capacity. The receptive relaxation of the stomach may be abolished by vagotomy (Olbe and Jackson, 1963; Weisbrodt *et al.*, 1969).

Rapid gastric emptying may lead to acute distension of the jejunum or rapid intestinal transit of food, both of which may lead to postprandial diarrhoea. On these grounds, however, it is difficult to explain episodic diarrhoea.

Whatever may be the cause of the altered pattern of emptying after operation, it is conceivable that an attempt to retain more normal gastric emptying by modification of operative technique in some or all patients might reduce the incidence of troublesome sequelae. Recent reports show that this has been achieved by the use of highly selective vagotomy without a drainage procedure (Humphrey *et al.*, 1972; Johnston *et al.*, 1972).

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Cyclophosphamide in Treatment of Systemic Lupus Erythematosus: 7 Years' Experience

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Summary

This paper describes our experience with cyclophosphamide in the treatment of systemic lupus erythematosus. Since 1965 42 such patients have been treated either singly with cyclophosphamide or in combination with steroid. Serious complications have been rare except for amenorrhoea, which occurred in 14 out of 32 patients within the reproductive period. Our experience suggests that cyclophosphamide has an important, though not primary, part to play in the therapy of this disease.

Introduction

Hill and Scott (1964) first described the successful use of cyclophosphamide in the treatment of a patient with systemic lupus erythematosus (S.L.E.) who had failed to respond to steroids. Their results were confirmed by Seah *et al.* (1966) and Hadidi (1970). Similarly, Cameron *et al.* (1970) successfully treated three cases of lupus nephritis with cyclophosphamide. In experimental studies, Russell and Hicks (1968) showed that cyclophosphamide in appropriate doses decreased the incidence of severe spontaneous autoimmune renal disease from 100% to 6·7% in female (NZB and NZW) F1 hybrid mice. It appears, therefore, that cyclophosphamide could be a useful drug in the long-term management of S.L.E. We report here our experience with cyclophosphamide in the management of S.L.E. over a seven-year period. The patients originally reported on by Seah *et al.* (1966) are included.

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Patients and Methods

Forty-two patients were studied. All fulfilled the criteria for S.L.E. as proposed by Dubois (1966). Thirty-seven patients were female and five were male, again showing the preponderance of females over males. Age at onset varied from 15 to 62 years, but was mostly (71% of cases) between 15 and 30 years. A positive L.E. phenomenon was found in 83%, hypergammaglobulinaemia in 80%, and a raised E.S.R. (more than 40 mm in one hour) in 85% of the patients. Fifty-five per cent, were anaemic (haemoglobin less than 10 g/100 ml), 30% had thrombocytopenia (platelets less than 100,000/mm^3), and 25% had leucopenia (W.B.C. less than 4,000/mm^3). Abnormalities in the urine were found in 77% of the patients, and six presented with the features of classical nephrotic syndrome. Altogether 40 renal biopsies were carried out in 31 patients.

All the patients were admitted to the medical unit at Thomson Road General Hospital. Biochemical tests were carried out as described previously (Seah *et al.*, 1966). Patients with severe constitutional symptoms were given prednisolone 60-30 mg daily, and those with minor systemic disturbances were started on prednisolone 15 mg a day. As soon as improvement occurred the dose of prednisolone was gradually decreased and cyclophosphamide was instituted. Initially this was given intravenously as a single weekly dose of 400 mg, but after discharge oral tablets were substituted, the dosage being 100 mg four times a week. All patients reported regularly to the follow-up clinic and cyclophosphamide was continued unless the total white cell count fell below 3,000/mm,^{3}

when the drug was stopped for one week. Treatment was terminated when severe side effects occurred. Small doses of steroids were maintained in some cases. All biochemical tests were repeated at six-monthly intervals.

Results

The period of treatment after initiation of cyclophosphamide therapy extended from six to 84 months, with an average follow-up period of 34 months. The response to treatment was rated as (1) very good—complete remission of clinical and biochemical abnormalities; (2) good—minimal clinical and/or biochemical abnormalities but patients able to lead a normal life; and (3) poor—minimal or no improvement, with patients leading a restricted life.

The therapeutic response is summarized in table I. There were six deaths in the series, two from renal failure, three from cerebral involvement, and one from cryptococcal meningitis with terminal uraemia.

TABLE I—*Therapeutic Response of Patients at Various Times after Starting Treatment*

	6 Months	12 Months	Present
Very good	7	15	16
Good	26	20	12
Poor	9	4	5
Death	—	1	5
Total patients	42	40	38

TABLE II—*Classification of Initial Renal Biopsy Specimens in S.L.E. (according to Pollak and Pirani; Dubois, 1966)*

Grade		No. of Patients
I	Normal	2
II	Lupus glomerulitis. Mild local and focal basement membrane thickening and proliferative changes	10
III	Lupus glomerulonephritis. More severe involvement of glomeruli associated with tubular and interstitial tissue abnormalities	19

At the time of writing we were able to stop treatment in 17 patients. Nine were on a weekly dose of 200-400 mg cyclophosphamide, and five, in addition to cyclosphosphamide, were receiving prednisolone 2·5-5 mg daily. The remaining seven patients, who had poor response, were on cyclophosphamide 400 mg a week and prednisolone 30 mg daily.

RENAL ASPECT

Since the principal cause of death in S.L.E. is renal failure and at least 75% of patients have renal changes at necropsy (Pollak *et al.*, 1964; Wilson *et al.*, 1963) renal biopsies formed an important part of this study. Thirty-one patients who had clinical evidence of renal involvement in the form of either microscopical haematuria or significant proteinuria, or both, or gave their consent were biopsied before treatment. Seven of these patients had repeat biopsies about a year after treatment. The results were categorized by one of us (E.P.C.T.) according to the criteria of Pollak and Pirani (Dubois, 1966) and are shown in table II. Of the seven patients who had repeat biopsies two showed improvement and there was no change in the other five. An interesting feature was that in spite of the persistent histological abnormalities in these five patients three did not have proteinuria or haematuria. It appears, therefore, that renal biopsy specimens taken at various periods during therapy do not correlate very well with the clinical status of the patients. The clinical outcome in relation to the urinary and biopsy findings is shown in tables III and IV.

COMPLICATIONS OF THERAPY

Serious complications were rare. Eight patients complained of varying degrees of alopecia, but in the majority this was not distressing. Five developed herpes zoster and two contracted tuberculous infection, which responded well to treatment. Two patients had fungal infection of the skin. One patient had gross, painless haematuria, which cleared up spontaneously. One patient had severe leucopenia, which required frequent dosage adjustment.

Menstrual disturbances were, however, common. Out of 32 patients within the reproductive period 14 suffered menstrual disturbances. Although S.L.E. and steroid administration are known to cause such disturbances some of our patients developed amenorrhoea during the quiescent stage of the disease and when they were off steroids. This could be a complication of long-term cyclophosphamide therapy, since Miller *et al.* (1971) described ovarian atrophy in a young girl with severe rheumatoid arthritis treated with cyclophosphamide

TABLE III—*Clinical Outcome in Relation to Urinary and Biopsy Findings in Patients who had a Single Biopsy*

Case No.	Blood Urea (mg/100 ml)	Urine Findings				Histological Classification	Result
		R.B.C. (/mm³)	W.B.C. (/mm³)	Cast	Protein		
1	34	Occ.	1-2	Nil	Trace	III	V. Good
2	23	Nil	1-2	Nil	Nil	II	V. Good
3	45	2-3	6-8	Few	+	III	Good
4	20	80-100	6-8	Few	++	III, Nephrotic	V. Good
5	21	2-5	1-2	Nil	+	II	V. Good
6	41	15-20	25-30	Nil	++	III, Nephrotic	V. Good
7	51	6-8	4-6	+	++	III, Nephrotic	Good
8	19	2-5	8-10	Nil	+	III	Died—cerebral involvement
9	15	Nil	2-3	Nil	Trace	II	Good
10	48	5-6	6-8	Few	+	III	Good
11	36	Nil	Occ.	Nil	Nil	II	Died—cerebral involvement
12	31	2-3	3-5	Nil	+	I	Died—cerebral involvement
13	23	Occ.	2-3	Nil	Trace	II	V. Good
14	18	20-30	4-6	Few	Trace	III	V. Good
15	37	30-40	2-3	Nil	Trace	III	V. Good
16	26	15-20	5-6	+	++	III, Nephrotic	Good
17	39	3-4	7-8	Nil	+	III	Poor
18	40	1-2	15-20	Nil	Trace	I	V. Good
19	31	20-25	40-60	+	++	III, Nephrotic	Poor
20	24	6-10	3-4	Nil	+	III	Died—uraemia
21	39	Occ.	3-4	Nil	++	III, Nephrotic	Poor
22	22	4-5	20-30	Nil	+	III	Good
23	56	30-40	8-10	Nil	+	III	Good
24	40	15-30	2-3	Few	++	III	Poor

TABLE IV—*Clinical Outcome in Relation to Urinary Content and Findings on Repeat Biopsy*

Case No.	Blood Urea (mg/100 ml)	Urinary Findings: R.B.C. (/mm³)	Urinary Findings: W.B.C. (/mm³)	Urinary Findings: Protein	Histological Classification	Interval Between Biopsies	Results
25	19	6-8	8-10	++	II	12 Months	V. Good
	24	3-4	Occ.	Trace	II		
26	15	1-2	2-3	Nil	II	20 Months	Defaulted
	19	Occ.	Occ.	Trace	II		Died—uraemia
27	32	25-45	5-6	+	II	18 Months	Died—cryptococcal meningitis
	15	2-4	3-4	+	II		
28	24	10-20	2-3	+	II	12 Months	V. Good
	24	5-7	Occ.	+	II	12 Months	
	17	2-3	Occ.	+	I		
29	28	15-30	6-10	+	III	20 Months	Good
	28	6-8	1-2	+	III		
30	15	Occ.	8-10	Trace	II	16 Months	V. Good
	19	Occ.	2-3	Trace	II		
31	30	3-4	1-2	+	III	20 Months	V. Good
	24	2-4	Occ.	+	II		

for two years. Amenorrhoea also occurred in some patients with the nephrotic syndrome treated with cyclophosphamide, as reported previously (Feng, 1972).

Discussion

Since 1952, when the use of corticotrophin and cortisone in S.L.E. was first described (Dubois *et al.*, 1952; Soffer and Bader, 1952), steroids have remained the cornerstone of therapy in this disease. Different regimens have been used (Pollak *et al.*, 1961; Zweiman *et al.*, 1968). In a disease which is so protean in its manifestation and variable in its course and prognosis (Rowell, 1969) it would be difficult to compare the efficacy of different drugs or even different treatment schedules of any one drug. Nevertheless, we believe we have shown that cyclophosphamide is a useful alternative drug and could be used singly in patients who cannot tolerate steroids or those with severe steroid side effects. Similarly, it could be used as an adjunct to low-dosage steroids. With our present treatment regimen more than 80% of the patients were leading normal lives. Renal deaths are rare and we agree with Larson (1961) and Dubois (1966) that renal impairment, though an important cause of mortality in S.L.E., is not necessarily a cause for immediate concern.

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Systemic Lupus Erythematosus Syndrome Induced by Practolol

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Summary

Three patients with angina pectoris treated with practolol in varying doses developed a syndrome of arthralgia, particularly of the small joints of the hands, rash, fever, a raised E.S.R., and positive tests for lupus erythematosus (L.E.) cells and antinuclear antibody. The syndrome responded partly to withdrawal of the drug, but steroids were required to produce adequate symptomatic improvement. These disease features suggest that this is an example of drug-induced systemic lupus erythematosus (S.L.E.). The impaired ability of lymphocytes from these patients to transform in vitro indicates a testable hypothesis for the pathogenesis of the syndrome.

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Introduction

Many drugs may induce a syndrome similar to systemic lupus erythematosus (S.L.E.) in susceptible patients (Alarcon-Segovia, 1969). Drugs used for the treatment of cardiovascular disorders have been particularly implicated, and of these procainamide is prominent (Ladd, 1962; Fakhro *et al.*, 1967). We report on three patients who developed an S.L.E. syndrome while being treated with an adrenergic beta-blocking agent, practolol, for angina pectoris. We also describe our attempts to elucidate the mechanism of the lupus syndrome induced by practolol. These suggest the possibility that practolol therapy may interfere with lymphocyte triggering and thereby induce aberrations in the immunological reactivity of patients receiving the drug.