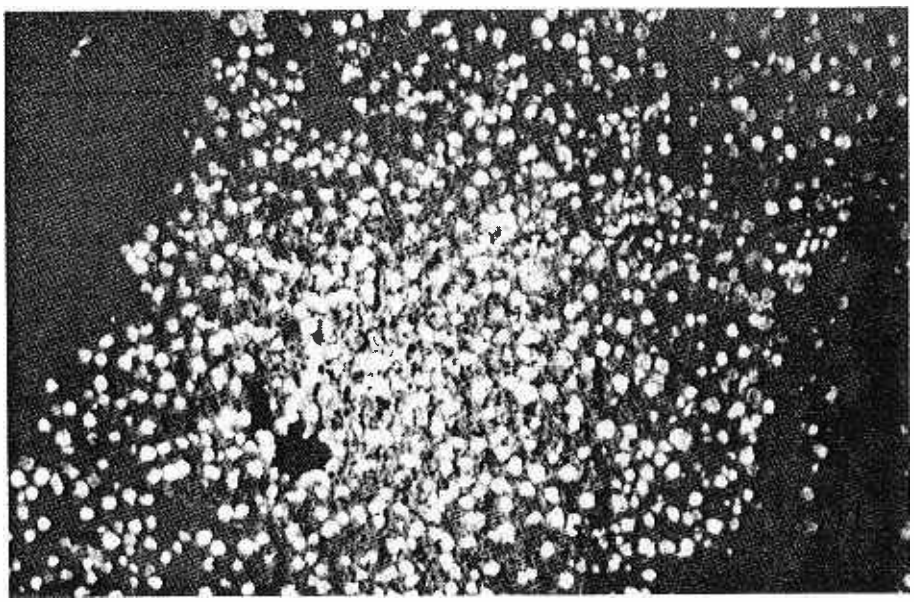

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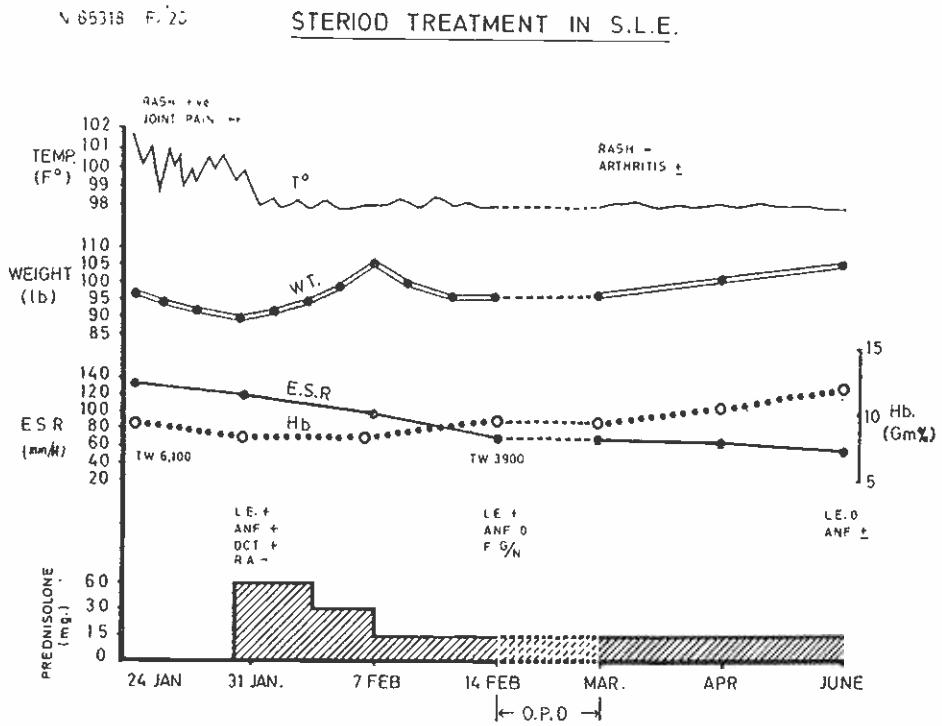

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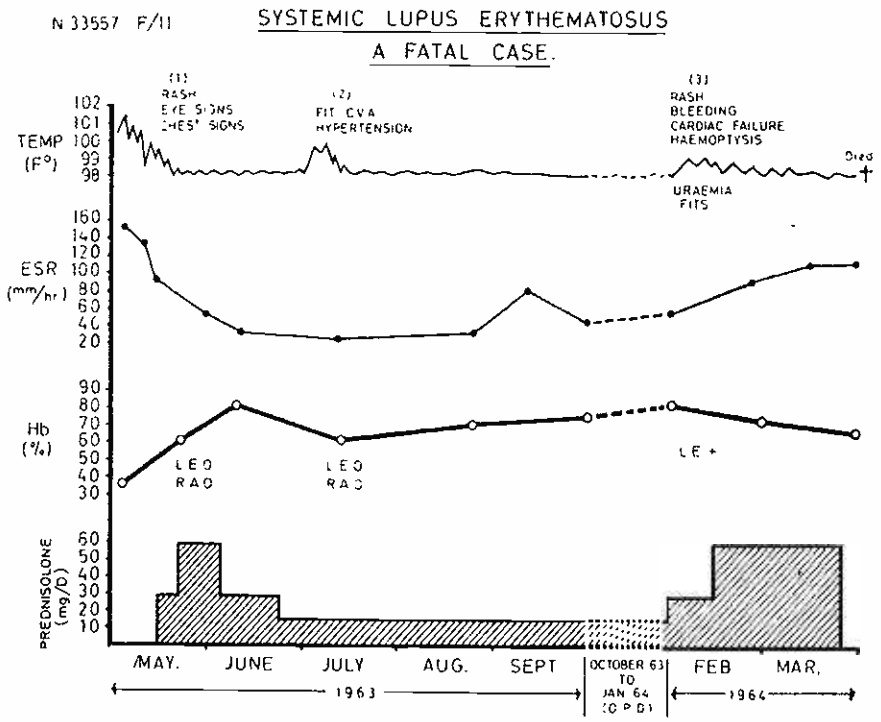

Fig. 8.

TABLE III

SIDE-EFFECTS OF DRUGS

Steroid:	
1. Cushingoid appearance	46·7%
2. Acne	24·3%
3. Bruises/haemorrhage	12·8%
4. Striae	9·8%
5. Fluid retention	9·8%
6. Cataract	4·8%
7. Myopathy	4·8%
8. Osteoporosis	3·2%
9. Aseptic necrosis	3·2%
10. Bacterial infection	32·2%
11. Fungal infection	20·6%
12. Viral infection	6·8%
13. Psychosis	10·4%
Chloroquine:	
1. Hyperpigmentation	4·8%
2. Retinal damage	4·8%
3. Neuropathy	3·2%
Endoxana:	
1. Alopecia	9·5%
2. Marrow depression	6·8%
3. Depression	3·8%
4. Infections	6·5%

TABLE IV

PROGNOSIS, SURVIVAL AND MORTALITY RATES AND CAUSES OF DEATH

Prognosis:		
For under one year		93·7%
For one to two years		88·7%
For two to three years		87·5%
For three to four years		86·2%
Survival Rates:		
Survived under 5 years	42 cases	52·5%
Survived five to 10 years	9 cases	11·25%
Survived over 10 years	7 cases	8·75%
Mortality Rates:		
Overall mortality	12 cases	15·0%
Died under one year	5 cases	6·2%
Died between 1 to 2 years	4 cases	5·0%
Died between 2 to 3 years	1 case	1·2%
Died between 3 to 4 years	1 case	1·2%
Died on the 11th year	1 case	1·2%
Causes of Death (12 Cases)		
Renal failure	7 cases	58·0%
Septicaemia/Broncho-pneumonia	2 cases	16·5%
Meningitis (Fungal and bacterial)	2 cases	16·5%
Liver failure	1 case	8·3%

Long-term steroid therapy was effective in controlling most S.L.E. e.g. Fig. 7, but some deteriorated rapidly in spite of increasing doses (Fig. 8). Numerous side-effects of steroids encountered were tabulated in Table III. Later, 9 cases were changed to Cycophosphamide because of steroid resistance or adverse effects. On oral chloroquine, 8 patients developed ocular and cutaneous complications and this antimalaria drug has since been discontinued.

The long-term prognosis, survival rates, mortality rates and causes of death in this series are summarized in Table IV.

DISCUSSION

Systemic Lupus Erythematosus (SLE) is not rare in Singapore although the incidence rate per year, as shown in our previous study (Tay and Khoo, 1970) is lower than those reported in western centres (Siegel *et al*, 1962; Leonhardt, 1966; Dubois and Tuffanelli, 1964; Maddock, 1965; Nobrege *et al*, 1966; Rowell, 1968; Kurland *et al*, 1969). For instance, an average of 5 new cases was diagnosed annually in this unit over the past 15½-years, whereas in the United States, Larson (1961) and Dubois and Tuffanelli (1964) collected 10 to 40 cases per year. The local incidence, however, is on the increase (Fig. 1) and much of the recent case discoveries is attributed to the general medical awareness of this disease, the improved laboratory facilities and the availability of various immunological tests.

Predominance of the female sex ratio—(8:1) found in this and other series is well known and led Buch and Rowell (1963) to postulate a hypothesis that S.L.E. is restricted to a subpopulation characterised by a specific genotype involving three dominant X-linked alleles.

The Chinese were more affected by this condition than the other ethnic groups in Singapore. Although Indian and Malay cases (Srivasta *et al*, 1965) have been described, their incidence has not been established. Racial pigmentation plays no part in S.L.E. (Dubois, 1966; Kurland *et al*, 1969) although in one earlier survey, the Caucasians were reported to be less affected than the coloured races (Puerto Ricans and Negroes) (Siegel *et al*, 1962). Another explanation was the racial variation in the normal serum gammaglobulins (Siegel *et al*, 1962) or immunoglobulins (Tay and Khoo, 1970).

Compared with the western patients, the age of onset in our cases is earlier, reflecting the younger age population in Singapore, half of which is under the age of 20. Forty percent of our cases were in the second decade, and thirty percent in the next decade, whereas the western series are evenly distributed over the second, third and fourth decades. As shown in Fig. 4, there are differences in major clinical presentation and systemic involvement between our series and other western series, using Dubois' data (1964) for this purpose.

Fever was the commonest presentation in our cases (75%) and it was the initial symptom in 40%. Temperature curves may be of any types, varying from low grade evening febrile episodes to continuous or remittent fluctuations to occasional daily spikes. Prolonged fever is often associated with chills, malaise and weight loss, and in the absence of obvious joint lesion and/or skin rash, such cases are commonly investigated as P.U.O. (Pyrexia of Unknown Origin). Even though the diagnosis of S.L.E. is clinched, the origin of pyrexia should still be traced as these patients are vulnerable to various other infections due to the depressed immunological state. Without prior investigations, premature administration of steroids could cause dissemination of pre-existing sepsis and a rapid fatal outcome.

Cutaneous lesions of all categories were observed in 68·75%. In 45% of this study, skin involvement was the initial presentation along with others. Thus in a recent dermatological survey of 62 cases [Tay, 1969; Tay, 1970 (a)], over 30 different types of cutaneous disorder were described. The comparatively higher incidence of photosensitive and "butterfly" rash and the rarity of Raynaud's phenomenon were possibly due to the tropical sunlight and warmth in this region. Another interesting observation was the small numbers of cases with hyperkeratotic lesions and psoriasiform rash (3% to 5%). These lesions were frequently found in Hong Kong Chinese (Wong, 1969) but extremely uncommon elsewhere. Wong postulated that both these lesions are genetically determined especially for the Chinese.

Arthritic involvement, the commonest manifestations of S.L.E. in Westerns (Friedman *et al*, 1953; Slocumb, 1940; Harvey *et al*, 1954; Larson, 1961; Dubois and Tuffanelli, 1964) was found in 65% of this series. Polyarthropathy, usually symmetrical and involving the smaller joints, was often attended by arthralgia, tissue swelling, limitation of movement and fever. However, larger joints are not totally spared, and sometimes, subcutaneous nodules may appear. Most workers have noted the discrepancy between the arthritic symptoms and the paucity of physical signs as joint deformities in S.L.E. are uncommon (15% in our series). Thus in the early stage of joint involvement, cases may be diagnosed as fibrositis, polymyositis, rheumatic fever, and a vast majority with interphalangeal arthralgia and spindling was

labelled as rheumatoid arthritis (40%). Rheumatoid-like arthritis has been observed to progress to multiple system disorders of S.L.E. years later and this type of disease should be distinguished from the classical Rheumatoid arthritis with positive L.E. cells which is not S.L.E. (Friedman *et al*, 1957). It must be remembered that L.E. Phenomenon has also been found in many other autoimmune diseases besides S.L.E. (MacKay and Burnet, 1963).

The importance of renal damage in S.L.E. has been recently recognised because of its natural history. With or without treatment, most patients ultimately succumb to renal failure. However, the incidence of renal involvement is variable due to the inconsistence of criteria used. Based mainly on urinalysis (Shern and Pirofsky, 1952; Harvey *et al*, 1954; Jessar *et al*, 1953) the reported incidence was 60%, whereas, based on the clinical picture and renal histology, the incidence varied from 46% to 87% (Meuhrcke *et al*, 1957; Larson, 1962; Soffer *et al*, 1961; Pollack and Pirani, 1964; Dubois and Tuffanelli, 1964; Zweiman *et al*, 1968; Pollack and Pirani, 1969). In this series based on urinalysis, clinical and histological picture, 44% were found to have some degree of renal involvement. Nephrotic syndrome was found in 22·5% and 9% developed in renal failure. Nearly half of our cases had renal biopsies and of these, the majority (63%) showed focal glomerulonephritis and 25·4% had membranous glomerulonephropathies. In most instances, broad clinicopathological correlations are lacking (Comerford and Cohen, 1967; Zweiman *et al*, 1968; Pollack and Pirani, 1969); however serial renal biopsies are useful to gauge the progression of renal damage in individual cases. Cardiac lesions in S.L.E. have been extensively reported. Since the classical description by Libman and Sacks (1924), the reported incidence ranged from 52% to 89% (Armas-Crus *et al*, 1958; Brigden *et al*, 1960; Jessar *et al*, 1953; Harvey *et al*, 1954; Shearn, 1959). The changes include pericarditis, pericardial effusion, myocardial damage, mural (Libman-Sacks) endocarditis, systemic hypertension and cardiomegaly, congestive cardiac failure, conduction defects and various electrocardiographic abnormalities. Although 30% of our patients had some cardiac involvement, the lesions, except for one case of Libman-Sacks endocarditis, were rather nonspecific. Thus besides the primary cardiac damage, the cardiac signs and symptoms may due to other factors like associated vascular, renal or pulmonary diseases.

Neurological involvement in S.L.E. patients is found in increasing frequency as more cases survive longer now than during the pre-steroid era. Incidences reported were 25% to 75% (Harvey *et al*, 1954; Clark and Bailey, 1956; O'Connor, 1959; Johnson, 1962; Dubois, 1966). This particular aspect of S.L.E. in Singapore has been recently reviewed (Tay, 1971), and the local incidence was found to be low (28·7%). As in most studies, psychological disturbance was the commonest presentation and symptoms varied from mild neurosis to frank psychosis. Cares and Weinberg (1958) and Dubois (1966) attributed the mental changes, in most instances, to cerebral angitis of S.L.E. They stressed that the usual mistake was to blame corticosteroids and stop the drug. On the contrary, we have found that steroid psychosis is by no means rare in our cases. By withdrawing the steroid and later, re-exposing the patient to the same drug, one can, by observing the mental status of the patient, conclude whether the steroid is the offending agent. The psychosis of S.L.E., on the other hand, responds only to large doses of corticosteroids. Although central and peripheral nervous systems are rarely involved in S.L.E. (15% and 7·5% respectively in our series), death from neurological complications ranked first or second in some large series (Dubois and Tuffanelli, 1964; Klemperer, 1941).

Clinical manifestations of respiratory lesions in S.L.E. are protean and nonspecific. Radiological and pathological changes are equally variable (Garland and Sisson, 1954; Gould and Davies, 1955; Moersch *et al*, 1956). The reported incidence varied from 20% to 74%. They commonly presented as pleuritis, pleural effusion, patchy or lobar pneumonia or radiologically as pulmonary infiltration and may simulate common diseases such as pulmonary tuberculosis, bacterial or fungal pneumonitis or pulmonary neoplasms. The latter conditions, however, are not uncommonly found in S.L.E. patients and must be first excluded prior to steroid treatment.

Lymphadenopathy, first described in S.L.E. by Kaposi (1872) was recorded in one-third to one-half of some series (Harvey *et al*, 1954; Moore *et al*, 1956; Larson, 1961; Dubois and Tuffanelli, 1964) but is rare in our patients. Lymph gland enlargement is usually generalised and histological changes varied from sinus hyperplasia to haematoxylin body formations.

In the present series, a lower incidence of eye, gastrointestinal tract, muscle and bone involvements were recorded. Lack of strict criteria in most series explains the wide variation in incidence of each category.

Laboratory findings in our series were, by and large, not dissimilar to those found in western centres. Thus the majority of the patients were

anaemic and leucopenic with raised E.S.R. and hyperglobulinaemia. Five cases presented with thrombocytopenia purpura and nine with haemolytic anaemia. Antinuclear antibody factor (ANF) was found in three-quarter of the cases and L.E. cells was positive in 69%.

A steroid agent was the main drug used for the treatment of all our cases. It was given parentally or orally in dividing doses according to the state of activity and the body weight. The mechanisms of action of this drug in S.L.E. are many and complex. Clinical response is assessed by the quick return of temperature to normal, the relief of joint symptoms, and other systemic conditions, the lowering of E.S.R., and the rise of haemoglobin and body weight, and the disappearance of L.E. or A.N.F. (Fig. 7). Some cases, however, do not respond to this drug. Side-effects of steroids are numerous and are sometimes lethal (Table III). Alternatively, Cyclophosphamide, a cytotoxic drug was exhibited (9 cases) and this often proved useful when corticosteroid fails. Following the reports of serious eye damage (Hemkind and Rothfield, 1963), oral chloroquine was not used in all our patients. Retinal damage developed in 4 cases previously treated with these drugs for 3 to 5 years.

The prognosis and mortality rate of this series are not dissimilar to those reported from elsewhere (Merrell and Shulman, 1955; Kellum and Haresick, 1963; Dubois and Tuffanelli, 1964). The survival rates of our cases appear to be lower because of the shorter follow-up period in the majority of the cases.

Uraemia, septicaemia and neurological complications were the principle causes of death in this and other series, and thus such conditions should be frequently searched and treated as early as they arise.

Ill-effects of pregnancy on the course of S.L.E. are well known (Madsen and Anderson, 1961; Donaldson and de Alvarez, 1962; Dubois, 1966). In this series, 8 cases were precipitated by pregnancies, of which one perished after two stormy weeks.

Drug-induced Lupus syndrome has recently been described (Alarcon-Segovia, 1969) and many drugs have been implicated. Solar damage and certain viruses too (Kawano *et al*, 1969) were also suspected as aetiological agents, but as far as we known, no definite causes have yet been found for this systemic disorder.

SUMMARY

Eighty cases of S.L.E. found at one Medical Unit in Singapore over the past 15½-years are analysed. The majority of the cases are Chinese females in the second or third decades. Common presentating features are: Fever (75%), skin rash (68·75%), joint lesions (65%), renal damage (44%) and various other systemic involvements. A comparison of this series with other large western studies revealed a number of significant differences in the incidence and the clinical presentations. Thus, in the present series, a lower incidence of joint, nervous, respiratory and gastrointestinal involvement is recorded. Lymphadenopathy too is rare. However, "butterfly" and photosensitive rash, psoriasiform and hyperkeratotic skin lesions, anaemia and hyperglobulinaemia seem to be more evident in the present study.

Most cases respond to steroid therapy and 9 required Cyclophosphamide because of the adverse effects of steroids.

The mortality rate and long-term prognosis are similar to those reported elsewhere and the usual causes of death in this and other series are uraemia, septicaemia and neurological complications.

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