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IMMUNOLOGICAL STUDIES IN PATIENTS WITH JUVENILE-ONSET MYASTHENIA GRAVIS AND IN THEIR RELATIVES

SARAH BUNDEY, DEBORAH DONIACH AND J. F. SOOTHILL

M.R.C. Clinical Genetics Unit, Institute of Child Health, and Institute of Neurology, and the Departments of Immunology at Middlesex Hospital Medical School and the Institute of Child Health, London

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SUMMARY

Fifty-four patients who developed myasthenia before the age of 20 had an increased incidence of autoantibodies similar to that in adult-onset myasthenics, except that there was no significant increase of striated muscle antibodies. The increase in thyroid antibodies was associated with an increase of thyroid disease.

Their 150 relatives showed a significant increase in thyroid antibodies, in thyroid disease, and a non-significant increase in the five other autoantibodies studied. There was aggregation of thyroid antibodies in some families.

Two patients and one relative were deficient for immunoglobulins (one patient and one father for IgA and one patient for IgM).

These familial immunological abnormalities, which are more marked in the families of patients with juvenile-onset myasthenia than in the families of adult-onset patients, point to a fundamental genetic immunopathogenesis of the disease.

INTRODUCTION

Myasthenia gravis is associated with thymic pathology (Goldstein & Mackay, 1969): 15% have thymomas and 80% of the remainder have hyperplasia with germinal centre formation (Castleman, 1955). Experimental work that links myasthenia and thymic abnormality includes the neuromuscular block associated with thymitis which follows injection of bovine thymus extracts in guinea-pigs (Goldstein, 1968; Kalden *et al.*, 1969), and the normal inhibitory effect of the thymus on neuromuscular transmission (Goldstein & Hofmann, 1969). The increased incidence (30–40%) of antibodies which react with striated muscle and myoepithelial cells has been considered as a marker of autoimmunity involving

Present address: Dr Sarah Bundey, The Moore Clinic, The Johns Hopkins Hospital, Baltimore, Maryland, 21205, U.S.A.

Correspondence: Dr J. F. Soothill, Department of Immunology, Institute of Child Health, 30 Guilford St, London, W.C.1.

the thymus, and there is also an increased incidence of other autoantibodies in myasthenia gravis (Strauss *et al.*, 1965; Osserman & Weiner, 1965).

The thymus plays an important part in the normal development of specific cellular immunity (Miller & Mitchell, 1969), and thymus defects may be associated with abnormalities of immune mechanisms including both immunodeficiency and autoimmunity. It is, therefore, interesting to look for such defects among patients with myasthenia gravis and their relatives. Much that has so far been reported concerns adult patients. The increased incidence (5–6%) of thyroid disease in myasthenics (Simpson, 1968; Hokkanen, 1969) is an example of autoimmune disease involving an organ other than the thymus or muscle, and an increased frequency of other autoimmune disorders has been reported by Simpson (1960), Oosterhuis (1964) and Downes, Greenwood & Wray (1966). The only previous immunological study (Wright & Kerr, 1967) on the relatives of myasthenics, reported no significantly increased incidence of autoantibodies in relatives of adult patients, although some families apparently showed a remarkable aggregation of thyroid antibodies. There are reports of high levels of gammaglobulin in myasthenic patients (Lowenthal & Van Sande, 1956; White & Marshall, 1962; Simpson, 1964; Oosterhuis, Van der Geld & Feltkamp, 1967), but of immunodeficiency only when associated with thymoma. Osserman & Weiner (1965) reported a lower incidence of muscle/thymus antibodies in children with myasthenia than in adults, but there have been no reports on other immunological phenomena in their relatives.

There are both clinical and genetic reasons for considering that childhood myasthenia may be different from the adult disease (Teng & Osserman, 1956; Millichap & Dodge, 1960; Bundey, 1972). It is milder but more persistent; familial cases that have been reported have an early age of onset and infantile myasthenia is as common in males as in females. We have therefore made a family study of childhood myasthenia, including estimations of autoantibodies and immunoglobulins in both patients and in their first degree relatives.

MATERIALS AND METHODS

Patients and controls

Fifty-eight index patients, diagnosed in four hospitals, who had developed symptoms of myasthenia gravis before their 20th birthday (an arbitrarily chosen upper limit for juvenile myasthenia) and who lived within reach of London were selected for the study. Three of the index patients had died and one was abroad, but their relatives were included. Five of the index patients examined had no accessible relatives. Finally, therefore, fifty-four index patients and fifty-three families are in the present study. Five index patients had developed symptoms before the age of two (early-juvenile) and forty-nine had developed symptoms between 4 and 20 years (late-juvenile); for some purposes these two groups have been analysed separately. Most of the patients had developed their symptoms and been diagnosed long before the study, so that many classified by age of onset as juvenile patients were adults at the time of testing. In the fifty-three families, 190 relatives (95% of those living) were seen (Table 1). Where possible blood was taken for autoantibody and immunoglobulin studies. For various reasons very young relatives were not included in the immunological studies, and thus the patients' thirty-one offspring were excluded.

We used as controls for the autoantibody studies nineteen spouses of myasthenic

patients or of their relatives, 146 pregnant women, eighty-seven friends of patients with rheumatoid arthritis, fifty-six schoolgirls and members of school staff, thirty inmates of an old people's home and twenty-eight male technicians and hospital staff. As the control series did not match the patients for age and sex, and owing to the higher incidence of autoantibodies in older people and females χ^2 comparison was made for the two sexes, and in three age groups (7–29, 30–49 and over 50 years) separately. The separate results of χ^2 analyses were combined (Birch, 1964). We also compared results with those found in a separate series of seventy-nine adult myasthenics (aged 25–87) who had been referred consecutively for antibody studies.

The controls for the immunoglobulin studies were the nineteen spouses of myasthenic patients or of their relatives, and forty-four spouses of patients with dystrophia myotonica or their relatives (sera collected in two batches in 1968 and 1970, seventeen of whom were reported by Bundey, Carter & Soothill, 1970).

Clinical

The patients and their relatives were all visited by one of us (S.B.) a medical history was taken, and a standard examination carried out of facial and hand muscles, joints, skin and thyroid gland. The patients' clinical records were also studied.

Immunological

Sera were tested fresh or after storage for short periods at −20°C. The indirect immunofluorescence technique was used for the detection of antibodies to striated muscle, thyroid cytoplasmic, gastric parietal cell, nuclear, smooth muscle and mitochondria. For striated muscle antibodies fresh unfixed rat diaphragm, quadriceps and heart were used. The sera were applied at a dilution of 1 : 10, with wash periods of 1½ hr before and after adding specific anti-IgG FITC conjugate. All positive results were repeated and were titred by repeating the test with increasing serum dilutions. For the other antibodies cryostat sections were made from a composite block of human thyroid, stomach and kidney. For smooth muscle reactions rat stomach was used. Minimum serum dilutions were 1 : 10 and polyvalent antihuman Ig conjugates were used. Thyroid microsomal and mitochondrial antibodies were titrated by complement fixation (CFT) using human thyroid extract and purified rat liver mitochondria respectively. The tanned red cell (TRC) test for thyroglobulin antibodies was done with Burroughs Wellcome thyroglobulin coated sheep cells using a microtitration apparatus. Gastric parietal cell, nuclear and smooth muscle antibodies were titrated by immunofluorescence. The serum immunoglobulins G, A and M were measured by a modification of the gel diffusion method of Mancini, Carbonara & Heremans (1965). Results are expressed as international units per ml. Log transformation of data was made before statistical calculations.

RESULTS

Clinical findings of juvenile-onset patients

The clinical findings have been reported in full elsewhere (Bundey, 1972). The patients' ages when tested ranged from 9 to 46 years with a mean of 28 years. Among the five families of early-juvenile cases one sib out of eight had myasthenia and two sets of parents were first cousins. They had a milder, less fluctuant illness than the late-juvenile patients, who

clinically resembled adult myasthenics. There was an excess of thyroid disease (thyrotoxicosis, hypothyroidism and symptomless goitre) among these late-juvenile patients (*vide infra*) but no increased incidence of other autoimmune disorders. Among their relatives two (a sister and a son) had myasthenia. One set of parents were second cousins.

Forty-five late-juvenile patients (of whom forty-one were tested immunologically) had had a thymectomy, the indications for which were not always apparent or consistent. None had a thymoma. Time lapse since the onset of symptoms, and since thymectomy at

TABLE 1. Juvenile-onset myasthenia gravis: Patients and relatives studied

	Total born live	Dead	Alive and not seen	Seen	Autoantibodies studied	Immunoglobulins studied
Index Patients	58	3	1	54	52	51
Mothers	53*	8	0	45	45	42
Fathers	53*	13	3	37	37	34
Sisters	38	2	1	35	32	30
Brothers	45	5	3	37	33	31
Half-sisters	2	1	0	1	0	0
Half-brothers	6	0	0	6	3	3
Children	31	0	2	29	0	0

* The families of five patients were not included (see text).

TABLE 2. Duration of illness, and interval since thymectomy, at time of study

	Years						
	1–4	5–9	10–14	15–19	20–24	25–29	30+
Duration of illness (fifty-four patients)	8	10	14	4	7	7	4
Interval since thymectomy (forty-one patients)	8	9	8	6	8	2	0

the time of study are shown in Table 2. The three patients who died did so within a year of thymectomy. The average interval since thymectomy of those who survived was 11 years. The thirteen patients who did not undergo thymectomy had developed myasthenia 1–30 years previously. None of the patients or their relatives gave a history of repeated infection, suggestive of immunodeficiency. There was an increased incidence of thyroid disease in the relatives as well as the patients, four parents having thyrotoxicosis. One patient's father had pernicious anaemia.

Autoantibodies

Only three early-onset patients and ten of their relatives were studied. No significant difference was detected in the incidence of autoantibodies or in the immunoglobulin concentrations between the early and late juvenile-onset patients or their relatives, so all the juvenile patients have been considered together for subsequent calculations. The data on

347 of the controls was obtained during previous studies. The remaining nineteen controls were included 'blind' with the test samples in the present study. The prevalence of autoantibodies is similar in these two groups of controls, and in other control series (White & Marshall, 1962; Downes *et al.*, 1966; Dingle *et al.*, 1966) except that two of the nineteen, who were unrelated spouses of patients, had antibodies to striated muscle, an unusually high incidence. For comparisons we used the combined series of 366 controls, of whom 336 had mitochondrial antibodies tested and 106 had muscle antibodies tested. The incidence of these autoantibodies was greater in females and in older age as reported previously (Dingle *et al.*, 1966; Doniach & Roitt, 1969), so the results are presented in groups separated by sex and age at time of testing (Table 3).

TABLE 3. Incidence of autoantibodies in patients with myasthenia gravis of juvenile onset, their relatives, patients with adult onset, and controls

Age at testing	7–29						30–49						> 50			
	Patients		Relatives		Controls		Patients		Relatives		Controls		Relatives		Controls	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Nos tested:	8	26	18	17	12	160	4	16	24	21	12	85	31	38	29	68
Type of antibody																
Striated/cardiac muscle*	1	0	1	1	0/1	1/9	0	2	4	5	0/4	0/35	5	4	0/10	3/47
Antinuclear	1	3	0	0	0	4	0	4	1	0	0	2	2	10	3	4
Mitochondrial†	0	0	0	1	0	0	0	3	0	2	0	1	1	2	0	1
Smooth muscle*	0	1	0	2	0/1	1/9	1	3	2	3	0/4	0/35	6	5	0/10	1/47
Thyroid	2	13	2	5	0	14	1	8	5	11	0	14	11	18	3	21
Gastric parietal cell	0	5	0	3	0	0	0	1	2	3	0	2	2	4	3	12

* Only 106 controls were tested for muscle antibodies.
† Only 336 controls were treated for mitochondrial antibodies.

The results in the separate series of patients with adult-onset myasthenia are similar to those in other series, with significantly increased incidence of antibodies to striated muscle, nuclear, thyroid and gastric parietal cell (Table 4). The results in the patients with juvenile-onset myasthenia show some differences. The incidence of striated muscle antibodies was not significantly greater than in controls and it was significantly less than in adult-onset patients. Antinuclear antibodies were significantly commoner than in controls, but less frequent than in adult-onset patients. In view of the small number positive in any group the significance of comparisons for mitochondrial antibodies is not reported. The incidence of thyroid, gastric and mitochondrial antibodies was similar to the adult-onset cases. There was no association between the presence of autoantibodies and the severity or duration of the myasthenia, nor the length of time following thymectomy.

The incidence of thyroid antibodies in the patients' relatives is greater than in controls.

This increase, in both patients and relatives is significantly related to the incidence of thyroid disease (Table 5), which is probably greater than that of the general population (Kilpatrick *et al.*, 1963). The frequency of high levels of thyroid antibodies is significantly related to the incidence of other antibodies in the relatives ($\chi^2 = 7{\cdot}66, P < 0{\cdot}025$) but not in the patients, perhaps because they were younger. Mitochondrial antibodies were found in six relatives, of whom three parents had high titres (CFT 128–512) without evidence of liver disease. Such high values are very rare in a random population, so this is a remarkable finding. Also, though the numbers positive are perhaps too small for analysis, the incidence of this antibody was greater in the myasthenic families as a whole, than in the control population. Indeed, though not always significant, the incidence of every autoantibody tested is greater

TABLE 4. Incidence of autoantibodies, among juvenile-onset patients, their relatives, and adult-onset patients

Type of antibody	Juvenile-onset myasthenic patients	Their parents, sibs and half-sibs	Controls	Adult-onset myasthenic patients
Striated/cardiac muscle	$\frac{3}{54}$ (5·6%)‡	$\frac{20}{149}$ (13·4%)	$\frac{4}{106}$ (3·8%)	$\frac{32}{79}$ (40·0%)†
Antinuclear	$\frac{8}{54}$ (14·8%)†‡	$\frac{13}{149}$ (8·7%)	$\frac{13}{366}$ (3·5%)	$\frac{31}{79}$ (39·2%)†
Mitochondrial	$\frac{3}{54}$ (5·6%)	$\frac{6}{149}$ (4·0%)	$\frac{2}{336}$ (0·6%)	$\frac{3}{79}$ (3·8%)
Smooth muscle	$\frac{5}{54}$ (9·2%)	$\frac{18}{149}$ (12·1%)	$\frac{2}{106}$ (1·9%)	$\frac{8}{79}$ (10·1%)
Thyroid	$\frac{24}{54}$ (44·4%)†	$\frac{52}{149}$ (34·9%)†	$\frac{52}{366}$ (14·2%)	$\frac{29}{79}$ (36·7%)†
Gastric parietal cell	$\frac{6}{53}$ (11·3%)†	$\frac{14}{147}$ (9·5%)	$\frac{17}{366}$ (4·6%)	$\frac{17}{79}$ (21·5%)†

† Significantly different from controls, when adjusted for sex, and age at testing (see text); $P < 0{\cdot}01$.

‡ Significantly different from adult-onset patients, when adjusted for sex, and age at testing (see text); $P < 0{\cdot}01$.

in both groups of patients and in the relatives as compared to the controls, so there is clearly a general tendency for auto-immune phenomena in these families. It is of interest that striated muscle antibodies were less frequent in the juvenile myasthenics than in their relatives.

There was a high incidence of thyroid antibodies in three families: No. 14 (seven out of nine members positive) No. 16 (five out of eight positive) and No. 41 (five out of five positive). Even if these three families are excluded, the incidence of antithyroid antibodies in the relatives from other families was still significantly greater than in the controls ($\chi^2 = 13{\cdot}6$ $P < 0{\cdot}01$). In these other families, all antibodies appeared to be randomly distributed.

Immunoglobulins

The immunoglobulin estimations were performed during a 7-week period on sera stored for varying lengths of time before analysis. However, there was no correlation between the levels of immunoglobulins G, A or M and length of storage, and the distributions in the three control groups was similar. Also, there was no correlation of immunoglobulin levels with age, and no difference in the results for the two sexes.

The means and standard errors for the controls, patients and relatives are shown in Table 6. The distributions of IgG, IgA or IgM levels for patients and relatives were similar to controls. However, there were two patients and one elderly father with very low levels of individual immunoglobulins—IgA or IgM. The two with IgA deficiency had high levels

TABLE 5. Association of thyroid antibodies with goitre

	Thyroid antibodies			
	High levels*	Low levels	Absent	Total
A Index patients				
Goitre†	4	1	1	6
No goitre	7	12	27	46
Total	11	13	28	52
B First degree relatives				
Goitre‡	5	1	6	12
No goitre	17	30	91	138
Total	22	31	97	150

A, $\chi^2 = 9{\cdot}31$, $P<0{\cdot}01$; B, $\chi^2 = 7{\cdot}46$, $P<0{\cdot}025$.
* Either a positive CFT, or a TRC titre of >1 in 1000 or both.
† Two patients had been thyrotoxic, and two were hypothyroid.
‡ Four parents had been thyrotoxic.

TABLE 6. Immunoglobulin concentrations (IU/ml)

	63 Controls			Fifty-one patients with juvenile-onset myasthenia			140 Relatives		
	Mean log value	S.E.M.	Anti-log (IU/ml)	Mean log value	S.E.M.	Anti-log (IU/ml)	Mean log value	S.E.M.	Anti-log (IU/ml)
IgG	2·028	0·016	106·7	2·084	0·024	102·0	2·031	0·013	107·4
IgA	1·952	0·028	89·5	1·866	0·044	73·4	1·950	0·022	89·1
IgM	2·047	0·033	111·4	2·101	0·042	126·2	2·059	0·025	101·4

of IgM; these findings are given in Table 7. None of them had had recurrent infections or significant illnesses (other than myasthenia). Both patients had undergone thymectomy, but in this series there was no relation between thymectomy and immunoglobulin concentra-

tion, since the distributions of all three immunoglobulins were similar in thymectomized and non-thymectomized patients and were unrelated to interval since thymectomy. Neither were immunoglobulin concentrations related to the severity or duration of the myasthenia, to the presence or absence of autoantibodies or to the presence of associated thyroid disturbance.

TABLE 7. Individuals with hypo-immunoglobulinaemia

	Sex	Age	Clinical findings	Immunoglobulins IU/ml			Auto-antibodies present†
				IgG	IgA	IgM	
Patient No. 13*	M	18	Onset of myasthenia aged 7 years. Thymectomy at 8 years. Now well	84	68	8	None
Patient No. 58*	F	39	Onset of myasthenia at 19 years. Thymectomy at 22 years. Initial improvement but relapse at 25. Now mild muscle weakness. No other symptoms	200	<2·5	256	STM; SM10; T16; TRC640;
Father of No. 22*	M	71	Well	104	<2·5	520	SM10; ANA 100

* Numbers in the appendix of Bundey (1972).

† STM = striated muscle; SM = smooth muscle; T = thyroid microsomal; TRC = thyroglobulin; ANA = antinuclear. Titres given where appropriate.

DISCUSSION

Clinical findings

The clinical findings in these patients with juvenile-onset myasthenia (arbitrarily defined as onset before the age of 20 years) have been reported elsewhere, and are consistent with the findings of other workers. Patients developing myasthenia before the age of 2 fall into two groups. There are the few infants of myasthenic mothers who have a transient congenital illness; such infants have not been included in the present study. Other patients developing myasthenia before 2 years have a milder but more persistent disease than those developing symptoms later. They differ also in sex ratio and in frequently having affected sibs. It is likely that their disease is recessively inherited (Bundey, 1972).

The clinical course of the late-juvenile onset patients (those with onset between 2 and 20) is similar to that of adult-onset patients. However, the finding of two affected relatives among the forty-nine families is probably greater than the incidence in families of adult patients (Jacob, Clack & Emery, 1968). Such an increased incidence of myasthenia in juvenile families is consistent with the fact that patients with familial myasthenia reported in the literature have usually had an early onset of symptoms. This suggests that individuals with most genetic predisposition to myasthenia tend to develop the illness in early life, but no mode of inheritance is established. A similar relationship was found in childhood autoimmune thyroiditis (Doniach, Nilsson & Roitt, 1965). Since only three of the very early-onset patients were included in this study, and their immunological findings did not differ from those of the late-onset group, our immunological results in juvenile-onset myasthenia have been considered as a whole.

A number of autoimmune phenomena have been reported in patients with adult-onset myasthenia, and there is considerable evidence for an autoimmune pathogenesis (Goldstein & Mackay, 1969). This includes the association with other diseases regarded as autoimmune, which is established for thyroid disease and suggested for some others (Simpson, 1960; Oosterhuis, 1964; Downes *et al.*, 1966). Our finding of six patients with goitre, including four patients with disturbance of thyroid function confirms that the juvenile-onset disease is similar in this way.

Autoantibodies in patients

The incidence of all antibodies studied was greater in our adult patients than in controls, significantly so for striated muscle, nuclear, thyroid, and parietal cell antibodies. This is consistent with previous findings in many reports. Similarly, the incidence of these antibodies in our juvenile-onset patients was greater than that in our control population, though for three antibodies this increased incidence was not significant at the 1% level which we regard as appropriate for such a study. It is likely that the thyroid antibodies are pathogenic for the thyroid disease in these patients since their incidence is closely related to it (Table 5). There is no evidence that any of these antibodies are pathogenic for myasthenia. Indeed, the only one ever considered in this way, that to striated muscle, shows the least increase in incidence.

Although the tendency for an increase of a range of autoantibodies is similar to that in adult-onset patients, there are differences of detail. For instance striated muscle and nuclear antibodies are less common than in the adult-onset patients. Osserman & Weiner (1965) and Weiner & Osserman (1966) obtained similar results concerning muscle antibodies. This could reflect a lesser degree of myositis in children, and the better effect of thymectomy in young patients. The incidence of mitochondrial antibodies is similar to that seen in autoimmune haemolytic anaemia (Blajchman, 1971) and almost as high as in the collagen disorders (Walker, Doniach & Doniach, 1970).

Autoantibodies in relatives

The only existing report of immunological findings in first degree relatives of myasthenics (Wright & Kerr, 1967) was, we believe, confined to the families of adult patients. The incidence for antithyroid antibody of 30% was not considered to be greater than that of the control population, and no increase of thyroid disease was noted in the group as a whole, but three families showed remarkable aggregation of both. The well-known familial tendency for such diseases makes their failure to show an overall increased incidence surprising, so a study of such phenomena in relatives of juvenile-onset patients who showed a greater familial incidence of myasthenia seemed valuable.

All the autoantibodies were more frequent in the relatives than in the controls, but only the increase in antithyroid antibodies was significant at the 1% level. It is interesting that muscle antibodies, which are closely related to this disease, were commoner in the relatives than in the patients, though not significantly so. Our detection of mitochondrial antibodies in the relatives is perhaps related to the report by Whittingham, Mackay & Kiss (1970) of a family with both autoimmune liver disease and myasthenia gravis.

Association with immunodeficiency

The role of the thymus in immunological function is complex, and there are large species

differences, but it is mainly concerned with the development of specific cell-mediated immunity function. Most autoimmune diseases are associated with raised immunoglobulin concentrations, so it is surprising that only some of the studies of electrophoretic γ-globulin, or immunoglobulin concentrations demonstrated raised levels (Oosterhuis *et al.*, 1964; Kornfield, 1964; Mackay *et al.*, 1968). Our patients with juvenile-onset myasthenia gravis, and their relatives do not differ significantly from our control series for IgG, IgA and IgM. Myasthenia gravis and thymoma has been reported to be associated with both M proteins (Rowland *et al.*, 1969) and low levels of immunoglobulins (Te Velde, Huber & Van der Slikke, 1966). The latter were attributed to the known association between hypoimmunoglobulinaemia and thymoma (Jeunet & Good, 1968), but one of us (J.F.S.) has seen a boy with hypogammaglobulinaemia, whose maternal great-aunt had had thymectomy for myasthenia. This pointed to the possibility of a familial association between myasthenia and immunodeficiency, as exists in some other autoimmune diseases (Fudenberg & Solomon, 1961). Our detection of a patient and a patient's father in whom serum IgA was undetectable, out of 191 individuals studied is an unusually high number in view of the established incidence in healthy populations of about 1 in 700 (Bachmann, 1965). Another patient had a very low level of IgM, which is very much rarer in a healthy population. We cannot completely exclude coincidence for these observations, but they strongly suggest that there is indeed an association in patients and a relative between immunodeficiency and myasthenia, without thymoma. Both patients had had thymectomy some years previously, but this seems unlikely to be the cause of the abnormality, since we know of no experimental evidence to suggest that thymectomy leads to an isolated immunoglobulin deficiency, and there is no evidence in the series as a whole that thymectomy has influenced the immunoglobulin concentrations.

It is perhaps worth noting that most of these forty-five thymectomized patients, including ten whose operation was over 20 years ago, are healthy and have no symptoms of immunodeficiency. Since we believe that the thymus performs most of its role in the development of immunological function in very early life, if the thymic dysfunction which leads to myasthenia were to have an effect on immunological function it would perhaps be most obvious in the early-onset group and in congenital myasthenia in off-spring of myasthenic mothers. Though we did not do cellular immunity function tests in our patients with onset before two years, there was no clinical suggestion of such immunodeficiency, and we know of no such evidence in congenital myasthenia.

It has been suggested that the thymus also plays a part in recognition of self (Mackay & Goldstein, 1969), so the association of a disease which is probably directly mediated from the thymus with both immunodeficiency and autoimmunity points to a common pathway in the thymus. The abnormal incidence of autoantibodies and probable autoimmune disease in these families suggests that there is a fundamental immunological defect that is underlying all these abnormalities, and one that is presumably genetic. Our demonstration of a form of immunodeficiency which is not likely to be thymic in origin in two patients and in a non-myasthenic relative, points to the view that this defect does not lie in the thymus but is at the level of antigen recognition by immunologically competent cells. The thymitis and thyroiditis might both result from this immunological defect. However, as with all complex familial immunological disorders it is impossible to separate genetic effects from environmental ones such as chronic viral infections. Probably both are relevant.

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