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RESULTS OF THYMECTOMY IN SYSTEMIC LUPUS ERYTHEMATOSUS: OBSERVATIONS ON CLINICAL COURSE AND SEROLOGICAL REACTIONS

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SUMMARY

1. Thymectomy was performed as a treatment of severe systemic lupus erythematosus in three females aged 20, 14 and 56 years: two of these had not received corticosteroids pre-operatively.

2. There was no immediate improvement post-operatively, and full treatment with corticosteroids was required in each case.

3. All three patients remained in moderate to good health, with few hospital admissions over observation periods of 1–3 years.

4. In two cases negative Coombs and antithyroglobulin tests became transiently positive after thymectomy.

5. Thymectomy had no effect on the titre of antinuclear autoantibody, which remained high throughout the period of observation in all patients.

6. The post-operative fall in titre of anticytoplasmic antibody (AICF reaction) was considered to be an effect of prednisolone.

7. Thymectomy as a treatment of autoimmune diseases other than myasthenia gravis may be effective only in childhood when any proliferative process involving lymphoid cells would be predominantly active in the thymus and thymectomy could be expected to remove a highly significant fraction of that activity.

This paper describes the results of surgical thymectomy in three patients with systemic lupus erythematosus (SLE) observed over periods of 1–3 years. The rationale for thymectomy in SLE was as follows. First, the thymus is an important site of normal lymphocyte production in early life (Miller, 1964) and, by inference, may be the source of the abnormal lymphocytes which mediate autoimmune reactions. Second, there are histological lesions in the thymus in human autoimmune disease (Mackay & Goldstein, 1965). Third, thymectomy is effective treatment in certain autoimmune diseases in man, including myas-

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thenia gravis and autoimmune haemolytic anaemia in infancy (see 'Discussion'). Fourth, the thymus is concerned with the development of autoimmune disease in New Zealand black (NZB) mice (Howie & Helyer, 1965).

METHODS

The haematological and clinical biochemical procedures used as indices of 'activity' of lupus erythematosus included the level of haemoglobin and serum iron, the lymphocyte count, and the erythrocyte sedimentation rate (ESR, Westergren). These were performed by standard methods. Other laboratory procedures included estimation of serum albumin and γ-globulin levels, LE cell preparations, estimation of antinuclear factor (ANF), 'autoimmune' complement fixation (AICF) tests for anticytoplasmic antibody with human liver and kidney homogenates, tanned cell haemagglutination for antithyroglobulin titre, the Coombs test, and the sensitized sheep cell agglutination test for rheumatoid factor: the methods were as cited by Mackay & Wood (1962) and Mackay & Ritchie (1965). Human leucocytes were used as the source of cell nuclei in the test for antinuclear factor (Hasker *et al.*, 1965): this was titrated by testing serum serially diluted in phosphate buffered saline, pH 7·3, with the end-point being the dilution of serum at which most of the nuclei in duplicate preparations failed to show fluorescence (Smalley & Mackay, 1965). The method of titration of serum complement was that described by Dacie & Lewis (1963).

CASE REPORTS

Case 1

R.A., a female aged 20 years, developed SLE in October 1962. The disease was classical, except for the absence of nephritis, and she suffered relapses coincident with withdrawal of corticosteroids (Mackay, Goldstein & McConchie, 1963). Pneumomediastinography (Hare & Mackay, 1963) revealed a 'small' thymus, with a cross-sectional area of 2·3 cm^2. Thymectomy was performed in September 1962. The thymus weighed 5·0 g and histologically there was atrophy, absence of cortex, and spindle-epithelial cell aggregates and germinal centre-like structures in the medulla. There was no immediate improvement post-operatively, and an increment of corticosteroid dosage from 10 to 60 mg daily was required 14 days after thymectomy. The initial laboratory findings and progress for 10 months after thymectomy were reported by Mackay *et al.* (1963).

In 1963, in September, she was well and had resumed full employment; she was taking 15 mg of prednisolone daily. In 1964, in January, she had a transient fever and pneumonitis; in July the prednisolone dosage was reduced to 10 mg daily; in October she complained that she had had severe attacks of migratory polyarthritis and blue numb fingers throughout the winter, but she continued at work. In 1965 she continued to take 10 mg of prednisolone daily; in April she had severe mental depression after a spontaneous abortion. In August she had an acute respiratory tract infection associated with fever, generalized muscle pains and hypotension suggestive of adrenal insufficiency; she improved rapidly after treatment with hydrocortisone intravenously for 2 days, and thereafter she resumed her maintenance dosage of prednisolone of 10 mg daily.

The results of serial laboratory estimations are shown in Tables 1 and 2, and Fig. 1. Three years after thymectomy there was mild anaemia (haemoglobin 11·6 g/100 ml), lymphopenia (270 lymphocytes/mm^3) and a raised ESR of 65 mm/hr. The LE cell test remained positive throughout and the titre of antinuclear factor remained high and unchanged between 1/300 and 1/500. The anticytoplasmic (AICF) titre remained elevated after thymectomy but fell after the increase in dosage of prednisolone. The antithyroglobulin titre became transiently positive, to a titre of 1/1280, 6 months after thymectomy.

Summary. A female aged 20 years with SLE was treated by thymectomy in 1962. An increment of prednisolone was required 2 weeks post-operatively, and she eventually received a maintenance dosage of prednisolone similar to the pre-operative level. There was no change in the titre of antinuclear reactions after thymectomy.

Case 2

B.E., a female aged 14 years, presented in June 1963 with SLE of 6 weeks duration. The family history was noteworthy: her mother had had SLE from which she died after an illness lasting 3½ years, her father suffered from chronic ulcerative colitis, a paternal aunt suffered from chronic rheumatism, tuberculosis, and suspected SLE and her only sibling, an older sister, had membranous glomerulonephritis with a negative LE cell test. The clinical manifestations in B.E. were painful swollen joints especially the ankles and fingers, a lupus rash on the face and hands, fever, tachycardia, pleurisy and proteinuria. The blood pressure was 110/75 mmHg. The electrocardiograph showed widespread inversion of T-waves interpreted as myocarditis. Pneumomediastinography showed a 'small' thymus, the cross-sectional area being 2·0 cm^2.

Laboratory investigations. There was anaemia, neutropenia, lymphopenia, hypoproteinaemia and a highly elevated ESR (Table 1). The urinary protein excretion ranged from 2 to 4 g daily, the urine contained numerous erythrocytes, leucocytes and casts, the blood urea ranged from 70 to 80 mg/100 ml and the creatinine clearance from 70 to 95 ml/min; a renal biopsy confirmed the diagnosis of lupus nephritis, there being thickening of the basement membrane with fibrinoid necrosis and cellular proliferation within the tufts. The LE cell preparation showed numerous LE cells but an ANF titre was not performed; the AICF titre was weakly positive at 1/4–1/8, the titre for rheumatoid factor was 1/256, for antithyroglobulin 1/320, and the titre of serum complement was low at 1/2–1/3 (Table 2).

Progress. The temperature ranged from 37 to 38°C and symptoms persisted for 3 weeks whilst no specific treatment was given. Thymectomy was then performed uneventfully in July 1963. The thymus weighed 7·1 g and microscopically there was loss of cortex and the medulla contained germinal centres and accumulations of spindle-epithelial cells (Mackay & de Gail, 1963; Burnet & Mackay, 1965).

After thymectomy there was remission of arthritis but the temperature ranged between 38 and 39°C; the facial rash persisted, there was cardiac failure with triple rhythm, and there was no change in the laboratory indices (Tables 1 and 2). After 22 days it was considered necessary to give prednisolone. The initial dosage of 40 mg daily produced an immediate fall in temperature to 37°C and overall improvement, although the blood pressure rose gradually to 150/100 mmHg. Seven weeks after thymectomy she developed generalized oedema followed by a series of grand mal seizures and Jacksonian fits; these symptoms were controlled by diuretics and increasing the dosage of prednisolone to 80 mg daily. A renal biopsy in October 1963 showed 'active' glomerulitis with increase in the degree of thickening of the basement membrane.

In 1964, in January, there were further episodes of polyarthritis and oedema. Hence azathioprine, 175 mg/day, was added to a maintenance dose of prednisolone of 45 mg daily: thereafter the dose of prednisolone was progressively reduced to 20 mg daily, and she remained in remission except for occasional episodes of polyarthritis. In July she had an acute febrile illness with headache; a renal biopsy showed 'active' glomerular lesions consistent with quiescence. In 1965, in January and February, she had two episodes of innominate vein thrombosis, and in April pneumonia after an upper respiratory tract infection. In July she had painful swollen joints: the dosage of prednisolone was increased temporarily from 20 to 30 mg daily, and the maintenance dosage of azathioprine was kept at 150 mg daily. Her general health was otherwise moderately good and she was able to do light work at home. The blood pressure had remained at 150/90 with standard hypotensive treatment.

The results of serial laboratory estimations are recorded in Tables 1 and 2, and Fig. 1: these showed no change after thymectomy, but reflected the clinical improvement which occurred

after prednisolone was given. Two years after thymectomy there was mild anaemia, lymphopenia and persisting elevation of the ESR. However renal function had improved in that proteinuria had decreased from 2·0–4·0 to 0·5 g/day, the level of serum albumin had risen from 1·7 to 2·4 g/100 ml, the urinary sediment was unremarkable, and the level of blood urea had fallen from 70–80 to 25–40 mg/100 ml: this improvement could well be attributed to sustained treatment with prednisolone. The LE cell test remained positive throughout; the titre of ANF was not determined pre-thymectomy, but remained high (1/2000–1/1000) over the period of 6–24 months after thymectomy. There were no significant changes in titre of anticytoplasmic antibody, antithyroglobulin, and rheumatoid factor. The rise of 1/3–1/32 in complement titre was related to treatment with prednisolone.

Summary. A female aged 14 years with a strong family history had severe SLE and glomerulonephritis. Thymectomy did not initiate improvement, and she required maintenance treatment with prednisolone and later azathioprine. She maintained fair health but had occasional relapses. The LE cell test remained positive and the titre of ANF remained elevated at 1/2000; a low titre of serum complement rose only after prednisolone was given.

Case 3

M.T., a female aged 56 years, had thyrotoxicosis in 1931, intermittent polyarthritis with painful swollen hands since 1937, muscle cramps since 1962 and a ruptured biceps tendon in January 1964. She presented in July 1964 with fever, abdominal discomfort, painful swollen joints, oral ulceration and slight proteinuria. Myocardial disease was diagnosed on the basis of a raised jugular venous pressure to 4 cm and abnormalities of the S-T segment on electrocardiography; the transverse diameter of the heart by radiography was 15·0 cm. Pneumomediastinography showed a 'small' thymus with a cross-sectional area of 3·7 cm^2.

Laboratory investigations. There was anaemia, neutropenia, lymphopenia, a raised ESR of 79 mm/hr, and hypoproteinaemia, the serum albumin level being 2·3 g/100 ml (Table 1). There was no evidence of lupus nephritis. The LE cell test was positive and the titre of ANF ranged from 1/3000 to 1/5000; the AICF titre was 1/32; the other autoimmune serological tests were negative.

Progress. Her symptoms persisted for 4 weeks whilst no specific treatment was given. Thymectomy was then performed uneventfully in September 1964. The thymus weighed only 5·0 g and microscopically there was atrophy, absence of cortex, and in the medulla accumulations of epithelial cells, numerous plasma cells, and one germinal centre on serial section. A thyroid biopsy showed normal thyroid tissue.

After thymectomy she became lethargic and feverish. She developed pericarditis, auricular fibrillation, and increasing cardiac failure; the transverse diameter of the heart increased to 21·5 cm. After 28 days prednisolone was given, initially 60 mg daily for 4 weeks, with reduction to a maintenance dose of 7·5 mg daily over 8 months. In March 1965 she suffered a spontaneous rupture of the left Achilles tendon, in June she was free of symptoms, but in September she complained of arthralgia and aching muscles and the dose of prednisolone was increased from 7·5 to 15 mg daily. The results of serial laboratory estimations are shown in Tables 1 and 2. These showed no change after thymectomy, and thereafter reflected improvement attributable to prednisolone. The LE cell test remained strongly positive; the titre of ANF of 1/3000–1/5000 in the pre-operative and early post-operative tests fell temporarily to 1/800–1/1000 after prednisolone was given. The AICF titre remained elevated at 1/32 after thymectomy, but became negative when prednisolone was given. It was of interest that 4 weeks after thymectomy the Coombs test and antithyroglobulin test became transiently positive, the latter to a titre of 1/1280.

Summary. A female aged 56 years with SLE was treated by thymectomy in 1964. She did not improve in the early post-operative period and required maintenance treatment

TABLE 1. Indices of disease activity after thymectomy in three patients with SLE*

Time (months)	Days in hospital *per annum* pre- and post-thymectomy			Dosage of prednisolone (mg/day)			Laboratory indices																	
							Haemoglobin (g/100 ml)			Serum iron (μg/100 ml)			Lymphocytes (No./mm³)			ESR (Westergren (mm/hr)			Serum albumin (g/100 ml)			Serum γ-globulin (g/100 ml)		
	1†	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Pre-thymectomy	37	21	37	10–15	Nil	Nil	8·9	10·3	10·3	52–69	65–76	52	440	510	620	79	115	106	2·8	1·7	2·3	1·6	0·7	1·8
Post-thymectomy																								
1‡				10–45	0–40	0–60	9·7	11·1	10·3	96	60	40	1120	1840	270	120	100	88	3·0	1·6	1·8	1·2	0·8	1·7
3				20	40	30	12·7	10·2	12·8	175	208	140	1200	600	480	15	120	51	3·7	1·7	2·7	1·5	0·6	1·0
6				20	60	15	13·0	9·6	14·6	185	108	126	700	1140	836	24	66	20	3·6	1·5	3·4	2·1	0·6	0·9
12	59	278	93	15	20	15	11·8	12·1	10·2	130	72	53	1200	832	381	45	72	74	3·9	1·9	3·5	1·4	0·8	1·7
24	4	75		10	30		12·4	12·1		96	92		600	855		n.t.	59		3·7	2·4		1·6	1·1	
36	11			15			11·6			75			270			65			2·7			1·3		

* Case 1 observed for 3 years, Case 2 for 2 years, Case 3 for 1 year.
† Case number.
‡ Prednisolone was given during or at the end of the first month in all cases.
n.t., Not tested.

TABLE 2. Autoantibody reactions after thymectomy in three patients with SLE*

Months after thymectomy	LE cells† in LE cell preparation			Antinuclear (ANF) titre			Anticytoplasmic (AICF) titre			Rheumatoid factor titre			Antithyroglobulin titre			Coombs test			Complement titre¶		
	1‡	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Pre-thymectomy	++	+++	+++	200–300	n.t.	3000–5000	256	8	32	256	256	−ve	−ve	320	−ve	−ve	−ve	−ve	n.t.	3	n.t.
Post-thymectomy																					
1§	+	++	+++	n.t.	n.t.	3000	512	n.t.	32	128	n.t.	n.t.	−ve	n.t.	2500–25000	−ve	n.t.	+ve	n.t.	2	n.t.
3	+	++	+++	n.t.	n.t.	1000	64	n.t.	−ve	n.t.	n.t.	−ve	320	n.t.	250	n.t.	−ve	±ve	n.t.	20	32
6	+++	++	+++	n.t.	2000	800	32	−ve	−ve	−ve	−ve	−ve	1280	−ve	250	−ve	n.t.	−ve	n.t.	30	50
12	+	++	++	300	2000	4000	16	−4	−ve	512	512	−ve	40	−ve	−ve	n.t.	−ve	−ve	30	20	64
24	+	++		300	2000		32	−4		n.t.	−ve		−ve	−ve		n.t.	n.t.		80	32	
36	+++			300			32			−ve			−ve			−ve			16		

* Case 1 observed for 3 years, Case 2 for 2 years, Case 3 for 1 year.
† Ranging from + = scanty to +++ = many.
‡ Case number.
§ Prednisolone was given during or at the end of the first month in all cases.
¶ Normal range 70–150.
n.t., Not tested.

TABLE 3. Results of thymectomy in experimental and human autoimmune disease

Authors	Species	Disease	No. of animals or cases	Time of thymectomy	Effect on disease	Effect on autoantibodies
Holmes & Burnet (1964)	NZB mice	Autoimmune haemolytic anaemia	26 34	1 week 4 weeks	None None	2–3 month delay in onset of positive Coombs test
Howie & Helyer (1965)	NZB mice	Autoimmune haemolytic anaemia	17	Neonatal	None	No observations—high death rate
	NZB–NZW hybrid mice	Lupus nephritis	47	Neonatal	Augmentation	Earlier onset and increased incidence of positive tests
Janković & Isvaneski (1963)	Chickens	Autoallergic encephalomyelitis	7	At hatching	Attenuation	
Simpson (1958)	Human females	Myasthenia gravis*	182	Adult	Remission in 58% versus 36% in non-operated contrast cases	
Schwab (1961)	Human females	Myasthenia gravis*	101	Adult	Remission in 61% versus 21% in non-operated contrast cases	
Henson, Stern & Thompson (1965)	Humans 28 females	Myasthenia gravis*	30	Adult	Remission in 67% versus 31% in non-operated contrast cases	
Osserman & Weiner (1965)	Humans	Myasthenia gravis: no thymoma	25	Adult		43% +ve for muscle antibody pre-thymectomy, 8% +ve post-thymectomy
		Myasthenia gravis: thymoma	12			100% +ve for muscle antibody pre- and post-thymectomy
Various (see Mackay, 1965)	Humans	Erythroid aplasia with thymoma	29	Adult	Lasting remission in four	
(a) Wilmers & Russell (1963) (b) Kariaklis *et al.* (1964)	Human 1 female Human 1 male	Autoimmune haemolytic anaemia	2	Infancy	Complete remission	Coombs test positive to negative
Present cases	Human females	SLE	3	14 years, 20 years, 56 years	Uncertain	No effect on antinuclear antibody

* Cases with thymoma excluded.

with prednisolone. The LE cell test remained positive, and the titre of ANF fell from 1/3000 to 1/800 only after prednisolone was given. There were transiently positive Coombs and antithyroglobulin reactions after thymectomy.

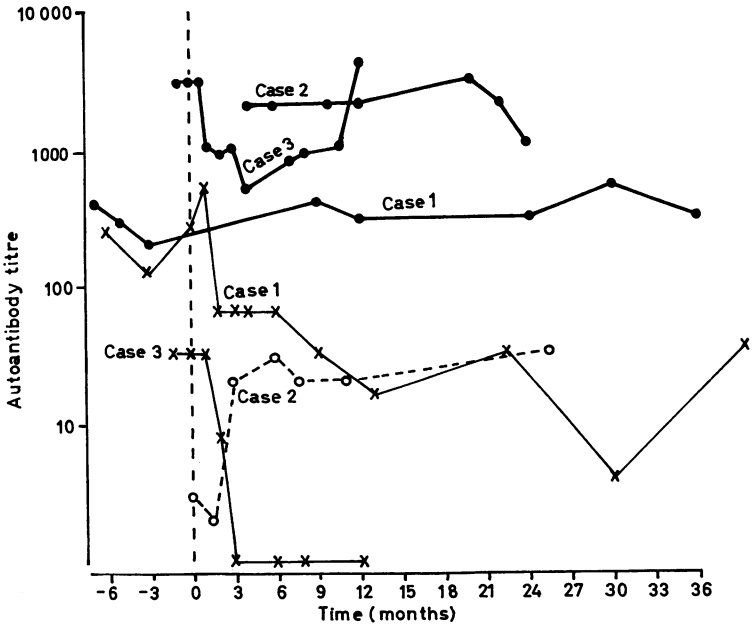

FIG. 1. Results of serial estimations of titre of autoantibodies before and after thymectomy (month zero), for observation periods of approximately 36 months in Case 1, 24 months in Case 2 and 12 months in Case 3. The titre of antinuclear factor is plotted for Cases 1, 2 and 3, of anticytoplasmic antibody (AICF reaction) for Cases 1 and 3, and of complement for Case 2. The sharp changes in titre shortly after month zero coincided with commencement of treatment with prednisolone. ●, Antinuclear factor; ×, anticytoplasmic antibody; ○, complement.

DISCUSSION

In the introduction to this paper we listed the theoretical, histological, therapeutic and experimental considerations which constituted the rationale for thymectomy in the treatment of lupus erythematosus.

Theoretical considerations

The thymus functions essentially in early life as a site of lymphocyte production and as a source of a humoral factor which enables lymphocytes to undergo the normal proliferative response to antigens (Miller, 1964).

Thus on theoretical grounds the thymus might be implicated in autoimmune disease, particularly if the present formulation of thymic function by Burnet (1965) should be correct. It holds that the thymus has two inter-related functions: (i) to induce stem cells reaching the thymus from the bone marrow to differentiate to immunocytes carrying primary

immunological patterns of reactivity, and (ii) to eliminate any such new differentiated cells which carry patterns capable of reacting with antigens present in the thymic environment.

Histological considerations

The thymus in human autoimmune disease shows characteristic alterations. In myasthenia gravis the medulla contains germinal centres and in SLE the medulla contains spindle-epithelial celled masses, occasionally typical germinal centres, plasma cells and numerous cystic Hassall's corpuscles (Burnet & Mackay, 1965; Goldstein & Mackay, 1965). Moreover benign tumours of the thymus—thymomas—are associated with systemic disease processes of autoimmune nature, including myasthenia gravis, bone marrow aplasia, myositis, agammaglobulinaemia and SLE (Mackay, 1965).

It is as yet undecided whether the histological changes in the thymus in autoimmune disease point to the thymus as a source of pathogenic cells or antibody, or whether these changes reflect damage to the thymus as a target organ.

Therapeutic considerations

There is well documented evidence of benefit from thymectomy in (a) myasthenia gravis, as shown by three series in which contrast cases, thymectomized and non-thymectomized, are available (Table 3); and (b) in two infants with autoimmune haemolytic anaemia who were cured by removal of a pathological thymus after standard treatment with corticosteroids and splenectomy had failed (see Mackay & Goldstein, 1965).

On the other hand, there are reports that thymectomy, whether for tumour or for the treatment of myasthenia gravis, has been followed by the occurrence of autoimmune disease, including myasthenia gravis, lupus erythematosus and Hashimoto's disease, which were either not present or not recognized before the operation (see Alarcón-Segovia *et al.*, 1963; Fisher, 1964; Simpson, 1964; Kerr *et al.*, 1965).

Experimental considerations

There are characteristic thymic lesions in murine autoimmune disease. Thus germinal centres and later expanded areas of epithelial proliferation in the medulla appear in NZB mice at 3–6 months of age when the Coombs test converts from negative to positive, but thymic lesions do not bear a consistent relationship to this conversion (Burnet & Holmes, 1964). Holmes & Burnet (1964) found that complete thymectomy in NZB mice, either neonatally or at 4 weeks of age, significantly delayed the onset of the positive Coombs reaction, but most of the surviving mice eventually developed it. On the other hand, Helyer & Howie (1963) found that neonatal thymectomy in NZB and NZB–NZW hybrid mice accelerated the onset and increased the incidence of autoimmune serological reactions and increased the severity of the renal lesions (Table 3).

The observations on our present three patients with SLE treated by thymectomy early in their disease may be summarized as follows. None showed any evidence of benefit in the immediate post-operative period: in fact, their overall condition deteriorated, perhaps as a result of the combined effects of a major surgical procedure and the presence of uncontrolled lupus erythematosus. Thus all three required full treatment with prednisolone within 2–4 weeks of thymectomy, and then showed the expected degree of improvement, and all

continued to receive a maintenance dosage of prednisolone of 10–20 mg daily to prevent exacerbations of their disease. All three patients thereafter remained reasonably well and active over observation periods of 1–3 years, and experienced a progressive decrease in the number of days spent in hospital *per annum*.

There was no change in titre of antinuclear autoantibodies after thymectomy in any of the three patients, as judged by persistence of the positive LE cell phenomenon and the high titre of antinuclear factor. The fall in titre of anticytoplasmic antibody (AICF) reaction) in each case occurred after, and could be explained by, treatment with corticosteroids. It was of interest that after thymectomy there was a transient increase in titre of antithyroglobulin antibody in Cases 1 and 3, and a positive Coombs test in Case 3, suggesting that thymectomy could allow the expression of autoimmune reactivity. There is one other report on the influence of thymectomy on autoantibody reactions in man, this being by Osserman & Weiner (1965) on the incidence of anti-muscle autoantibody before and after thymectomy in cases of myasthenia gravis: after thymectomy the serological reactions with muscle tended to become negative in cases without thymoma, but persisted in cases wherein a thymoma had been present.

Our present experience would indicate that thymectomy in our three patients with severe lupus erythematosus may have had at best an ameliorative effect on the long-term course of the disease, but thymectomy clearly did not induce a sustained remission, nor prevent the need for maintenance treatment with corticosteroid drugs, nor influence the serum titre of the most characteristic autoantibody of lupus erythematosus, the antinuclear autoantibody. Our experience is in contrast with the two reports of striking benefit from thymectomy in autoimmune haemolytic anaemia in infancy, suggesting that thymectomy for human autoimmune diseases other than myasthenia gravis may be most effective in infancy or childhood: at this time any proliferative process involving lymphoid cells would be predominantly active in the thymus and thymectomy could be expected to remove a highly significant fraction of that activity.

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