MANAGEMENT OF THE PATIENT WITH MYASTHENIA GRAVIS FOR THYMECTOMY*

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Whatever is unknown is magnified

TACITUS,
The Life of Agricola, Section 30
A D 54

I INTRODUCTION

THE VALUE OF thymectomy in myasthenia gravis remains controversial¹ Despite the lack of a clear understanding of the aetiology of this disease, it is generally accepted that the thymus has some causal or contributory relationship to myasthenia gravis and that thymectomy should be performed in selected patients Many patients demonstrate improvement following this operation Furthermore, drug therapy for myasthenia gravis, chiefly with anticholinesterases, is only partially effective and may frequently be accompanied by unpleasant or serious side-effects Surgery and anaesthesia may also carry a significant operative morbidity Nevertheless, in one large series of cases the mortality rate was *even higher* in those patients treated with anticholinesterases *alone* than in those having thymectomy¹

In this presentation we shall not attempt to discuss the interesting background for thymectomy in myasthenia gravis,^{2 3} but rather to outline our management of these patients

II METHOD

We shall present a method of management from our clinical experiences over the past fourteen years (1950–63 inclusive) involving twenty-one myasthenia gravis patients who have undergone thymectomy The salient features of the patients in this series are tabulated in Table I This study has been divided, retrospectively, into two periods because our management during the last five years (1959–63 inclusive) has been altered significantly from that of the first nine years⁴ (1950–58 inclusive) because of the influence of three recent major advancements

(1) the usage of the decamethonium diagnostic test in a myasthenia gravis diagnostic clinic,

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(2) the improvement in the assessment and the management of respiratory insufficiency,

(3) the avoidance of anticholinesterase drugs as treatment in the immediate and early postoperative recovery period

The two groups of patients are comparable (Table I) There were eleven patients in the first nine years and ten patients in the last five years of the study period There was a total of sixteen females, eight in each period, with similar age distribution There was a total of five males, three in the first group and two in the latter period All the males had either a thymic tumour or hyperplasia of the thymus Distinctive pathological lesions were absent in four patients of the initial group and in two patients during the last five years Prophylactic tracheostomy was not performed during the first nine years, but three of the last ten patients had prophylactic tracheostomies

TABLE I
21 PATIENTS WITH MYASTHENIA GRAVIS FOR THYMECTOMY (1950-63)

		1950-58 (11 patients)	1959-63 (10 patients)
Sex	F	8	8
	M	3	2
Age	Range	10-54	16-52
	Average	31.4	32.5
Stage	1 Resistance (ocular)	1	1
	2 Dual block (generalized)	10	8
	3 Refractory (myopathic)	0	2
Thymus	Hyperplastic	3	4
	Tumour	4	4
	Irradiated	1	0
Tracheotomy—prophylactic		0	3

The patients were representative of all three clinical forms or stages of myasthenia gravis (Table I) There were no myopathic refractory patients in the first nine years, but two in the last five years These patients are not generally considered suitable for thymectomy, as the incidence of improvement is low In addition, they may present grave problems in anaesthetic management

Not all the patients in this series had a decamethonium diagnostic test, but recently we have found this test to be of value as an additional adjunctive confirmatory procedure The neostigmine and edrophonium (Tensilon) tests are often equivocal and the "curare test" is of limited value in the mild case of myasthenia gravis The decamethonium diagnostic test has consistently demonstrated its definitive diagnostic value as it enables the identification of three distinct phases or stages in the development of myasthenia gravis This aids in assessing the prognosis and subsequent type of management of an individual case The application of this test in a myasthenia gravis diagnostic clinic has been recorded in detail^{5,6} Of prime importance is the fact that this test has also

provided a continuity of personnel from the preoperative clinic to the operating room, as an anaesthetist is a member of the diagnostic team in association with a neurologist and a physiatrist

The anaesthetic and surgical management of myasthenia gravis patients for thymectomy presents serious problems. These patients may have impaired activity of their respiratory system, they are frequently of poor nutritional status, they are susceptible to infection, they have a labile emotional status, and they have altered reactions to many drugs used before surgery, during surgery, and after surgery (for example, antibiotics, narcotics, muscle relaxants, and general anaesthetics)

A Preoperative Preparation of the Patient

Admission to hospital a few days before operation is advisable. Rest reduces drug requirements. The patient's general response to oral anticholinesterase therapy can be assessed.

The various anticholinesterases used in the treatment of myasthenia gravis are tabulated in Table II. Their equivalent doses are summarized in Table III. The

TABLE II
ANTICHOLINESTERASES USED IN THE TREATMENT OF MYASTHENIA GRAVIS

Generic name	Trade name
Neostigmine bromide	Prostigmin bromide
Neostigmine methyl sulphate	Prostigmin methyl sulphate
Pyridostigmine bromide	Mestinon
Amбенonium chloride	Mytelase
Edrophonium chloride	Tensilon
Bis-neostigmine	
Bis-pyridostigmine	Hexamarium
Echothiopate iodide	Phosphate iodide

minimal dose is determined as that dosage which will provide an adequate respiratory exchange (tidal volume (TV) = 300 cc or more, vital capacity (VC) = 1800 cc or more as measured by Wright respirometer), normal $p\text{CO}_2$ and pH by the Astrup method, and the ability to chew and swallow. This assessment is of help in anticipating those cases which will more than likely need mechanical respiratory assistance and/or tracheostomy preoperatively or postoperatively.

TABLE III
EQUIVALENT DOSES OF COMMONLY USED ANTICHOLINESTERASES

Drug	Oral dose (mg)	I/M or I/V dose (mg)
Neostigmine (Prostigmin)	15	0.5
Pyridostigmine (Mestinon)	60	2.0
Amбенonium (Mytelase)	6	None available

On the day of operation the anticholinesterase medication is reduced. Decreasing or omitting this medication will influence favourably the acetylcholine-insensitive state and decrease the resistance of the patient to anticholinesterases. This provides for an easier adjustment of, and response to, such medication, if it is necessary in the postoperative period. Also, following thymectomy, the majority of patients have a short-lasting (18 to 48 hours) remission. In contrast, the administration of a high dose of preoperative anticholinesterase may cause a "cholinergic crisis" postoperatively.

Respiratory depressant drugs are avoided in pre-anaesthetic medication. Morphine sulphate respiratory depression is potentiated by neostigmine (Prostigmin).² Atropine and scopolamine are given for their drying effect on the respiratory tract and reduction of potentially harmful reflex effects from surgery and anaesthesia.

B The Conduct of Anaesthesia

Induction is usually with intravenous thiopentone via an indwelling percutaneously inserted No. 16 Rochester polyethylene catheter attached by extension to a three-way disposable plastic stopcock. This arrangement permits the administration of drugs, fluid, electrolytes, and blood with ease, either simultaneously or separately, both during surgery and in the postoperative period. The use of neuromuscular blocking agents before endotracheal intubation is not always necessary. Adequate topical anaesthesia of the pharynx and larynx under general anaesthesia is usually all that is required. If relaxation is necessary to facilitate endotracheal intubation, a single 0.4 to 0.6 mg/kg dose of succinylcholine may be used. Further use of the muscle relaxant is not required. A cuffed endotracheal anaesthesia is essential, in order to facilitate adequate ventilation, removal of accumulated tracheobronchial secretions, and avoidance of gaseous stomach distention. Maintenance anaesthesia is with cyclopropane or halothane (Fluothane). Respiration is controlled manually or with a mechanical ventilator. Thymectomy is attained through a median sternotomy incision.

If we anticipate that the patient's spontaneous respiratory activity or cough mechanism will be inadequate postoperatively, a prophylactic tracheostomy is performed before the removal of the endotracheal tube, at the completion of the operation. The site of the tracheostomy is slightly higher than usual to avoid contamination of the mediastinum. A tracheostomy tube with inflatable cuff (James tube) is used. This will allow intermittent positive pressure (IPP) respiratory assistance with a mechanical respirator. Controlled or assisted respiration is well tolerated in these patients. As the majority of postoperative deaths in myasthenics are due to respiratory complications, it is suggested that the indications for prophylactic tracheostomy be liberal for the myasthenic patient.

C The Postoperative Recovery Period

Following thymectomy, the most frequent causes of postoperative morbidity and mortality can be related to (1) *respiratory* or (2) *circulatory* complications or (3) myasthenic emergencies of which *over-medication with anticholinesterases* ("cholinergic crisis") is the most common.

1 *Maintenance of Adequate Respiration*

Fastidious care is given to the respiratory tract during the early postoperative period. If the respiratory exchange is adequate, the endotracheal tube may be removed and the patient allowed to breathe spontaneously. Patients with borderline respiratory exchange may be carried for a 24-hour period with mechanical assistance to respiration via an endotracheal tube. If the tidal volume was less than 300 c.c. and the vital capacity less than 1800 c.c. preoperatively, then a tracheostomy has usually been done. The patient's respirations are assisted or controlled by IPP respiration with 40–60 percent O₂ initially, and then air, saturated with warmed nebulized water vapour, until minute volume (M.V.), T.V., V.C., pH, and pCO₂ monitoring indicates that spontaneous respirations are adequate.

In these patients, there are many variable factors in this period that may result in respiratory difficulty, such as lack of anticholinesterases, thoracic splinting from operative pain, emotional upset, pneumothorax, pneumomediastinum, haemothorax, atelectasis, or residual depression from anaesthesia. We do not attempt to titrate the patient's anticholinesterase requirement in order to maintain muscle strength of adequate respiratory exchange, as the other factors may be responsible for this difficulty. Overenthusiasm with anticholinesterases may then result in "cholinergic crisis," a serious and unnecessary complication. This regime without anticholinesterases may involve several days' management. As the patient's condition improves, with or without gradual introduction of oral anticholinesterase (by nasogastric tube if necessary), and his spontaneous respiratory activity becomes adequate, the use of the mechanical ventilator can be gradually discontinued.

2 *Support of Circulation*

Specific morphological lesions have been described in the myocardium of myasthenics.⁷ These lesions may be the cause of sudden, unexpected death, as reported in some series. Careful attention, therefore, is given to the state of the circulation, with regard to blood volume, haemoglobin, fluid and electrolyte requirements. Significant amounts of fluid may be lost through mediastinal or chest drainage.

3 *Management of Myasthenic Emergencies*

The mechanism underlying myasthenic emergencies may vary, but whatever their cause, when untreated, their end result is usually respiratory failure. The first and most important factor in their management is the prompt institution of *adequate respiratory exchange*. This will keep the patient alive until the nature of the emergency can be diagnosed and it can be treated with appropriate drug therapy.

Depending on their pathophysiologic basis three types of myasthenic emergencies may be distinguished:

- (1) "Myasthenic crisis" from under-medication
- (ii) "Cholinergic crisis" from over-medication
- (iii) Development of an *acetylcholine-insensitive state*⁸. This may simulate

(1) "myasthenic crisis" or be associated with (11) "cholinergic crisis" It can only be diagnosed from the effects of therapeutic trials with edrophonium or other anticholinesterases Complete withdrawal of anticholinesterases and/or prolonged administration of *d*-tubocurarine with controlled respiration are indicated in order to "rest" the myoneural junction⁹

Drug therapy in these myasthenic emergencies is directed towards

(1) *Control of muscarinic side-effects* (in "cholinergic crisis") with an initial intravenous dose of atropine 0.4 to 1.0 mg, and subsequent 0.3 to 0.4 mg doses every three to five minutes until the desired effect is obtained

(11) *Improvement of muscle strength* (in "myasthenic crisis") If 10 mg intravenous edrophonium (Tensilon) indicates improved muscle strength, cautious intravenous administration of neostigmine (0.3 mg) or pyridostigmine (1.2 mg) can then be tried after prior injection of atropine (0.4–0.6 mg) Fractional doses thereafter of the anticholinesterases are usually half the initial dose

(III) *Prevention of infection of the respiratory tract* Because of the myasthenic's susceptibility to pneumonia and other infections of the respiratory tract, antibiotics may be given prophylactically It is well worth remembering that some antibiotics, for example, neomycin, streptomycin, and polymyxin B, have a mild, but definite, non-depolarizing neuromuscular effect which may accentuate the neuromuscular block in myasthenics sensitive to these agents

ILLUSTRATIVE CASE—PATIENT E. M. J.

This patient epitomizes several of the many problems that are associated with the care of the patient with myasthenia gravis

A 52-year-old, white housewife, apart from a known irregularity and inequality of pupils since 1953 and isolated episodes of untreated paroxysmal auricular tachycardia, was well until November 1960, when she experienced a sudden onset of choking sensation, difficulty in clearing mucus from her throat, slurred speech, difficulty in swallowing, and ptosis of eyelids These manifestations progressed intermittently over the next two years She arrived in the emergency ward at Vancouver General Hospital on December 30, 1962, with laboured respirations, nasal slurred speech, weakness of the masseters, and bilateral facial weakness She also had generalized muscle weakness, especially of the neck muscles She appeared to have diffuse wasting of her limb muscles She had occasional ventricular extrasystoles Her normal weight was 130 lb, but she now weighed 89 lb The Tensilon test was negative and the cerebrospinal fluid pressure was normal She was tentatively diagnosed as a bulbar palsy On January 4, 1963, she developed a bout of paroxysmal auricular tachycardia, for the first time in the presence of a physician This was easily controlled with medication On January 5, she developed a right lower lobe atelectasis She became dyspnoeic and cyanotic She was not able to cough A tracheostomy was performed under local anaesthesia and oxygen On return to the P. A. R. she had a cardiac arrest External cardiac massage was begun immediately followed by open-chest resuscitation Under direct vision the heart was seen to be in complete standstill Four manual compressions of the left ventricle instituted a strong, forceful myocardial contraction The B. P. returned to normal She was placed on I. P. P. assisted respiration through the James tracheostomy tube By January 10 her speech and swallowing had improved markedly She was able to cough reasonably effectively

An electromyographic study on January 22 suggested myasthenia gravis There was no electromyographic evidence of denervation or of myopathic changes in the frontalis, masseter, or orbicularis oris muscles Her condition improved appreciably on a trial dose

of Mestinon 60 mg She was discharged, much improved, on January 23, 1963, with Mestinon 60 mg B I D

On March 14, 1963, she was readmitted because of sudden severe precordial pain However, her B P, heart rate, and E C G were found to be normal She now weighed 80 lb She was also now receiving atropine medication because of the gastrointestinal muscarinic side-effects of Mestinon

On April 2 the decamethonium test was performed Following the initial dose of 0.5 mg decamethonium (one half the usual given) she became apnoeic Tensilon 10 mg and prostigmine 1.0 mg improved her respiratory activity but it remained inadequate with a tidal volume of only 150 c c An endotracheal tube was inserted She was given assisted ventilation and observed in the intensive care unit The following day, April 3, her spontaneous tidal volume was still only 150 c c On April 5 a tracheostomy was performed During induction of anaesthesia for this procedure, she became hypotensive, her heart rate was 160/min There was distention of neck veins She was digitalized Post-tracheostomy she was gradually weaned from the mechanically assisted respirator On nasogastric feedings she gained eight pounds Her haemoglobin was 14.6 gm, electrolytes and plasma proteins were normal

Because of the increasing muscarinic side-effects of anticholinesterase treatment, the need for ever-increasing doses of medication, and the suggestion on tomography that there was a thymic tumour, a thymectomy was performed on April 22 A thymoma was removed

This patient was managed in the immediate preoperative, operative, and postoperative period as outlined in our method, with an uneventful course She was discharged improved on May 10, 1963

When seen in O P D in December 1963, she weighed 98 lb, was eating well, and ambulatory She still required anticholinesterase treatment, but it was much reduced and effective, without side-effects

III RESULTS AND DISCUSSION

Table IV suggests that following this form of management during the past five years (1959-63 inclusive) operative risk has been reduced from that during the previous nine years (1950-58 inclusive) of this period of study

TABLE IV
OPERATIVE MORTALITY AND MORBIDITY IN 21 PATIENTS
WITH MYASTHENIA GRAVIS AND THYMECTOMY

	1950-58 (11 patients)	1959-63 (10 patients)
Mortality	1	0
Morbidity		
Pneumothorax with atelectasis	4	0
Pneumonia	4	1
Emergency tracheostomy	3	0
"Cholinergic crisis"	3	0
Improved	9	9
Not improved	2	1

During 1950-58 there was one death, during "cholinergic crisis." Four patients had postoperative pneumothorax and pneumonia. This high incidence may be related partly to intercostal thoractomy, the usual approach during this period of study. Also, prophylactic tracheostomies were not performed. Three required emergency tracheostomy in the postoperative period. Three had episodes of "cholinergic crisis."

During 1959-63 there were no deaths, despite the fact that two of the ten patients in this series were poor-risk myopathic, refractory patients. Staphylococcal pneumonia developed in one patient secondary to an infected tracheostomy. There were no complications with "cholinergic" or "myasthenic" crisis.

The over-all mortality rate was 4 per cent in this series. This compares favourably with an accepted operative mortality for thymectomy in most institutions of 4-5 per cent. This figure may be doubled for myasthenics with tumours,¹ and eight of the twenty-one patients in our series had tumours. Drug-therapy management, alone, may carry high mortality rates, as one large series¹ demonstrated a 16 per cent mortality rate.

Improvement (that is, full remission, or with only minor weakness or only subjective improvement) occurred in eighteen of the twenty-one patients. Three patients were not improved.

Until the aetiology and pathogenesis of myasthenia gravis is known, the debate on the usefulness of thymectomy will undoubtedly continue. Certainly, the recent auto-immune reaction theory of myasthenia gravis^{10, 11} attractively correlates the thymus and a defect in neuromuscular transmission. In this theory it is believed that the myasthenic patient develops antibody against some component of skeletal muscle. The thymus reacts to protein derived from the motor end-plate. This antibody may become fixed to the muscle membrane and in turn bind serum complement to this structure causing cytolytic or subcytolytic alterations. These changes may decrease sensitivity to acetylcholine and cause the defect of neuromuscular transmission of a reversible or irreversible nature. Antibody production may occur in the absence of the thymus, suggesting that perhaps the thymus has seeded its antibody-producing lymphocytes (thymocytes) to other areas, such as the spleen and lymph nodes, which may then take over the function.¹ The development or persistence of myasthenia gravis months or years following total removal of the thymus could be explained by the presence of active thymocytes in the spleen or lymph nodes. This conceivably could limit the effectiveness of removal of what was perhaps the initial source and site of the auto-immune response and suggests the efficacy of removing the spleen, in addition to the thymus.

SUMMARY

A method of management of myasthenia gravis patients for thymectomy has been presented. Preoperative preparation, conduct of anaesthesia, and care in the postoperative period is discussed. Emphasis has been placed on assessment and management of respiratory insufficiency and avoidance of anticholinesterase treatment in the immediate and early postoperative recovery period. This has

eliminated the all too common hazard of "cholinergic crisis" The results, suggesting a reduction in operative mortality and morbidity, have been discussed

RÉSUMÉ

Bien que la valeur de la thymectomie soit controversée dans le traitement de la myasthénie grave, plusieurs malades sont améliorés à la suite de cette opération

Jusqu'à présent, nous avons pratiqué une thymectomie chez 21 malades, à la suite de cette expérience clinique, nous avons établi une ligne de conduite à l'égard des porteurs de cette pathologie Nous avons modifié trois aspects du problème que posent ces malades

(1) l'emploi du décaméthonium comme épreuve diagnostique nous a permis de distinguer trois étapes différentes dans l'évolution de la myasthénie grave,

(2) nous avons amélioré l'évaluation et le traitement de l'insuffisance respiratoire,

(3) nous avons abandonné le traitement à l'anticholinestérase au cours des suites opératoires immédiates Ce geste a fait disparaître le hasard du dosage excessif (la crise cholinergique)

La préparation du malade comprend l'admission à l'hôpital quelques jours avant l'opération On évalue ses réactions au traitement en donnant des anticholinestérasiques, per os On précise la dose optimale Le jour de l'opération, on réduit la dose des anticholinestérasiques On évite de donner des dépresseurs de la respiration dans la prémédication

Nous faisons l'induction de l'anesthésie avec du thiopentone (pentothal sodium) Nous pratiquons une intubation endotrachéale après l'administration d'un myorésolutif dépolarisant Nous maintenons l'anesthésie soit avec le cyclopropane, soit avec l'halothane Nous contrôlons la respiration avec un ventilateur mécanique (Bird) La thymectomie se pratique à travers une incision sternale médiane Après l'opération, certains font une trachéotomie

Au cours des suites opératoires, le malade reçoit des soins méticuleux trachéo-bronchiques

Nous assistons ou contrôlons la respiration des malades en recourant à la pression positive intermittente (Bird) jusqu'à satisfaction, ce que nous apprécions par la mesure de l'air courant, du volume-minute (respiromètre de Wright), du pH, de la $p\text{CO}_2$ et des CO_2H (Astrup) Ce traitement peut durer des heures et des jours sans thérapie anticholinestérasique et nous le continuons jusqu'à ce que nous ayons réussi à déterminer la médication orale optimale

En adoptant cette ligne de conduite au cours des cinq dernières années, nous avons réussi à diminuer le risque comparativement à celui des huit années antérieures que couvre cette étude Bien davantage souvent, nous donnons ainsi aux malades déprimés leur unique chance de survie

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