DISSERTATION FOR MPHIL (INTENSIVE CARE), U.C.T.

MYASTHENIA GRAVIS AT GROOTE SCHUUR HOSPITAL

AN AUDIT (1970 - 1990)

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Foreward

The Respiratory Unit at Groote Schuur Hospital has, since its inception in the mid 1960's, assisted the Department of Neurology in the management of patients with Myasthenia Gravis; particularly those who require ventilatory support at times of crisis or post-thymectomy. During the past 10 years I have had the privilege of working in the Respiratory Unit, initially as a registrar under the expert guidance of **Professors Alex Ferguson** and **Solly Benatar** and, subsequently, as a specialist with **Professor Peter Potgieter**. In this multi-disciplinary intensive care environment I have learnt how to care for critically ill patients in respiratory failure, including those with myasthenia gravis. I am particularly indebted to **Professor Peter Potgieter**, my peer, colleague and friend, for teaching me most of what I have learnt about intensive care practice over the past 8 years.

Dr Derek Philcox, senior specialist neurologist, who has always had a particular interest in myasthenia gravis, has shown me the gentle art of the long term treatment of the myasthenic patient. I am extremely grateful to **Dr Philcox** for supervising the preparation of this dissertation.

Furthermore, I wish to acknowledge the assistance of **Mr Anton Potgieter** who compiled the computer record and analysis programme for the myasthenia gravis patients, **Professor Michael James** who allowed me the use of his computer reference programme to compile the reference files described in this dissertation, and **Mrs Sylvia Pienaar** for the word processing of this dissertation.

INTRODUCTION AND DEFINITION

I have reviewed all of the available international literature on myasthenia gravis (MG) up to the end of 1989, and I have established a databank of this literature for future retrieval and publications (see Annexure I).

Myasthenia gravis is a fascinating neuromuscular disease, the specific precipitating cause of which remains obscure after a century of clinical experience and five decades of scientific research (Simpson, 1983) The disease is specifically characterized by the development of clinically demonstrable weakness in voluntary muscle groups (Rowland, 1982). This weakness is accentuated by repetitive muscular activity and improved by resting the muscles (Simpson, 1981; Drachman, 1978). It is this feature of the disease, namely, the demonstrable fatiguability of striated muscle which tends to improve after periods of muscular inactivity and responds to the initial administration of acetylcholinesterase inhibitors, which distinguishes MG from other neurological and muscular disorders (Harvard, 1973).

The fundamental abnormality in the most common form of MG (adult generalized) is an immunologically mediated premature degradation of acetylcholine receptors in the neuromuscular junction (Drachman, 1978; Walton, 1981). A model of classical MG has been constructed by immunologists with the thymus featuring as the leading actor and it is on this model that current medical and surgical therapy is based (Harvard, Scadding, 1983; Engel, 1984; Simpson, 1987; Genkins et al, 1987). There is an abundance of clinical, pathological and immunological evidence confirming the heterogenicity of myasthenia gravis (Efthimiou, 1985; Compston et al, 1980).

Many questions regarding MG remain unanswered and controversy abounds, particularly relating to the technique and timing of thymectomy and the choice of therapy in different manifestations of the disease in older patients, in children and in patients with associated diseases such as thyrotoxicosis, systemic lupus erythematosis and diabetes.

MYASTHENIA GRAVIS PATIENTS AT GROOTE SCHUUR HOSPITAL

In order to study myasthenia gravis in depth (for the purposes of this dissertation), as well as for future research and optimal patient management, I have established a databank of all patients treated at Groote Schuur Hospital with the disease (see Annexure II). There is a wealth of information on these patients and any feature of their disease or therapy can be analysed.

General appreciation of the natural history of different forms of MG has been hindered in the past by the small numbers of afflicted patients seen by most clinicians. The identification of referral centres for myasthenia gravis in academic hospitals and the tendency to distinguish different forms of myasthenia gravis during analysis of outcome and response to therapy is likely to improve understanding of this complex disease.

The Department of Neurology at Groote Schuur Hospital has been a referral centre for patients with MG for many years.

In 1987 a regular monthly Myasthenia Gravis Clinic was established in the Neurology Outpatients Department. The attendant consultant physicians at this clinic include a neurologist, a paediatric neurologist and an anaesthetist. In addition, these personnel maintain a liaison with consultants in the Departments of Thoracic Surgery (for thymectomy), Obstetrics and Gynaecology for (C/S and deliveries) and Haematology (for plasma exchange). The benefits of this clinic are readily apparent, both to patients and the attending physicians. A forum is provided for discussion and careful planning of each patient's long term care. New patient referrals are made known to all the relevant specialists and the patient's details are recorded in the MG computer data bank. The clinic has therefore facilitated consolidation of the databank of patient's with MG and has paved the way for good research and development opportunities in this field. A serum store has been established for patients with active MG requiring plasma exchanges where serum samples are kept pre- and post-exchange for antibody level determination.

Medic Alert discs are arranged for all MG patients attending the clinic and the patients are advised to present early to the relevant Department if deterioration in their MG occurs. Better control of the individual patient has been achieved with reduced numbers of unnecessary outpatient visits due to better planning.

A management plan for adult patients with MG at Groote Schuur Hospital as been formulated as a result of improved inter-Departmental liaison (see Annexure III).

HISTORICAL PERSPECTIVE

The first reported description of a patient with MG was by Thomas Willis in 1672 (Willis, 1972). Early classical descriptions of MG followed by Erb, Goldflam and Jolly in the nineteenth century and the clinical picture was firmly established by Campbell and Bramwell in 1900. Weigert first noted the relationship between MG and the thymus in 1901. In 1913 Schumacher reported marked improvement in a patient with hyperthyroidism and myasthenia in whom he performed a transcervical thymectomy. The description by Dale in 1934 of chemical transmission at motor nerve endings was a major historical factor in the understanding of MG and in the same year Mary Walker described the treatment of MG with physostigmine. She followed this with a description of the use of prostigmine to treat MG in 1935 (Walker, 1935). In 1939 Blaylock reported successful and beneficial removal of the thymus gland containing a thymoma in a young woman with MG. This was followed by further reports by Blaylock in 1941 and 1944 of thymectomy in MG. Perhaps the most important development was the recognition by Simpson in 1960 that MG was an autoimmune disease. Limited success was experienced by workers as early as 1951 with steroids and steroid precursors in the treatment of MG, but this form of therapy was only reported as being successful in the literature in 1971 (Millikan, Eaton, 1951; Grob, Harvey, 1952; Kjaer, 1971; Dalby et al, 1971; Namba et al, 1971). Similarly, although azathioprine was first tried in the treatment of MG in 1969, it was only reported as a successful form of treatment of MG in 1981 (Mertens et al, 1969; Mertens et al, 1981). Plasma exchange was first mooted as a possible form of therapy for MG in 1976, however it was only much later with the development of safe plasma separators that plasma exchange became accepted as a form of therapy for certain situations in MG (Pinching et al, 1976; Dau et al, 1977; Dau, 1980; Dau, 1981).

Although there have as yet been no comparative or controlled studies on patients with myasthenia gravis at Groote Schuur Hospital, there are ample records of the early introduction of the newer forms of therapy as these were published from Europe and America. In particular, the dramatic benefit of plasma exchange to MG patients in respiratory failure was demonstrated as early as 1979 in a patient admitted to the respiratory unit and this has resulted in the regular, safe use of this form of therapy in our institution.

NATURAL HISTORY

The incidence of MG is variously reported in textbooks of medicine, ranging from 1 in 50,000 to as high as 1 in 10,000 of the population (Simpson, 1983; Rowland, 1982; Simpson, 1981; Aminoff, 1988; Chiu et al, 1987). These variations are due to different estimates in different population groups studied and appear to be influenced by the country of origin of the study, the race of the population group studied and, particularly, the clinical types of myasthenia gravis included in the estimates. I estimate the incidence of MG in the Cape Peninsula to be 1:30,000 as we have ± 100 patients with MG on record in Cape Town, in an estimated population of ± 3 million. The annual incidence of new cases reported by major referral centres is approximately 1 in 300,000 of the population groups studied (Rowland, 1982). The Neurology Department at Groote Schuur Hospital has between 5 and 7 new cases of MG referred from all over the Cape Province (an area of ± 1,000 square Kms) each year. The disease occurs in all decades and the patient is more likely to be female (Rowland, 1982). In young adults and children the female to male ratios reported vary from 4.5:1 to 3:1. (Simpson, 1981) In mature adults the sex incidence appears to be equal but in older patients and, particularly those with thymomas, the ratio reverses to affect males 3 times as frequently as females (Simpson, 1981). There are few familial cases reported and myasthenia gravis is not generally believed to be a familial disease. There is, however, an increased incidence of thyroid and other autoimmune diseases in myasthenia gravis patients and their families (Rowland, 1982; Simpson, 1981). The incidence of thyroid disease in our MG patients is approximately 6%. A genetic predisposition is believed to be present in two groups of patients, firstly, females younger than 40 years of age with no thymoma have a genetic predisposition with HLA, A1, B8, DRW3 antigens and in Japan, B12 antigens (Compston et al, 1980; Aminoff, 1988). Associated autoimmune diseases in this group are believed to be in the vicinity of 10%. The second group with a genetic predisposition are males older than 40 years of age with no thymomas who have a tendency to have HLA, A3, B7 and/or DRW2 antigens, while in Japan the A10 antigen predominates.

The profile of myasthenia gravis in various population groups has been reported to be different. Notable differences in the clinical spectrum have been reported between Chinese versus Caucasian patient

groups (Chiu et al, 1987). The incidence of MG amongst the black populations of South Africa is not known, but from our records the disease would appear to be extremely rare in the black populations of the Cape Province (perhaps as rare as 1:1,000,000). The incidence of MG in the white and coloured populations of the Cape Province is similar to that reported amongst whites in the United Kingdom.

The median age of onset of MG is about 20 years for each sex but because of the different distribution curves the mean age is a little lower for women (26 years) than men (31 years). These ages refer to patients without a thymoma. Myasthenia associated thymic tumour tends to appear at a later stage and is rare under the age of 30 years.

Simpson divides the clinical course of MG into three stages (Simpson et al, 1987), although it may be difficult to appreciate these stagings nowadays, following the surges of effective therapy of MG. The first stage is probably the best known and understood and lasts about 5-7 years. During this period the disease can be particularly labile; striking remissions may occur, as do most of the deaths directly attributable to the disease, and this stage can well be described as an active stage of MG. Many students of MG consider that it is best to carry out thymectomy early in the first stage, though statistical support is not available. The second stage is regarded as the inactive stage of MG and lasts for about 10 years. In this stage there are fewer remissions but death in this time is rare. Thymectomy appears to be of little or no value in this stage and the greatest danger to the patient is airway obstruction due to generalised non-reversible weakness. In the third stage the active disease is burnt out and slow improvement is not uncommon. The patient can be shown to have a fixed non-reversible weakness and is usually maintained on minimal medication.

Changes over the years in the medical and surgical treatment of MG have had a major impact on the timing and causes of death related to the disease (Simpson et al, 1987). Simpson has shown that 20 years ago patients were most likely to die in the early years from their MG because of cardiorespiratory arrest, whereas in the 1980's patients were more likely to die much later in the course, with most deaths

being ascribed to infection and other complications of prolonged immunosuppression therapy. Although Simpson has suggested that the death rate from MG has not fallen substantially over the last 20 years, this is probably due to the fact that many more patients with MG have survived into this period. Simpson has suggested that the mortality rate for MG has been unchanged by current therapy and that immunosuppression (thymectomy, steroids, azathioprine and plasma exchange) reduces morbidity in the short term and complicates the disease in the long term. In reviewing our mortality over the past 15 years - it is our opinion that most deaths were probably preventable with current knowledge of the disease and modern intensive care capabilities.

CLINICAL SPECTRUM

A. Symptoms

A disease that occurs at any age in either sex and spans the whole spectrum of weakness, from intermittent unilateral ptosis to fatal generalized muscular failure, has an understandably wide variety of presenting symptoms and signs. In addition, it may be by a consequence of impaired function rather than the weakness itself that attention is drawn to the underlying disorder, as when an infant, whose mother had complained of lassitude during pregnancy, sucks poorly and has a weak cry.

Weakness of the ocular, facial or bulbar muscles is usually the first symptom. As with myasthenic weakness elsewhere, it is characteristically intermittent, developing with use of the muscles and recovering on rest. Thus, slurring of speech may be noticed by the talkative, and by mothers who read to their children, but not detected by a taciturn businessman until he is required to make a speech. The case study of Thomas Willis in 1972 vividly describes the predicament of such a patient: "She for some time can speak freely and readily enough, but after she spoke long or hastily, or eagerly, she is not able to speak a word, but becomes mute as a fish, nor can she recover the use under an hour or two".

Diplopia is usually transient, even occurring for only a few seconds at a time, and it may be present in different directions of gaze or bilaterally, at different times. This variability may be compounded by variations in severity from day to day, and even by total remission for months or permanently. Such fluctuation, especially in anxious patients used to blaming "nerves" for their symptoms is likely to raise thoughts of emotional overbreathing, especially if concomitant variable ptosis, usually present, has not been observed by the patient nor detected by the doctor. Ptosis, if severe, will of course abolish the diplopia and it may, like other muscle weakness, be total and fixed (not fluctuating), a vivid reminder that while weakness followed by recovery on rest is typical of MG, the quality of constant weakness is a common presentation. Any unexplained ocular muscle weakness, with or without diplopia, must be presumed to be MG until disproved by failure to respond to IV edrophonium.

The bulbar muscles, i.e. those innervated from the pons and medulla, may be involved early about as often as the oculomotor muscles. Inability to bite with normal force or to continue normal mastication throughout a meal prolongs mealtimes, makes conversation at mealtimes difficult or impossible, and may result in an insidious loss of weight. In bad cases the lower jaw hangs open and requires the support of the thumb for closure towards the end of the meal, if not at all times in the erect position.

Weakness of the facial muscles is likewise usually of insidious onset. Weakness of orbicularis oculi commonly (perhaps always) accompanies ptosis or oculomotor weakness. Involvement of other facial muscles may alter expression to apparent laughter or a snarl without regard to the patient's feelings, or may result in slurring of speech and difficulty producing labial consonants. Pharyngeal weakness frequently accompanies facial and masticatory myasthenia, resulting in nasal gurgitation, nasal speech and dysphagia. As one of our patients expressed it with a nasal twang: "My throat gets smaller and smaller". Occasionally the only hint of bulbar muscle involvement is the complaint of inability to hold or lift up the head, when extensor weakness of the neck will usually be found to be accompanied by myasthenia of the sternomastoids. Truncal weakness or limb weakness usually follows rather than precedes weakness of the facial, ocular or bulbar muscles, and the presentation of the patient may well be determined, if he is an illiterate labourer, by the greater economic significance to him of arm weakness than transient diplopia. Whether such patients complain first of arm weakness or leg weakness will reflect the nature of their activity. The student may drop the books she is carrying or be unable to complete writing an examination, the housewife may complain of tiredness and weakness in the arms while hanging up the washing, and the football player will be unable to run with the ball.

Such then is the variety of symptoms in Myasthenia Gravis that the general physician is likely to encounter very few, and the surgeon and obstetrician even fewer. Their evanescent and, at times, uncertain nature, together with the ability of both patient and doctor to find sufficient stress to explain the symptoms all help to conceal the diagnosis until some catastrophe shatters reassurance beyond dispute. A few days may indeed be all that separates intermittent blurring of vision from acute respiratory

failure. Interestingly, the presenting signs and symptoms usually recur with exacerbations of the disease in the same patient.

B. Signs

Probably the most well known sign of MG is ptosis which may be unilateral or bilateral. Ptosis in MG must be differentiated from ptosis in other forms of localized or generalized weakness, third nerve lesions and sympathetic lesions (Horner's syndrome). Other classical signs involving the face are a mask-like or expressionless face with a "snarl" during talking or respiratory distress. Typically the patient may have nasal speech, drooling or an intermittent cough due to aspiration. Rarely a furrowed tongue has been reported (Simpson, 1981).

If physical signs are present on routine examination then at least one potential error is avoided. Such signs may be obvious, or require little ingenuity or clinical skill to elicit, if the diagnosis is being considered. In this category we would place the development of ptosis on sustained upward gaze, downward drift of the elevated arm, flexion of the neck on bending forward, and weakness on rising from the recumbent position 5 or 6 times without the use of hands. Clearly, repetitive actions of any type that produce weakness suggest the diagnosis of Myasthenia Gravis. Myasthenic patients sometimes show weakness in ways that are suggestive of neurotic responses - such as sudden collapse of the muscle group under test and even paradoxical movement of the limb or structure, as the writer was recently reminded by the slight flexion of the neck with forward movement of the head which was the response of one of his patients to the request to extend her neck - a few minutes before she was ventilated for respiratory failure.

(Muscle atrophy: Present in some 10% of chronic Myasthenia Gravis patients is rarely present in the early stages of the disease and a relationship then is dubious.)

Some signs have to be sought if one is to establish the diagnosis clinically. An apparent isolated internuclear ophthalmoplegia requires an edrophonium test to establish whether it is an unusual presentation of MG, but the "peek" sign (widening of the palpable fissure on voluntary sustained gentle lid closure) has to be sought if the examiner is considering this diagnosis. There are other appropriate eye tests (and their explanations) which are likely, at the vital moment, to evade the memory of all except expert neuro-ophthalmologists.

C. Presentation

Myasthenia gravis may present in the newborn baby of a myasthenic mother (neonatal MG), in childhood (congenital MG) or, more commonly, in adolescence (adolescent MG) (Simpson, 1981; Engel, 1984). The relatively high incidence of the disease in young females makes pregnancy with its increased metabolic state and higher body temperatures, a time when symptoms may be manifest or exacerbate (Ip et al, 1986; Fennell, Ringel, 1987; Pather, Rajput, 1988). MG may also present in the mature adult and may be particularly difficult to recognize and diagnose in the elderly, where there are so many more reasons for imbalance and fatigue, and the differential diagnosis widens. Presentation as prolonged paralysis after the use of non-depolarizing muscle relaxants during general anaesthesia for a surgical procedure is not rare (Simpson, 1981; Lumb, Calder, 1989). Unusual presentations of the disease are more common in older patients and are often associated with other disorders.

MG may be precipitated by the use of various drugs for co-existent diseases, e.g. D-penicillamine for rheumatoid arthritis or beta-adrenergic blockade for hypertension or anxiety (Balint et al, 1975; Szobor et al, 1979; Naidoo, 1981; Weber, 1982; Mastalgia, 1982).

DIFFERENTIAL DIAGNOSIS

Myasthenia gravis must be differentiated from the following:

Emotional disorders, e.g.	Hysteria
	Depression
	Exhaustion
Endocrinological disorders, e.g.:	Thyrotoxicosis
	Hypothyroidism
	Myasthenic-myopathic syndromes (including Eaton-Lambert)
Electrolyte abnormalities, e.g.	Hypokalaemic states
	Periodic paralysis
	Paroxysmal myoglobinuria
	Craft palsies
Neurological disorders, e.g.	Multiple sclerosis
	Motor neuron disease
	Parkinsonism
	Peripheral neuropathy
	Nutritional myopathy
	Critical illness polyneuropathy
	Myelitis
	Pseudo ptosis
	Mitochondrial myopathy
	Congenital ptosis
	Ocular myopathy
	Von-Graefe-Moebius syndrome
	Guillain Barré syndrome
	Muscular dystrophy
Poisons and toxins, e.g.	Botulism
	Envenomation (snakes, scorpions, spider bites)
	Porphyria
	Oganophosphate poisoning
	Drugs (Aminoglycosides)

The majority of the differential diagnoses can be excluded on clinical evaluation, but some require a therapeutic test with cholinesterase inhibitors or electrophysiological studies. A positive therapeutic test and classical electrophysiological results are convincing evidence of MG, and the presence of antibodies to acetylcholine receptors in the circulating blood is diagnostic. However, these antibodies are not detected in all cases, especially when the disease is restricted (as in ocular myasthenia) or of insidious onset and gradual development.

Distinction from the myasthenic syndrome (Lambert-Eaton syndrome) may not be easy clinically, but this disorder is very rare and almost invariably involves the limbs - especially the lower - before facial, ocular or pharyngeal musculature. The alert clinician may detect a mild, though temporary, increase in power after repeated voluntary activation of affected muscles in the myasthenic syndrome and on specific enquiry he may learn that the patient has a dry mouth and is impotent (the majority of patients being male). In approximately 70% of cases of myasthenic syndrome a malignancy of the bronchus or lung is present. The response to edrophonium in this disease is poor, but appropriate electrophysiological testing is diagnostic (Sandyk, 1983).

TABLE OF DIFFERENCES BETWEEN MYASTHENIA GRAVIS AND THE MYASTHENIC SYNDROME

		Myasthenia Gravis	Myasthenic Syndrome
Incidence		1:30,000	1:Million
Age of onset		Any age	Usually > 40
Sex ratio (Female:Male)		3:1	1:5
Symptoms	- Diploplia	+ +	+
	- Dysarthria	+ +	+
	- Dysphagia	+	+ +
Signs	- Ptosis	+ +	-
	- "Snarl"	+	-
	- Nasal speech	+ +	-
Muscle strength	- Facial	-	Normal
	- Mastication	--	-
	After rest	Improves	-
	- After activity	--	Improves
Reflexes		Normal	--
Associated malignancy		Thymoma (15%)	Cancer of bronchus or lung (70%)
Electrophysiological testing			
	Single stimulus	Normal	-
	Repetitive stimulus (slow)	--	+
	Tetanic stimulus	--	+
	Post tetanic facilitation	+ +	+

CODE:

+ + Usually present (or increased)

+ Occasionally present (or slightly increased)

- Usually decreased (or absent)

-- Markedly decreased (or absent)

CLASSIFICATION AND GRADINGS

The classification of various types of myasthenia gravis has been based on either clinical presentation or immunological concepts (Simpson, 1981; Engel, 1984; Bever et al, 1983). Non-specificity in the classification of myasthenia gravis has probably been responsible for much misunderstanding of the disease, for discrepancies in reported incidences and undue variation in the response to therapy. Sub-groups of patients with myasthenia gravis should be analysed separately, particularly with regard to their age, sex and the presence of thymoma.

The clinical groups that are separated are:

1. Neonatal
2. Congenital
3. Adolescent
4. Young adult female
5. Adult male
6. Ocular
7. Patients with invasive thymomas.

In addition, patients of different races should be analysed separately (Chiu et al, 1987).

As far as an immunological classification is concerned, each of the above clinical groups is further subdivided to differentiate between myasthenia gravis and other myasthenic syndromes (Engel, 1984).

1. Neonatal MG
   (a) Maternal antibodies transferred passively.
   (b) Transient foetal antibody production.
2. Congenital syndromes
   (a) Acquired juvenile autoimmune MG
   (b) Congenital myasthenic syndromes without demonstrable antibodies

3. Adolescent myasthenia gravis

   (a) Acquired autoimmune MG without thymoma

   (b) Acquired autoimmune MG with thymoma

4. Young female adult MG

   (Subdivisions as for 3)

5. Adult male MG

   (Subdivisions as for 3)

6. Ocular MG

7. Patients with invasive thymoma

A further sub-group can be added to each of the above where MG is associated with other immunological diseases such as thyrotoxicosis, thyroiditis, systemic lupus erythematosus or rheumatoid arthritis.

The grading of the severity of myasthenia gravis was described by Osserman in 1958.

1. Ocular myasthenia
2. (a) Mild generalized myasthenia with slow progression; no crises; drug responsive.

   (b) Moderate generalized myasthenia; severe skeletal and bulbar involvement, but no crises; drug response is less satisfactory.
3. Acute fulminating myasthenia; rapid progression of severe symptoms with respiratory crises and poor drug response; high incidence of thymoma; high mortality.
4. Late severe myasthenia; same as 3, but takes two years to progress from classes 1 or 2; crises; high mortality.

Osserman's clinical grading was described before the immunological basis of myasthenia gravis was understood and therapy did not include immunosuppression of any kind. The impact of modern therapy

on the morbidity of MG has greatly altered the prognostic aspects of Osserman's classification, but it is still of value as a severity grading for the natural history of MG.

Another method of clinical classification which could be used to analyse patients relates to the presence or absence of possible precipitating factors:

(a) post-viral acquired autoimmune myasthenia gravis

(b) thymoma-induced myasthenia gravis

(c) drug-induced myasthenia gravis (penicillamine and beta blockers).

(d) idiopathic myasthenia gravis.

ASSOCIATED DISORDERS

The commonest disorder associated with MG is disease of the thymus gland. In the healthy adult the thymus is normally an involuted structure without germinal centres. Abnormalities of the thymus can be demonstrated histologically and immunologically in almost all patients with MG, although the incidence of thymoma is only 10-15% (Simpson, 1958; Castleman, Norris, 1949). Myasthenia patients with thymomas tend to be older than those without, usually over 40 years, and are more likely to be male. Thymomas are usually encapsulated but may be locally invasive - they very rarely metastasize.

The patient may have a genetic predisposition to both myasthenia gravis and another disease such as diabetes mellitus, thyroid, etc. (Simpson, 1981). This is more common when thymoma is present. Thyroid disease, particularly hyperthyroidism, is more common in myasthenia gravis than in the normal population and may be as high as 9% in males and 10% in females (Simpson, 1981). It is not believed that myasthenia is caused by hyperthyroidism although many patients have been reported to have had thyrotoxic symptoms or signs for a few months prior to the onset of myasthenia gravis (Engel, 1961; Goodman, Ferrara, 1988).

It was, in fact, the occasional association of MG with autoimmune disorders that inspired Simpson to postulate so accurately the true nature of the disease (Simpson, 1960). The occurrence of rheumatoid arthritis and pernicious anaemia more frequently than would be expected, together with the presence of isolated cases of systemic lupus erythromatosis and sarcoid, suggested to him that MG may be an autoimmune disease. Recent figures support this, with evidence of one of these diseases in 3.6% of MG patients (Simpson, 1981; Engel, 1984). Most other diseases associated with myasthenia gravis are rare (Simpson, 1981; Aita et al, 1974).

TABLE OF INCIDENCE OF ASSOCIATED DISORDERS IN 102 PATIENTS WITH MG SEEN AT GROOTE SCHUUR HOSPITAL

Thyroid disease (hyperthyroidism):		6
Diabetes mellitus:		4
Hypertension:		2
Rheumatoid arthritis:		2
Asthma		1
Malignancies:	Breast:	2
	Melanoma	1
	Lymphoma	1
Peripheral neuropathy		2
Tuberculosis		1

When coincidental diseases occur they may have detrimental effects on each other. Such is the case when myasthenia gravis and asthma are associated (Shale et al, 1983). Here the weakness of myasthenia gravis can be a major problem during periods of increased bronchospasm, causing early fatigue. Furthermore, the anticholinesterases used to treat MG can aggravate bronchospasm and bronchorrhoea. Finally, certain drugs used to treat coincidental diseases may precipitate myasthenia gravis in a patient, as has occurred with the use of penicillamine in patients with rheumatoid arthritis or the use of beta blockers in patients with hypertension (Balint et al, 1975; Szobor et al, 1979; Naidoo, 1981; Weber, 1982; Mastalgia, 1982).

In 102 patients seen at Groote Schuur Hospital, MG was precipitated on 3 occasions in 2 patients with hypertension, when they were given Beta blockers by their general practitioners. In addition, 2 patients developed MG after receiving penicillamine for the treatment of rheumatoid arthritis.

IMMUNOLOGICAL STUDIES

A. Experimental autoimmune myasthenia gravis

The demonstration that the venom of a highly poisonous snake, the multi-banded krait, becomes attached to the receptor sites of the neuromuscular junction was a major turning point in laboratory investigation in myasthenia gravis (Chang, Lee, 1963). By labelling the venom alpha bungarotoxin with radioisotopes the acetylcholine receptor sites could be revealed and their densities could be measured. In 1973 Patrick and Lindström used this knowledge to identify receptor proteins from the electric organ of Torpedo California using affinity chromatography, and antibodies which they created against Torpedo protein could be shown to cause a myasthenia gravis-like syndrome when it was injected into rabbits (Lindström, 1976). This was the prototype model of experimental autoimmune myasthenia gravis and using this model it became possible to induce this myasthenic-like state in many species of animals. It has, however, not yet been possible experimentally to initiate endogenous antibody receptor production and the precipitating cause of antibody production has not been elucidated in animal studies.

B. Acetylcholine receptor antibodies

The acetylcholine receptor is highly concentrated on terminal expansions (crests) of the postsynaptic junctional fold of the neuromuscular junction (Dreyer, 1982). Here, the binding of acetylcholine results in the opening of cation channels and the influx of sodium ions. This is followed by the dissociation of acetylcholine from the receptor complex and hydrolysis of the acetylcholine. The receptor is a complex protein composed of 5 subunits which are partially embedded and partially projecting from the postsynaptic membrane. On the extracellular surface of the α subunits the main immunogenic region (MIR) is located. This is the site to which the majority of antibodies to acetylcholine receptors are directed and is distinct from the cholinergic binding site. These antibodies either block the opening of cation channels or initiate the degeneration of receptors (Drachman et al, 1982). Acetylcholine receptors are normally degraded and rebuilt in an average of 7 days. In a myasthenic patient this may be reduced to less than 48 hours (Efthimiou, 1985). The normal process of degredation of receptors is thought to consist of endocytosis firstly, followed by destruction within the muscle cells by lysosomal enzymes

(Drachman et al, 1987). The initiation of this process is believed to be accelerated by the binding of antibodies to the receptor and the subsequent precipitation of the complement cascade. The rate of degradation appears to be increased after cross-linking of acetylcholine receptors by antibody (Efthimiou, 1985).

In addition, it would also appear that damage to the postsynaptic membrane (probably complement induced) also occurs, resulting in permanent damage.

In 1976 Lindström reported the demonstration of circulating acetylcholine receptor antibodies to nearly 90% of patients with myasthenia gravis (Lindström et al, 1976). These antibodies are predominantly of the IgG type and in individual cases of myasthenia gravis acetylcholine receptor antibodies are composed of different sub-classes of IgG. The antibody response in myasthenia gravis is therefore polyclonal and monoclonal acetylcholine receptor antibodies can bind to a variety of sites on the receptors (Engel, 1984). That the antibodies against the MIR are pathologically significant is indicated by their ability to cross-link and modulate acetylcholine receptor activity (Drachman et al, 1978). In addition, the transfer of acute experimental autoimmune myasthenia gravis passively indicates that they can bind and fix complement. The pattern of antibody specificity revealed by various laboratory studies is difficult to correlate with the clinical form and severity of myasthenia gravis (Roses et al, 1981). The spectrum of antibody specificities in individual patients remains constant for years and is independent of the total acetylcholine receptor antibody concentration in the sera. Antibody characteristics that might correlate with clinical types of myasthenia gravis have been sought in laboratory investigations (Gilhus et al, 1984; Berrih et al, 1984). Acetylcholine receptor antibodies are predominantly of the IgG1 and IgG2 sub-classes and are relatively enriched with Kappa light chains (Engel, 1984; Lindström et al, 1976; Roses et al, 1981). Although differences in antibody characteristics in adult generalised forms of myasthenia gravis (with or without thymoma) have not been found, patients with ocular myasthenia gravis have a significantly greater portion of Kappa light chains and IgG3 sub-class antibodies than patients with generalised myasthenia (Engel, 1984; Knight et al, 1986). Also it has been found that

antibodies with ocular myasthenia gravis react somewhat better with acetylcholine receptor from ocular and normal muscle rather than from denervated muscle obtained by muscle biopsy (Engel, 1984).

The usefulness of the acetylcholine receptor antibody test has been confirmed (Engel, 1984; Lindström et al, 1976). The percentage of positive results is influenced by the source and method of preparation of acetylcholine receptor, the method of assay, the upper limits set for the titre in the control population, and the proportion of patients in remission or with ocular myasthenia gravis included in the series. As indicated above Lindström and colleagues show an 80% positive test in patients with myasthenia gravis. In Lindström's study human acetylcholine receptor labelled with ^{125}I-labelled bungarotoxin and protected from proteolysis was used as the antigen in immunoprecipitation assay (Lindström et al, 1976). In another large and representative series the percentages of positive tests in different clinical forms of myasthenia gravis were as follows: remission 24%, ocular 50%, mild generalized 80%, moderately severe or acutely severe 100%, chronic severe 89% (Tindall, 1981). In ocular myasthenia gravis the antibody titre tends to be low. In generalised myasthenia gravis it tends to be high in the presence of thymoma. In individual patients a decrease in antibody titre of more than 50% sustained for more than 12 months is nearly always associated with sustained clinical improvement (Limburg et al, 1983; Seybold, Lindström, 1981). Changes in titre correlate strongly with long term improvement induced by prednisone, azathioprine or thymectomy, but not with response to acetylcholine esterase drugs or with worsening caused by infection or emotional stress (Vincent et al, 1983). The transient decrease in titre induced by plasmapheresis is also associated with transient clinical improvement (Dau et al, 1977).

C. Genetic factors

Genetic factors which have an influence on the incidence and type of myasthenia gravis have been studied, particularly in relation to co-existing diseases (Simpson, 1981; Simpson, 1960; Simpson, 1968). In MG patients who have a thymoma, no sex or HLA antigen association has been determined, but the incidence of associated autoimmune disorders in this group is approximately 23%. (Engel, 1984).

Patients with no thymoma who are under 42 years are usually females with a higher likelihood of HLA A1 B8 DRW3 antigens and if they are Japanese they have B12 antigens (Engel, 1984). Associated autoimmune diseases are much less common in this group (± 10%). Patients who have no thymoma but develop MG after the age of 40 years are usually male with an increased chance of HLA A3 B7 and/or DRW2 antigens (A10 in Japanese). This group has a 33% incidence of associated autoimmune disease (Engel, 1984).

CONFIRMATION OF THE DIAGNOSIS

A. Therapeutic tests

The Edrophonium test: The clinical suspicion or diagnosis of MG may be confirmed by the edrophonium test, in which 2 mgs of edrophonium chloride is injected intravenously, followed 45 seconds later by an additional 8 mg if the first dose is without effect (Osserman, Kaplan, 1953; Simpson, 1981). Atropine sulfate (0.5 mg or more, intravenously) should be given if a severe reaction ensues. A positive response consists of an increase in strength and tolerance for exercise in affected muscles, which lasts for a few minutes. Exceptionally the effects may last much longer and in one of our patients it could often be demonstrated for 30 minutes.

In most cases a positive response will be evident within a few seconds of completing the injection. The ptotic lid rises, diplopia clears and a smile irradiates the flat, expressionless face; the voice becomes clearer and more powerful and the arms may be lifted joyously overhead. Whatever muscles are affected, there will the response be, dictating the particular form of a positive response. However, bizarre responses such as improved oculomotor function without elevation of the ptosed lid (until raised by the examiner) may occur, and responses may be blunted by the recent use of anticholinesterases. Indeed, a therapeutic trial prior to confirmation of the diagnosis may cause serious difficulties in that partial alleviation of myasthenic weakness may continue for about 48 hours after withdrawal of the drug and then cease abruptly. In other subjects the use of placebo, as well as edrophonium, may help to dispel uncertainty.

An ice pack test has been described by Sethie and others (1987) which they found to be as effective as edrophonium in reversing ptosis due to myasthenia gravis. It is well known that resting and cooling a muscle in a patient with myasthenia gravis will improve the myasthenic weakness. In this test ice is wrapped in a towel or surgical glove and placed over one lightly closed eye for two minutes (if the ptosis is bilateral the most affected eye should be cooled). In cases with bilateral ptosis the opposite

(uncooled) eye serves as a control. This test has not been widely used as the edrophonium test is the accepted method.

B. Electromyographic studies

The number of quanta of acetylcholine released at the synapse normally declines during repeated stimulation (Drachman, 1978; Dreyer, 1982; Standaert, 1982). In patients with MG this occurs in the presence of a reduced number of acetylcholine receptors with the result that repeated supramaximal stimuli result in fewer and fewer endplate potentials of sufficient strength to generate an action potential (Drachman, 1978). If, therefore, electrodes are placed on the surface of an affected muscle to measure the compound muscle action potential generated by a supramaximal stimulus, the amplitude of the response will progressively decline. This decremental response is most evident by the fifth stimulus when stimulating at 3-5 stimuli per second. The response can be restored to normality temporarily by IV edrophonium.

The test is positive in generalized MG in approximately 95% of patients whose muscles are sampled widely (Ozdemir, Young, 1976). It provides proof of disordered function of the neuromuscular junction, effectively distinguishing myasthenia from other causes of weakness such as disease of the anterior horn cells or peripheral nerves. It may also provide evidence of unexpected widespread myasthenia in patients who have ocular myasthenia gravis.

Single fibre electromyography is probably the most sensitive test available (Simpson, 1981). However, it is extremely time-consuming and is not performed by our electromyographers. We have no knowledge of the frequency with which this technique reveals diagnostic abnormalities not revealed by simpler manoeuvres.

C. Antibody levels

The following immunological investigations are appropriate to the patient with myasthenia gravis. Firstly, antibody titres against both human and denervated rat muscle acetylcholine receptors can be determined in the patient serum; the antibody titre of the serum being calculated from the amount of iodine-labelled alpha bungarotoxin acetylcholine receptor precipitated in various dilutions (Drachman et al, 1982). Secondly, immunoglobulin G can be precipitated and the concentration of IgG in the serum measured (Engel, 1984). Thirdly, the degradation rate of acetylcholine receptors can be measured by comparing the patient serum degradation rate to control degradation rate in normal sera (Drachman, 1982). Finally, enzyme-linked immuno adsorbent assays (ELISA's) can be used for detecting acetylcholine receptor antibodies (Engel, 1984). The amount of myasthenia gravis serum IgG that binds directly to this antibody can be measured, as well as the amount of acetylcholine receptor immobilized by the antibody. Striated muscle antibodies are known to exist in myasthenia gravis and their presence had been discovered long before acetylcholine receptor antibodies were found (Engel, 1984). The role of striated muscle antibodies in myasthenia gravis remains unknown but their association with thymoma is a clinically useful feature, being present in 84% of patients with a thymoma (Gilhus et al, 1984).

SPECIAL INVESTIGATIONS

The initial investigation of the patient with myasthenia gravis should include a search for the presence of thymoma and the exclusion of invasive thymoma, the detection of antibodies to acetylcholine receptors, the exclusion of associated medical diseases such as thyroid disease and collagen vascular disease, and objective measurements of muscle function pertinent to the weakness associated with myasthenia gravis.

A. Radiology of the thymus

The thymic gland is not usually seen on chest radiographs unless a thymoma is present (Janssen et al, 1983). Small tumours localised to part of the gland may also remain invisible. In addition to the standard chest radiographs (PA and lateral), computerised axial tomography of the superior mediastinum is necessary. Radioisotope scanning of the superior mediastinum has been reported to give good imaging of thymomas (Simpson, 1981). Gallium 67 has become the preferred isotope and may be valuable in detecting recurrences of malignant thymoma after operation. Other techniques suggested in the literature are pneumomediastinography and thymic vein venography, both investigations being difficult to interpret and, in some instances, dangerous (Simpson, 1981). The detection of a thymoma is regarded by most authors as an absolute indication for thymectomy to prevent local spread and potential invasion of surrounding vital structures.

B. The exclusion of associated medical conditions

Thyroid disease must be excluded by thyroid hormonal assays and antibodies to the thyroid must be measured. Collagen vascular diseases such as RA, SLE and polymyositis, must be excluded by measurement of sedimentation rate, muscle aldolases, (LDH, CPK) DNA antibodies, anti-nuclear antibodies, latex test, Rose Waller sheep cell agglutination test (SCAT), serum complement and immunoglobulin levels. Asthma must be excluded by specific lung function testing.

C. Lung function testing in myasthenia gravis

Objective measurements of respiratory function in the patient with myasthenia gravis should include the measurement of lung volumes, particularly residual volumes, total lung capacity, forced expiratory volume in 1 second (FEV_1) and forced expiratory capacity (FVC). The presence of variable airflow obstruction must be documented, bearing in mind that cholinesterase inhibitors used in myasthenia gravis can cause broncho constriction. Furthermore, the increased airways resistance created by small lung volumes or airflow obstruction can have a major impact on respiratory muscle fatigue in patients with myasthenia gravis. Respiratory function testing can be the best way to document muscle strength and fatigue with effort. This is done by using the sustained maximum expiratory pressure manoeuvre (MEP max-sustained) and the maximum voluntary ventilation (MVV). It is important to note that these objective measurements of respiratory strength and fatigue are the best pointers towards the possible need for mechanical ventilatory support, either post-surgery (thymectomy) or in the event of a respiratory infection (Younger et al, 1984). Blood gas analysis is virtually useless in the patient with myasthenia gravis who may develop a rising $PaCO_2$ but is just as likely to maintain normal arterial blood gases up to the point of respiratory arrest (Bennett, Bleck, 1988). The objective measurements of respiratory strength (and fatigue) often reveal lower than normal or predicted values, even during periods of apparent clinical remission. Many adults with generalized myasthenia gravis can be shown to have fixed "irreversible" weakness with these objective tests. Although the lung volumes are well preserved, the residual volume is characteristically higher than predicted (owing to the inability of a weak patient to expire maximally), and the maximum sustainable expired pressure and maximum voluntary ventilation are often 50% of predicted values. These findings are typical in patients with longstanding MG, even when they appear to be well.

THERAPEUTIC OPTIONS IN MYASTHENIA GRAVIS

A. Cholinesterase Inhibitors

Inhibitors of endplate acetylcholinesterase enhance the neuromuscular transmission by preventing hydrolysis of acetylcholine and so prolonging its availability at the post-synaptic receptor sites (Koelle, 1975). As the basis of weakness in MG is a reduction in the number of acetylcholine receptors available for activation by acetylcholine, it may be surmised that prolongation of the life-span of released acetylcholine will result in excitation of more receptors and therefore increased response to the nerve impulse. Such today is the theoretical justification of the continued use of cholinesterase inhibitors almost 100 years after Jolly noted the resemblance of MG to curare poisoning, over 50 years since Walker showed prostigmine to be useful in the management of the disease, and some 25 years since the post synaptic localisation of the disorder (Walker, 1935; Simpson, 1958). Cholinesterase inhibitors do not increase the production of acetylcholine quanta and are therefore only effective if the transmitter is adequately released at the motor nerve endings. For optimal intermittent neuromuscular transmissions finite amounts of acetylcholine and, thereafter, cholinesterase are required to ensure efficient generation of action potentials and subsequent freeing of receptor sites for further transmissions (Drachman, 1978). It is clear that excessive amounts of either acetylcholine or cholinesterase will make neuromuscular transmission ineffective. The efficacy of cholinesterase inhibitors in myasthenia gravis is dramatically demonstrated by the edrophonium test. However, the potency and short half-life of edrophonium makes it unsuitable for symptomatic treatment of myasthenia gravis. Orally administered neostigmine and, particularly, pyridostigmine are the commonly used cholinesterase inhibitors in the symptomatic relief of myasthenia gravis. These agents are quartenary ammonium anti-cholinesterase compounds which do not cross the blood-brain barrier and therefore exert no central nervous system effects (Koelle, 1975). Tertiary amines such as physostigmine are not used in myasthenia gravis because of their free passage across the blood-brain barrier which interferes with the effects of acetylcholine on the central nervous system.

Cholinesterase inhibitors such as neostigmine and pyridostigmine vary tremendously in terms of their half lives and specific efficacy in patients with myasthenia gravis. These drugs must therefore be carefully chosen, be given at regular intervals and should initially be commenced in small doses with careful monitoring of their effect in patients with myasthenia gravis. When given at regular intervals during the day, muscle strength can be restored to an adequate level but rarely to absolute normality. It is important to establish the dose of anti-cholinesterase drugs which give the maximum therapeutic response. Most myasthenic patients can be improved only up to a certain level which may not restore muscle strength to normal under varying degrees of activity. The patient with myasthenia gravis must often learn to live with some degree of disability. Increasing the dose of drugs above the maximum response level in the attempt to achieve peak physical activity may often produce the opposite effect and progressive muscle weakness may finally end in a "cholinergic crisis". Myasthenic patients like any other individuals are subject to the fatigue of mental and physical strain and the temptation to increase the dose of medication to achieve excessive physical activity must be resisted. Furthermore, stress situations such as increased environmental temperature, menstruation, inter-current infection and emotional stress can dramatically alter the requirements for cholinesterase inhibitors in a specific patient. In these situations cautious and carefully supervised changes in drug dosage is essential.

Neostigmine is usually given in a dose of 15 mg 4 hourly which can be increased to a maximum of 30 mg 3 hourly if necessary. It is effective within 30 minutes and is a potent cholinesterase inhibitor. Cholinesterase inhibitors have both muscarinic and nicotinic effects of acetylcholine. Muscarinic activity affects smooth muscles and exocrine glands and excessive activity is manifested by abdominal colic, diarrhoea, nausea, salivation and lacrimation (Koelle, 1975). These symptoms usually indicate overdosage and it is unwise to counteract these effects regularly by the use of anti-cholinergic drugs such as atropine (Simpson, 1981).

Pyridostigmine has the advantage of a longer half-life with more prolonged action and rarely needs to be given more often than 4 hourly. A dose of 60 mg is equivalent to 15 mg neostigmine (Simpson, 1981).

An initial starting dose of 60 mg 6 hourly should be used, increasing to a maximum dose of 120 mg 4 hourly until a maximum benefit is obtained.

In contrast to the inter-patient variability in dose requirements of cholinesterase inhibitors, the bio-availability and plasma levels of orally administered pyridostigmine are quite predictable, making monitoring of plasma pyridostigmine levels unnecessary (Sorensen et al, 1984).

Increasing doses of cholinesterase inhibitors can cause weakness similar to that of myasthenia itself, creating a "cholinergic crisis" (Drachman, 1978). This can be impossible to differentiate from a myasthenic crisis and requires the withdrawal of cholinesterase inhibitors, careful monitoring of the patient with mechanical ventilatory support if necessary and careful reintroduction of the cholinesterase inhibitors as the patient recovers.

B. Corticosteroid therapy

Immunosuppression is the mainstay of therapy in generalized myasthenia gravis and prednisone given orally is the most commonly used corticosteroid. Although the beneficial effect of corticotropins on myasthenia gravis was suggested as early as 1951, controversy surrounded the use of adreno-corticotropin (ACTH) for some 20 years despite the immunological basis of myasthenia gravis being recognised by Simpson in about 1960 (Millikan et al, 1951; Simpson, 1960). The widespread use of corticosteroids in myasthenia gravis was established in 1971 when oral treatment with prednisone replaced injections of ACTH (Kjaer, 1971; Namba et al, 1971).Although there have been reports of hundreds of patients with myasthenia gravis being treated successfully with long term corticosteroid therapy, there have as yet been no adequately controlled studies comparing steroid therapy to placebo in myasthenia gravis (Pascuzzi et al, 1984; Sghirlanzoni et al, 1984). Because of the natural history of myasthenia gravis with exacerbations and remissions, a controlled study of steroid therapy in myasthenia gravis would require hundreds of patients and would now be ethically unacceptable. There is uncertainty in the literature regarding the relative value of various regimens of corticosteroid therapy as

well as the concomitant use of other modalities (Pascuzzi et al, 1984; Brunner et al, 1976). Some authors have suggested high dose intravenous methylprednisolone pulses, while others prefer high dose prednisilone daily orally (Arsura et al, 1985). Some suggest that high dose prednisone should be given on alternate days, while others suggest starting with low dose alternate day prednisone, increasing as required (Warmolts, Engel, 1972; Seybold, Drachman, 1974). In this way it is hoped to avoid the well known temporary aggravation of symptoms that may occur in the first few weeks of steroid therapy (Simpson, Thomaides, 1987; Seybold, Drachman, 1974; Miller et al, 1986). The concomitant use of azathioprine treatment, thymectomy, plasmapheresis for crisis and of course cholinesterase inhibitors make analysis of cases and reports very difficult.

Prednisone given orally is seldom given in doses exceeding 60-80 mg/day until the onset of improvement when the dose is usually reduced slowly, often to an alternate day dose for several years duration. The beneficial effects of steroids have been reported in ocular as well as generalized myasthenia gravis and especially in late onset MG (over 50 years of age) with some reports showing improvement in every single case treated, with most reports showing a greater than 80% improvement rate (Simpson, Thomaides 1987; Pascuzzi et al, 1984; Sghirlanzoni et al, 1984; Taylor et al, 1989). Improvement is usually noted within 10-13 days and is often maximal within a few weeks but may continue for 5-6 months.

The many side effects and complications of prednisone therapy limit the drugs usefulness. Steroids may be contraindicated if any of the following complications are present: obesity, diabetes mellitus, hypertension, cataracts, osteoporosis, aseptic necrosis, viral or fungal infections, glaucoma, or gastric or peptic ulcer.

During steroid therapy regular chest radiographs are mandatory in areas where Tuberculosis is common.

Long term steroid therapy is resisted by many patients (particularly young females with weight gain and acne). Opportunistic infections are more common when azathioprine and plasmapheresis are used regularly.

Withdrawal of corticosteroid therapy can result in a relapse or exacerbation of myasthenia gravis even when the disease has apparently been controlled for many months or even years (Grob, Harvey, 1952; Scherpbier, Oosterhuis, 1987; Johns, 1987). Reduction in steroid therapy should occur very gradually over many months and most authors agree that once steroid therapy has been started it should be continued for at least 2 years. Steroid therapy has been shown to lower circulating acetylcholine receptor antibodies in myasthenia gravis and to reduce the daily requirements of cholinesterase inhibitor therapy. Patients with myasthenia gravis on steroids have fewer exacerbations and crises and fewer admissions to hospital during the active stage of their disease (Pascuzzi et al, 1984; Sghirlanzoni et al, 1984; Scherpbier et al, 1987; Johns, 1987). The use of steroids prior to thymectomy has been shown to markedly reduce the peri-thymectomy morbidity and most authors recommend that thymectomy should not be performed within three months of starting steroid therapy in order to obtain the maximum benefit (Pascuzzi et al, 1984; Sghirlanzoni et al, 1984; Brunner et al, 1976; Arsura et al, 1985; Warmolts, Engel, 1972; Seybold, Drachman, 1974; Miller et al, 1986; Taylor et al, 1989; Scherpbier, Oosterhuis, 1987; Johns, 1987).

C. **Azathioprine**

The recognition of the autoimmune nature of myasthenia gravis resulted in studies of a variety of immunosuppressive agents such as azathioprine, methotrexate, mercaptopurine and actinomycin D and, more recently, cyclosporin (Simpson, 1981; Mertens et al, 1969; Mertens et al, 1981; Niakan et al, 1986; NybergHansen, Gjerstad, 1988; NybergHansen, Gjerstad, 1988). As with corticosteroids most studies have shown a greater than 80% improvement or remission rate using these immunosuppressors in myasthenia gravis, the most impressive results with the fewest side effects or complications being seen in patients with azathioprine who had not responded well to corticosteroids (Witte et al, 1984; Matell, 1987; Mantegazza et al, 1988).

Azathioprine immunosuppression offers a useful alternative to patients who do not tolerate corticosteroids or who have significant side effects on these drugs (Mantegazza et al, 1988).

Azathioprine is not without its toxicity and side effects which include pancytopaenia and hepatic toxicity (Kern, Stewart, 1986; Hohlfield et al, 1988; Fonseca, Harvard 1988; Smith, Boughton, 1989). The recommended dose of azathioprine is 2 mg/kg/day with careful monitoring of full blood count and liver function tests. The dose can be increased by 50 mg a day at 2 to 3 month intervals if optimal immunosuppression has not been achieved. The goals of immunosuppressive therapy are a white blood count of approximately 4 x 10^9/l, a 25% reduction in platelet count and an MCHC of greater than 76% (Witte et al, 1986). Benefit is not normally observed within 3 months and maximum response may be delayed considerably longer.

As with steroids, relapse may follow rapid tapering of azathioprine, even after many months of apparently complete clinical remission (Witte et al, 1984; Michels et al, 1988). Azathioprine therapy should therefore also be continued for 1 to 2 years and the dose reduced slowly with careful monitoring. Azathioprine is appropriate therapy for patients with myasthenia gravis who are intolerant of corticosteroids and should be considered early in selected patients where symptomatic relief is not easily obtained with cholinesterase inhibitors. It may be effectively combined with steroids for rapid relief and continued after withdrawing steroids 3-6 months later (Mantegazza et al, 1988).

D. Plasmapheresis

The rationale for the use of plasmapheresis as a therapeutic modality in myasthenia gravis is convincing (Hertel et al, 1978; Arrigo et al, 1979; Newsom-Davis et al, 1978; Denys et al, 1979; Newsom-Davis et al, 1979; Consensus Co, 1986; Seybold, 1987). It is indeed fortuitous that recognition of the role of antibodies to acetylcholine receptor in the pathogenesis of myasthenia gravis coincided with technological advances in plasma separators.

Remission of myasthenia gravis following plasmapheresis was first described by Pinching et al in 1976, when two out of three cases improved after a series of plasma exchanges (Pinching, Peters, 1976). The

following year Finn and Coates noted transient improvement in a patient with myasthenia gravis who received plasma exchange (Finn, Coates, 1977).

Dau et al, in 1977, reported in the New England Journal of Medicine (NEJM) that five patients, who were severely myasthenic despite thymectomy and prednisone, had a striking clinical improvement following plasma exchange and azathioprine (Dau et al, 1977). Antibody levels fell to 20% of original levels in these patients. It is important to note that the response to azathioprine alone is often slow and delayed and not nearly as rapid as with plasma exchange.

Since 1979, 13 patients with MG have had serial plasma exchanges at Groote Schuur Hospital.

TABLE OF RICU EXPERIENCE WITH PLASMA EXCHANGE IN MYASTHENIA GRAVIS

13 patients in 10 years		
8 males / 5 females		
Adult generalised MG	11	
Predominantly bulbar, respiratory	2	
Number of exchanges/patient	2 - 69	
Average volume 3 litres		
Replacement fluid:	Plas B with Albu	8 patients
	FFP	5 patients

All except 2 patients weaned from mechanical ventilation within 7 days

Complications:	Haemorrhage	2
	Hypotension	1
	Untoward reaction (Alb)	1

No mortality related to plasma exchange

The beneficial effects of plasmapheresis are seen in almost all myasthenia gravis patients on which the technique is used (Newsom-Davis et al, 1979; Kornfeld et al, 1981; Olarte et al, 1981; Perlo et al, 1981; Cornelio et al, 1987). The benefits may be slight or great and may last days or months and the delayed effect may be unrelated to measured antibody titres (Riley, Monaghan, 1980; Campbell et al, 1980). There are no reports of controlled trials of plasmapheresis in myasthenia gravis. It is therefore not clear whether concomitant use of pharmacological immunosuppression accelerates or enhances the response to plasma exchange or not.

The time course of clinical response to plasma exchange in myasthenia gravis is interesting. In a study using electrophysiological testing (EMG) to measure evoked potential amplitudes in four female patients with myasthenia gravis, Campbell et al showed improvement only seven days after starting a series of plasma exchanges which corresponded well with the clinical response (Campbell, et al, 1980). This is in contrast to earlier studies which report much earlier and more dramatic responses to plasma exchange. Some authors have suggested that there are other factors besides the removal of acetylcholine receptor antibodies which may account for the observed beneficial effects of plasma exchange. Suggestions include placebo effect, changes in serum electrolytes, dilution of excessive anticholinesterases, changes in body temperature, and removal of substances causing a direct neuromuscular blocking effect.

There are a number of reasons why controlled studies of the use of plasma exchange in MG are not feasible and these include the small numbers of suitable patients, the fluctuating nature of the disease, the variations in combinations of therapy, as well as the obvious benefit of plasma exchange during myasthenic crises. Furthermore, "sham" plasma exchange is considered unethical by most clinicians.

A consensus development conference on The Utility of Therapeutic Plasmapheresis for Neurological Disorders, was held from 2 - 4 June 1986, convened by the National Institute of Neurological and Communicative Disorders, the Clinical Centre and the National Health Office of Medical Applications of Research of North America (Consensus Co, 1986). This was attended by experts from North America and Europe who concluded that plasma exchange can be useful in strengthening patients with

myasthenia gravis before thymectomy and during the post-operative period. They also agreed that plasma exchange was valuable in lessening symptoms during the initiation of immunosuppressive drug therapies as well as during an acute crisis.

Plasma exchange is not without risk and meticulous attention to detail is required.

TABLE OF THE POTENTIAL RISKS OF PLASMAPHERESIS

Equipment related

- Overheating
- Inaccurate fluid/anticoagulant replacement
- Haemolysis

Vascular access related

- Vascular perforation - haemorrhage
- Arterial, nerve injuries
- Embolism (thrombo- / air-)
- Line sepsis
- Venous thrombosis
- Disconnections

Procedure related

- Haemorrhage following anticoagulants
- Activation of coagulation/fibrinolysis
- Creation of factor deficiencies
- Electrolyte imbalances
- Fluid shifts
- Allergic reactions
- Transmission of infections

E. Thymectomy

The relationship between the thymus and myasthenia gravis was first noted by Weigert in 1901. Schumacher and Roth reported in 1913 that removal of the thymus might lead to clinical improvement in patients with myasthenia gravis. Between 1939 and 1944 Blalock published results of thymectomies in the treatment of myasthenia gravis (Blalock et al, 1939; Blalock et al, 1941; Blalock, 1944). It was on the basis of Blalock's experience that thymectomy was gradually adopted, particularly after the recognition of the immunological nature of myasthenia gravis by Simpson (Simpson, 1960).

In the early days the operative mortality for thymectomy was considerable, but so was the overall mortality in established generalized myasthenia gravis. With the introduction of immunosuppression, much controversy was aroused regarding the relative therapeutic benefits of thymectomy versus immunosuppression (Rowland, 1980; Drachman, 1978). Fortunately the advent of immunosuppression and intensive care medicine reduced the peri-operative mortality from thymectomy to an absolute minimum (Simpson, Thomaides, 1987). During the 1970s thymectomy became accepted standard therapy for patients with generalized myasthenia, even in the absence of thymoma (Perlo et al, 1971; Mulder et al, 1974; Papatestas et al, 1975; Buckingham et al, 1976; Jaretzki et al, 1977; Fraser et al, 1978).

Despite the current understanding of the immunological basis of myasthenia gravis, it is still not entirely clear whether thymectomy is beneficial because of removal of a source of antibodies, or because the source of antigen is removed (Kao, Drachman, 1977; Levinson et al, 1984; Cox et al, 1986). Thymectomy certainly has been shown to be of benefit in otherwise untreated patients, but there is still some controversy as to the benefits of thymectomy in patients with mild myasthenia gravis who respond readily to small amounts of immunosuppression (Olanow et al, 1987). Unfortunately thymectomy is not a cure for myasthenia gravis. Thymectomy has certainly been shown to promote remission and may make the course of myasthenia gravis more benign (Olanow, Roses, 1984; Mulder et al, 1983; Mulder et al, 1989). There is no clear indication of the optimal timing of thymectomy, nor which patients may go into

remission spontaneously and not need thymectomy at all. The response to thymectomy is unpredictable but is usually delayed for at least a few months and may be for up to two years. As many cases of myasthenia gravis would go into spontaneous remission within a two year period, it is extremely difficult to compare results between thymectomy, immunosuppression and combinations of therapy. The rationale for thymectomy internationally is based on many reports in the literature which indicate that thymectomy is followed by improvement in 80 - 90% of patients, particularly when there has been no thymoma found at histology (Mulder et al, 1983; Mulder et al, 1989; Jaretzki et al, 1988; Hatton et al, 1989). Most authors would agree that all myasthenic patients once controlled with anti-cholinesterase drugs and steroids should be offered thymectomy provided that they can be under the constant care of a neurologist, an anaesthetist and a thoracic surgeon who have worked together in the treatment of this disease (Genkins et al, 1987; Hatton et al, 1989; Mikkelson, 1986; Whyte et al, 1989).

The surgical technique (median sternotomy or trans-cervical incision) is a controversial matter (Rowland, 1980; Whyte et al, 1989; Campbell et al, 1970; Cooper et al, 1988; Jaretzki, Wolff, 1988; Rowbottom, 1988; Brodrick, Wainwright, 1988). A novel transverse sternotomy incision is another option (Otto, Strugalska, 1987). There is no doubt that the trans-cervical approach has less operative morbidity and greater patient acceptability but complete removal of the thymus and the surrounding fat tissue is less certain with trans-cervical surgery (Henze et al, 1984). There have been reports that incomplete removal of the thymus is more likely to result in a relapse which is believed to be related to thymic remnants not removed at initial surgery (Rosenberg et al, 1983) Some authors even recommend extended thymectomy for pure ocular MG (Yang et al, 1989).

Histology of thymic tissue removed at surgery in many studies has shown that > 75% of patients have some abnormality of the thymus which is theoretically associated with myasthenia gravis (Simpson, 1981). In 70-85% of these the thymus has been shown to be hyperplastic with germinal centres and in 10-15% of cases a thymoma has been present (Castleman, Noris, 1949). Immunological studies on T-lymphocyte in thymic tissue removed from patients with MG suggests that most patients can be shown

to have T cells directed against acetylcholine receptors (Berrih et al, 1984; Scadding et al, 1981; Melms et al, 1988).

It is generally agreed that the long term outlook is much poorer if a thymoma is found although the outlook has definitely been shown to be better if the thymoma is removed (Olanow, Roses, 1984; Mulder et al, 1989; Jaretzki et al, 1988; Shamji et al, 1984; Mondon et al, 1985). It is interesting to note that there are records of myasthenia gravis becoming first clinically apparent months or years after the removal of a thymoma (Kuroda et al, 1984). There are two possible reasons for this occurrence - some authors have suggested that the balance between helper and suppressor cell ratios may be disturbed by thymectomy while others have suggested that these cases reflect the natural history of the myasthenia gravis (Berrih et al, 1984; Kuroda et al, 1984). Although it can easily be argued that adequate chemical immunosuppression removes the need for thymectomy in the short term, the long term implications of potent immunosuppression must be considered and now that thymectomy carries an insignificant operative mortality a controlled study of thymectomy versus immunosuppression seems unethical (Genkins et al, 1987).

In the presence of certain co-existing diseases, thymectomy may improve both the MG and the other disease (Aita et al, 1974; Ferguson et al, 1983; Szobor, 1984; Jansen et al, 1987).

PERIOPERATIVE MANAGEMENT OF THYMECTOMY

Thymectomy should only be undertaken in a referral centre where anaesthetists, thoracic surgeons and intensivists have experience of myasthenia gravis and only after the disease has been adequately controlled by immunosuppression if required. Most patients undergoing thymectomy will not need more than a few hours of postoperative ventilatory support, though the potential for late respiratory complications is great if the disease is not controlled adequately or postoperative respiratory care is inadequate. Preoperative preparation should include objective measurement of respiratory function and the best indicators of the need for postoperative ventilation are the adequacy of the sustained maximum expired pressure manoeuvre and the competence of bulbar function (Younger et al, 1984; Gracey et al, 1984). Immunosuppression should be maintained peri-operatively and the use of corticosteroids and plasmapheresis preoperatively reduces the incidence of postoperative complications (Pouyau et al, 1982; D'Empaire et al, 1985). Premedication for anaesthesia should include an anticholinergic "drying" agent and a non-respiratory depressant anxiolytic. Cholinesterase inhibitors should be omitted 4-6 hourly pre-anaesthetic and non-depolarizing muscle relaxants should be avoided if possible during anaesthesia (Redfern et al, 1987). If it is found necessary to use non-depolarizing muscle relaxants intra-operatively, then small amounts (approximately one third of the normal dose) of a short-acting drug, e.g. vecuronium or atracurium should be used (Macdonald et al, 1984; Bell et al, 1984; Ward, Wright, 1984). Even patients who are in apparent remission can have prolonged paralysis after non-depolarizing agents (Lumb, Calder, 1989). Postoperatively the patient should be admitted to an intensive care unit for optimal analgesia and monitoring of respiratory function.

OUR EXPERIENCE WITH THYMECTOMY AND FOLLOW UP

Approximately 5 new cases of MG are seen at our hospital every year. During the period 01/01/79 - 31/12/83, 15 adults with generalised MG underwent elective thymectomy. All patients were admitted at least 1 week prior to surgery to ensure optimal medication.

There were 15 patients with a female:male ratio of 2:1. The mean age was 32 years (females 27 years, males 41 years). The elapsed time since the onset of MG was a median of 7 months, range 1 - 24 months). 15 patients were on anticholinesterase therapy at the time of surgery and 10 patients were receiving steroid therapy. Objective measurements of respiratory function were done prior to surgery in most patients and included FEV_1, FVC, MIP, MEP and MVV.

The pre-operative plan used by anaesthetists in our institution was as follows:
Anticholinesterase therapy was omitted 4- 6 hours pre-operatively in all cases. Steroid therapy was doubled and given intravenously. Diazepam 5 mg was given orally 1 ½ hours pre-operatively as an anxiolytic. Bronchodilator therapy (when appropriate) was continued by inhalation and intravenous routes.

General anaesthesia was induced with intravenous thiopentone 2-3 mg/kg, while ventilation was assisted by hand using a facemask and a circle absorption system. N_2O/O_2 and halothane 1-2% was administered. Topical anaesthesia of the mucosa of the oropharynx and larynx using a maximum of 5 mg/kg of a 4% lignocaine solution was then administered with a Macintosh spray and endotracheal intubation was accomplished without the use of non-depolarising muscle relaxants. Intermittent positive pressure ventilation was continued using a circle absorption system driven by a Bird ventilator maintaining normocarbia.

During surgery, balanced anaesthesia was achieved using the N_2O/O_2 halothane combination and intermittent intravenous narcotic analgesia (usually fentanyl). Only 3 patients had inadequate muscle relaxation and subsequently required small doses of alcuronium (5 mg max).

Surgical Details

Median sternotomy:	11
Trans-cervical approach:	4

Findings:	Thymic hyperplasia	10
	Thymoma	3
	Normal thymus	2
		15

All the patients were electively ventilated post-operatively for an average of 48 hours. Anticholinesterase medication, starting with half of the previous dose was re-introduced only when function of the gastro-intestinal tract allowed oral medication. Weaning from ventilatory support was monitored using serial measurements of vital capacity and arterial blood gas analysis.

POST-OPERATIVE MANAGEMENT PLAN

- Elective ventilation (mean = 48 hours).
- IPPV + PEEP ---> IMV + PEEP ---> CPAP.
- Nasogastric tube.
- Analgesia (usually 1-2 mg morphine iv hourly).
- Steroid therapy continued intravenously.
- Oral anticholinesterase re-introduced via nasogastric tube when gastro-intestinal tract functional, starting with half of previous maintenance dose.
- Objective measurements of respiratory function (vital capacity, maximum expiratory pressure, arterial gas analysis).
- Progressive wean from ventilatory support as respiratory function improved.

The overall peri-operative morbidity was 33%. Three patients developed respiratory tract infections post-operatively which precipitated myasthenic crises and necessitated re-intubation, prolonged ventilatory support and appropriate antibiotic therapy. There was no peri-operative mortality.

TABLE OF POST-OPERATIVE COMPLICATIONS

- Nosocomial infections (requiring re-intubation): 3 patients
- Basal atelectasis (treated with physiotherapy and PEEP): 2 patients
- Overall peri-op morbidity = 33%
- Peri-operative mortality = 0

Two years post thymectomy 60% of the patients were in remission and another 20% were significantly improved. Two patients have required re-admission to the Respiratory ICU during this time due to episodes of respiratory failure.

OUTCOME [2 YEAR FOLLOW UP]

0 - 3 months:	No detectable clinical improvement and medication unchanged in all patients.
3 - 6 months:	Gradual improvement recorded in 9 patients (60%) with medication reduced. [One death at 4 months - invasive thymoma with cardiac and renal failure].
6 - 12 months:	Continued improvement in 12 patients (80%). Medication reduced in 8 patients and discontinued in 4 patients.
At 2 years:	6 patients asymptomatic off therapy. 3 patients asymptomatic on $\leq$ 10 mg prednisone alternate days only. 2 patients much improved on $\leq$ 20 mg prednisone alternate days and $\leq$ 60 mg pyridostigmine 6 hourly. 2 patients still symptomatic on therapy and having had at least one hospital admission with respiratory failure. 1 patient lost to follow up.

The deleterious effects of general anaesthesia and surgery in patients with MG necessitate that elective thymectomy be performed in a unit with experience of the procedure and facilities for intensive care to ensure a low incidence of post-operative complications. The incidence of remission of MG increases with the number of years post-thymectomy. Complete remission or improvement may be expected in up to 80% of patients.

INTENSIVE CARE MANAGEMENT OF RESPIRATORY FAILURE

The most feared scenario in the patient with MG is the development of respiratory failure during exacerbation of the disease (Cohen, Younger, 1981; Bennett, Bleck, 1988). However, because of advances in respiratory intensive care and immunosuppressive therapy (including plasma exchange), patients with MG who develop respiratory failure have a low mortality and can usually be weaned from mechanical ventilatory support within 10 days (Perlo, 1983; Bennett, Bleck, 1988).

Respiratory failure may develop insidiously in the myasthenic and can occur despite apparently good peripheral muscle strength. With increasing weakness of the bulbar muscles, coughing becomes ineffective and the patient is unable to clear secretions from the airway. Continuous aspiration of secretions results in broncho-pneumonic infection and reduced pulmonary compliance. Unless the attending physician recognizes the signs of impending respiratory failure, the patient may appear to decompensate rapidly and suffer a respiratory arrest. This is due to the fact that patients with MG often have facial and accessory muscle weakness and do not appear to be in respiratory distress. They often maintain a normal arterial oxygen tension and $PaCO_2$ up to the point of respiratory arrest (Bennett, Bleck, 1988). Arterial blood gas analysis is useless in this situation and the indications for intubation should be based on whether the patient is able to clear his secretions (Gracey et al, 1984), whether the maximum sustainable expired pressure is below 40 cms H_2O (i.e. less than 30% of predicted) and whether the vital capacity is less than 15 mls/kg of body weight.

TABLE OF PREDICTORS OF THE NEED FOR VENTILATORY SUPPORT

* History of previous episodes of respiratory failure.
* Evidence of bulbar dysfunction.
* Vital capacity < 15 ml/kg.
* Inability to cough and clear secretions
* Maximum expiratory pressure < 50% of predicted.
* Respiratory rate > 30/min.
* PaO_2 < 8 kPa on 40% O_2.
* $PaCO_2$ > 6 kPa.

Serial monitoring of these parameters and assessment before and immediately after chest physiotherapy can be extremely useful in detecting impending respiratory failure.

Respiratory failure often occurs post-operatively, usually after thymectomy or caesarean section, which are both common operations in patients with MG (Gracey et al, 1983). Other factors known to precipitate myasthenic crises and respiratory failure are upper respiratory tract infections, emotional stress, pregnancy, hyperthyroidism, certain drugs (such as aminoglycoside agents, D-penicillamine and thyroid hormones) and the institution of high dose corticosteroid therapy.

Furthermore, excessive use of cholinesterase inhibitors causing bronchorrhoea and bronchospasm (as well as diarrhoea with subsequent inadequate absorption of immunosuppressive drug therapy) or the reduction of immunosuppressive therapy, can precipitate a crisis.

Once a patient with MG is intubated, mechanical ventilatory support with adequate volumes and positive end-expired pressure should be applied to rest the neuromuscular junction and prevent lung volume loss and reduced pulmonary compliance. Infection in the lungs should be evaluated and appropriately treated with antibiotics and chest physiotherapy. Anticholinesterase therapy should be temporarily discontinued but immunosuppressive therapy (usually intravenous steroids) should be optimized and plasma exchange considered if a myasthenic crisis is proven.

After 24-48 hours of rest, anticholinesterase therapy should be reintroduced in small doses via the naso-gastric tube, starting with no more than 60 mg of pyridostigmine 8 hourly, until bowel function is restored and absorption ensured. The intravenous administration of cholinesterase inhibitors can be dangerous and misleading in that they cause fluctuating levels of muscle strength.

Once immunosuppression achieves improved muscle strength, usually within about 5 days of initiation of plasma exchange, the patient should be weaned from mechanical ventilatory support provided that the

vital capacity remains above 15 ml/Kg and the maximum sustainable expired pressure remains greater than 40 cm H_2O during the wean. The attending physician must bear in mind that the patient may fatigue after a period of a few hours of spontaneous ventilation despite having good parameters while being rested on mechanical ventilation.

OUR EXPERIENCE WITH RESPIRATORY FAILURE IN MG

Every patient admitted to the Respiratory Intensive Care Unit at GSH is entered into the RICU computerized data bank with a complete record of all aspects of that admission (Annexure IV).

Any of these aspects can by analysed separately or jointly, either for a particular year or for any previous years.

A retrospective analysis of all patients with myasthenia gravis who were admitted to the intensive care unit for respiratory support during the 13-year period 1st October 1971 to 30th September 1984 was performed.

The clinical presentation, the reason for admission and the subsequent management of the patients were reviewed. The precipitating cause of the respiratory failure was identified in each case by correlating the history and presenting features with the response to therapy and subsequent outcome.

Particular attention was paid to the duration of admission, duration of ventilatory support and drug therapy pertinent to myasthenia gravis.

During the 13-year period, 58 patients with MG were admitted to the RICU on 103 occasions for a mean duration of 9.1 days (range 2-50, median 6 days).

TABLE OF PATIENT DATA

Patients:	58 (female 40, male 18)	
Admissions:	103	
Mean age:	32 years (female 27 years, male 41 years)	
Duration of admission:	Mean:	9.1 days
	Median:	6.0 days
	Range:	(2 - 50 days)
Associated disease:	Thyrotoxicosis 3	
	Asthma 2	

Forty six admissions were for elective post-operative ventilation (thymectomy 40, laparotomy 2, Caesarean section 1 and other 3). Infections were responsible for precipitating respiratory failure in 20 admissions (primary pneumonia 17, aspiration pneumonia 2 and mediastinitis 1). Myasthenic crisis caused respiratory failure in 11 admissions (previously undiagnosed MG 3, exacerbations while on regular medication 6, withdrawal of medication 2). Drug induced respiratory failure occurred in 7 patients (cholinergic crisis 2, steroid medication precipitating weakness 5). Other precipitating factors were bronchospasm in 2 known asthmatic patients and diarrhoea in one patient, all of whom had been on regular anticholinesterase and steroid medication.

TABLE OF REASONS FOR ADMISSION

Elective post-operative ventilation	Thymectomy	40
	Laparotomy	2
	Other	4
Infections with respiratory failure	Primary pneumonia	17
	Aspiration pneumonia	2
	Mediastinitis	1
Myasthenic crisis	Previously undiagnosed MG	3
	Exacerbations while on regular medication	6
	Inadequate medication	13
	Withdrawal of medication	2
Drug-induced respiratory failure	Cholinergic crisis	2
	Steroid medication	5
Miscellaneous	Bronchospasm (asthmatics)	2
	Diarrhoea	1
	Pleural effusion	1
	Atelectasis	2

The mean duration of mechanical ventilatory support was 4.5 days (range 1-30, median 3 days). Prior to 1978, 7 patients had tracheostomies mostly done electively at the time of thymectomy. In the last 5 years only 1 patient required a tracheostomy for prolonged ventilatory support (21 days). Persistent myasthenic weakness due to exacerbation of the disease was treated with increased immunosuppression (steroids 47, azathioprine 8 and plasmapheresis 6).

TABLE OF THERAPY DURING ADMISSION

Admissions	Therapy		
103	Ventilatory support	Mean:	4.5 days
		Median:	3.0 days
		Range:	1 - 30 days
103	Anticholinesterase		
54	Antibiotics		
47	Steroids		
8	Azathioprine		
6	Plasmapheresis		

The complications which we experienced occurred in only 36 out of 103 admissions.

TABLE OF MORBIDITY AND MORTALITY

	Admissions
Nosocomial infections/reintubation	21
Persistent basal atelectasis (Physiotherapy and PEEP)	14
Mortality	1

COMMENT

The deleterious effects and potential complications of anaesthesia and surgery dictate that all patients with myasthenia gravis should be optimally prepared with appropriate doses of cholinesterase inhibitors and immunosuppression (including plasma exchange if necessary) prior to elective surgery. It is extremely difficult in "crises" to determine the optimal dose of cholinesterase inhibitors. A cholinergic crisis is easily precipitated in the weak "myasthenic" patient and it is best to discontinue cholinesterase inhibitors temporarily while the patient is supported by mechanical ventilation. The cholinesterase inhibitors can then be gradually re-introduced as the patient responds to specific appropriate therapy.

PROGNOSIS

Painstaking research and strokes of genius have exposed the basic flaw in the patient with MG and given clinicians an acceptable model for understanding the disease, as well as a basis for rational therapy. Prior to the immunosuppressive era, incapacity due to active generalized MG was often followed by the excessive use of anticholinesterases which resulted in respiratory failure. Mortality was related to respiratory arrest or overwhelming nosocomial pneumonia in patients who required prolonged ventilatory support. Nowadays, exacerbation of the disease can be suitably treated by neurologists and intensivists and deaths due to myasthenic weakness are preventable.

However, MG remains a dangerous and disabling disease with an unpredictable course for any individual patient. Modern immunosuppressive treatment certainly returns most patients to productive lives and the morbidity of the disease is reduced in the short term (Grob et al, 1987). Advances in anaesthesia and intensive care have eliminated the mortality from thymectomy; and plasma exchange has dramatically reduced the morbidity from respiratory failure. The quality of life of most patients can be improved to an acceptable level with thymectomy and modest levels of immunosuppression until remission allows gradual reduction of the drugs, usually after 3-5 years (Perez et al, 1981). More aggressive immunosuppressive therapy, including serial plasma exchange may be justified where incapacity threatens emotional stability, personal relationships, family security and ambitions. However, the long term hazards of potent immunosuppression are serious and include increased mortality (Simpson, 1987). In addition, the spectre of relapse hangs over the potently immunosuppressed patient when this therapy needs to be withdrawn and much still needs to be learnt about the effects of age and clinical grouping on the prognosis of treated patients.

Pure ocular myasthenia rarely generalizes if the symptoms have been confined to the ocular muscles for 2 years or more (Bever et al, 1983). Although 49% of patients with ocular MG will generalize within 2 years, the course of the disease is usually benign in younger patients. In patients over the age of 50 years at onset, the risk of respiratory failure is greater if the disease becomes generalized.

Most recent studies on thymectomy in generalized MG indicate an up to 96% improvement rate following extended thymectomy, provided that the disease was mild, of short duration since presentation and no thymoma was found at surgery (Olanow et al, 1987; Olanow, Roses, 1984; Mulder et al, 1983; Mulder et al, 1989; Jaretzki et al, 1988; Hatton et al, 1989; Mikkelsen, 1986; Whyte et al, 1989; Campbell et al, 1970; Cooper et al, 1988; Jaretzki, Wolff, 1988).

The prognosis after thymectomy in patients with thymomatous MG has also been reported to be better after extended thymectomy, but definitely worse than for patients with non-thymomatous MG.149

The majority of studies of patients with generalized MG treated with corticosteroids report improvement or remission in up to 80% of patients using 60-80 mg daily, followed by equivalent doses on alternate days after sustained improvement (Pascuzzi et al, 1984; Sghirlanzoni et al, 1984). The incidence of side effects is high (up to 60%) and in one study complete withdrawal of steroids was possible in only 3 out of a total of 60 patients (Sghirlanzoni et al, 1984).

As with corticosteroids most studies with azathioprine have shown a greater than 80% improvement or remission rate but only after at least 6 months of continued therapy with doses ranging from 1.1. to 3.8 mg/Kg/day (Mertens et al, 1981; Witte et al, 1984). The incidence of serious side effects with these doses is in the order of 25%, necessitating meticulous monitoring to ensure optimal therapy and timeous cessation of therapy if complications arise (Witte et al, 1986).

Plasma exchange, although potentially life-saving in the short term and dramatically reducing the mortality associated with respiratory failure, confers no measurable long term benefit in MG patients (Newsom-Davis et al, 1979; Kornfeld et al, 1981; Olarte et al, 1981; Perlo et al, 1981; Cornelio et al, 1987; Riley, Monaghan, 1980; Campbell et al, 1980). The reported, albeit rare, complications of the procedure are predominantly related to the technical and mechanical aspects of central venous catheter placement, as well as the haemodynamic and haematological aspects of the plasma exchange

procedure. Fortunately, the expert plasma exchange services offered by the Haematology Department at Groote Schuur Hospital over the past 10 years has ensured the rapid recovery of most patients with acute myasthenic crises allowing early withdrawal of mechanical ventilatory support and little morbidity.

CONCLUSION

In conclusion, it would appear that the prognosis in the individual patient with MG is related to early recognition of the disease and its severity, the appropriate use of early extended thymectomy and the meticulous selection and application of immunosuppressive therapy while anticipating a remission which may take many years. Anticholinesterase drugs, if used appropriately with understanding of their limitations and avoidance of excessive quantities, will enhance the quality of life until remission is achieved.

Patients confirmed to have generalized MG are regarded as having the disease latent even after many years of apparent remission and are advised to carry a "medic-alert" bracelet for the rest of their lives.

The messages contained in this dissertation need to be communicated to MG patients and their physicians, particularly the variable nature of the disease and the exceptionally good control possible with current knowledge and therapeutic alternatives.

A review of myasthenia gravis and its treatment, written by Dr Derek Philcox and myself, has been accepted by Disease-a-Month in the USA for international distribution.

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ANNEXURE I

A COMPUTERISED RECORD OF THE AVAILABLE LITERATURE

ON MYASTHENIA GRAVIS

Code: OMNIREF

Uses: DBase IV

Facilities:

* Select existing file
* Create new file
    * Add new references
    * Search or tag references
    * Print references
    * View or design print formats
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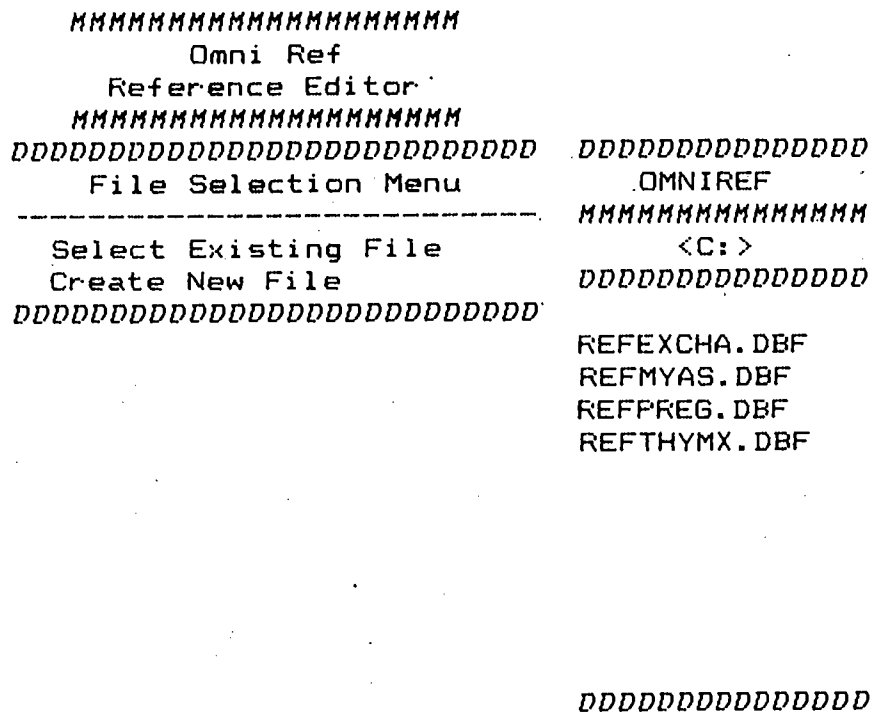
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PROGRAM CHOICES

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PRINT REFERENCES
VIEW OR DESIGN PRINT FORMATS
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***** Reference Editor *****

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Print Sequence Numbers

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*** Print Sequence Number Editor ***

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2. Reallocate numbers to numbered references
3. Renumber all references in present sequence

5. Return to previous menu

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1	Simpson	JA				1983
2	Rowland	LP				1982
3	Simpson	JA				1981
4	Drachman	DB				1978
5	Havard	CWH				1973
6	Drachman	DB				1978
7	Walton	JN				1981
8	Harvard	CWH	Scadding			1983
9	Engel	AG				1984
10	Simpson	JA	Thomaides			1987
11	Genkins	G	Kornfeld	Papatestas	Bender	1987
12	Efthimiou	J				1985
13	Compston	DA	Vincent	Newsom-davis	Batchelor	1980
14	Willis	T				1972
15	Campbell	H	Bramwell			1900

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*** Reference Printer ***

You may print references to disc file,screen or paper

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2. Print References to screen
3. Print References to paper
4. Print notes to disc
5. Print notes to paper

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1: CANTANZARITE VA, MCHARGNE A, SANBERG EC, DYSON DC. Respiratory arrest during therapy for premature labour in a patient with myasthenia gravis. 1984.
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ANNEXURE II

A COMPUTERISED DATABANK FOR ALL PATIENTS WITH

MYASTHENIA GRAVIS

Code: GSH Respiratory Unit Records (Resrec) - Myasthenia Gravis Study

Uses: DBase IV

Facilities:

* Enter new records
* Alter existing records
* View individual records
* Compare records
* Search records
* Utilities (back up and deletion)

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GROOTE SCHUUR HOSPITAL - RECORD SYSTEM:
=====================================

RUN <R>ESPIRATORY RECORDS OR <M>YASTHENIA GRAVIS STUDY?

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MYASTHENIA GRAVIS STUDY
- MAIN MENU -

A -- ENTER NEW RECORDS

B -- ALTER EXISTING RECORDS

C -- VIEW INDIVIDUAL RECORDS

D -- COMPARE RECORDS

E -- SEARCH RECORDS

F -- UTILITIES

Q -- QUIT

MMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMM

I N D I V I D U A L P A T I E N T R E C O R D

Name: SOLON R
Folder: 71880967
M/name:
Birthdate: 29/07/75
Age: 14
Date: 07/11/89
Race/sex: Coloured Female
Age of 1st Presentation: 13
Classification type: Adult, Generalised fulminating

INITIAL PRESENTING SYMPTOMS:

Diplopia:	Yes	Fatigue arm:	No
Dysphagia:	No	Fatigue leg:	No
Dyspnoea:	No	Ptosis, Unilateral:	No
Weak face/neck:	Yes	Ptosis, Bilateral:	Yes
Weak arm:	No	Tensilon test?	Yes
Weak leg:	No	Tensilon test +ve:	Yes
Fatigue face/neck:	No		

M.G. DIAG AT 1ST PRES: No

INITIAL MEDICAL THERAPY:

Anticholinesterase, oral: 1 - MESTIN
2 -
3 -

Steroids, oral prednisone: Yes
- Daily dose (mgs): 20
- Alt. daily dose : 0
Immunosupp. (oral) azo.: Yes
Plasma Pheresis: Yes
Other: No

SIDE EFFECTS OF MEDICATION:

- Anticholinesterase Inhibitors: SLIGHT SALIVATION
- Steroids: STEROID FACE
- Azothiaprine:
- Other:

COURSE FOLLOWING DIAGNOSIS:

- Immediately:	Worse (symptoms and/or medication increased)
- 1 month:	Worse (symptoms and/or medication increased)
- 3 months:	Worse (symptoms and/or medication increased)
- 6 months:	Worse (symptoms and/or medication increased)
- 1 year:	Definite Improvement (Medication reduced)
- 2 years:	No data
- 3 years:	No data
- 4 years:	No data
- 5 years:	No data
- 10 years:	No data

THYMECTOMY DETAILS: Thymectomy performed: Yes
Age performed: 13
Time from diagnosis to thymectomy: 0

OPERATIVE FINDINGS, MICROSCOPIC:

- Normal Thymus: Yes
- Hyperplasia: No
- Hassel's Corpuscles: No
- Thymoma: No
- Invasive Thymoma: No

POSTOPERATIVE COURSE:

- Days in I.C.U.: 7
- Days intubated: 5
- Days ventilated: 5
- Noscomial infection: No
- Required reintubation: No
- Cholinergic crisis: No
- Day on which anticholinesterase restarted: 3

MEDICATION IN I.C.U.:

- Steroids: Yes
- Azothiaprine: Yes
- Antibiotics: Yes AMFORT B
- Analgesia: Yes MORPHINE

COURSE POST THYMECTOMY:

- Immediately: No change (original medication - I.S.Q.)
- 1 month: No change (original medication - I.S.Q.)
- 3 months: Definite Improvement (Medication reduced)
- 6 months: Definite Improvement (Medication reduced)
- 1 year: No data
- 2 years: No data
- 3 years: No data
- 4 years: No data
- 5 years: No data
- 10 years: No data

ADMISSIONS TO RESPIRATORY I.C.U. FOR POORLY CONTROLLED M.G. :

No:	1	2	3
Date:	/ /	/ /	/ /
Days in ICU	0	0	0	0
Days Intubated	0	0	0	0
Days Ventilated	0	0	0	0

REASON FOR ADMISSION?			
Myasthenic Crisis:	No	No	No
Cholinergic Crisis:	No	No	No
Respiratory Infection:	No	No	No
Noscomial Infection:	No	No	No

NO OF ADMISSIONS FOR POORLY CONTROLLED M.G. OTHER THAN I.C.U. : 0

NAME	DNAME	RACE	SEX	AFP	CLAS
ALLIE G		2	1	43	4
AN OTHER					
ARENDSE I T		2	2	30	4
ATKINS C		1	1	23	4
ATKINSON K		1	1	16	5
BAKER M		1	2	26	4
BODLANI T	MNYANI	3	1	37	5
BONGERS J		1	1	49	6
BRIDGETT L		1	1	20	4
BROWNE EB		1	1	64	4
CAESAR S		1	1	13	4
CARLS PC		2	2	53	4
CASWELL E		1	1	3	2
CECIL P		2	2	5	
DANIELS B		2	1	53	6
DANIELS LD	RENSBURG	2	2	17	4
DARLINGTON E		1	1	59	4
DAVIDS I		2	2	38	3
DAWOOD AD		2	2	15	4
DE BOCK R		1	2	49	4
DE GOUVEIA AD		1	2	64	
DECEMBER AD		2	1	18	4
DEEDLING D		2	2	42	4
DELPORT J		2	1	23	5
DIEDERICKS M		2	1	48	3
DOVEY J D		1	2	54	5
DRUKER A		1	1	35	6
EDWARDS M		1	1	20	4
EESOM ME		2	1	45	6
EFFENDI EN		2	2	31	3
ELDIN A		1	1	24	4
ELLIS EJ		1	2	45	4
ENGLES C		1	1	35	4
FAKIER S		2	1	12	3
FOJI N		3	1	21	4
FORTUNE IF		2	2	25	3
FOURIE L		1	2	43	5
FOURIE NF		1	1	27	4
GCABA L		3	2		5
GOBEY A		2	1	14	4
GOLDIE F		1	2	38	5
GOODFORD RG		2	1	42	6
GQAMA P		3	1	23	4
GRADWELL E		2	2	48	4
GROBLER S		2	2	28	4
GUSTAFSON B		1	1	35	4
HAMMAN A		2	1	32	4
HARKER D		2	1		
HASSEN A		4	1		
HEESE W		1	1	35	4
HEGARTY JH		1	1	29	4
JOOSTE L	WOLMARANS	2	1	30	4
KELLY L		1	1	16	
KLEMP MK		1	1	23	4
KOTZE JK			1	42	3
KRIEL Y		1	1	15	4

LOUW JL		1	2	63	4
MARAIS D	KLEIN	2	1	37	3
MILLS G		1	1	62	5
MORRIS NM		2	2	21	4
MOSTERT E		2	1	30	4
MURRAY MF		2	2	37	4
MUSCUTT C		1	2	38	3
MYBURG L					3
NGUMBELA AN		3	2	34	4
NOKO A		3	2		4
PETER C		1	2	47	5
PETERSEN N	MORRIS	2	1	21	5
PICKARD B	MACKRIEL	2	1	23	4
PRINCE F		2	1		
PUCKERT M			2		
QUIMPO CQ		2	1	20	6
RADLEY J			1		4
RISPEL	MAY	2	1	41	4
ROSS MR	REID	2	1	29	4
SAAYMAN JH		1	2	34	4
SACHS AF		1	2	65	4
SAM G		3	1	32	3
SAME S		2	1	29	5
SIHLAHLA MA		3	1	17	4
SIMPSON JS		2	2	46	4
SKORDIS K		1	2	58	4
SOBEKETE N		3	2	17	3
SOLON R		2	1	13	5
STRAUS LS		2	1	21	4
TURNER A		1	1	26	4
VAN BREDA A		2	2	16	4
VAN DER WESTHUIZEN L		1	1	29	4
WEBB RM	MARS	2	1	14	6
WILKINSON		1	2	71	6
WILLIAMS MW		1	1		
WINDVOGEL H		2	1	29	4
XENGANA C		3	1	16	6
ZIVE M		1	1	14	4
ZOG J		2	2	38	3
ZWEDALA J		3	1	16	5
JULISEN AJ		2	2	14	3

AN ANALYSIS OF PATIENTS WITH MYASTHENIA GRAVIS

TREATED AT GROOTE SCHUUR HOSPITAL SINCE 1970

No. of patients in database: 102

Females	67
Males	35
Whites	44
Coloureds	47
Blacks	11

Age of first presentation of MG:

Range:	3 - 65
Median:	

Pure ocular MG	12
Pure bulbar/respiratory	9
Adult, generalised mild	65
Adult, generalised fulminating	13
Congenital MG	3
Pure ocular which became generalised	6

Initial presentations:		
Diplopia		56 (± 52%)
Unilateral ptosis		18 (± 24%)
Bilateral ptosis		45 (± 41%)
Bulbar/respiratory symptoms		49 (± 46%)
MG missed at first presentation		± 65 (60%)
Tensilon test negative		±4 (4%)
MG precipitated by beta Blockers		2
MG precipitated by Penicillamine		2
Associated disorders:		
Thyroid disease (hyperthyroidism)		6
Diabetes Mellitus		4
Hypertension		2
Rheumatoid arthritis		2
Asthma		1
Malignancies (4)	Breast	2
	Melanoma	1
	Lymphoma	1
Peripheral neuropathy		2
Tuberculosis		1

ANNEXURE III

MANAGEMENT PLAN FOR ADULT PATIENTS WITH MYASTHENIA GRAVIS AT GROOTE SCHUUR HOSPITAL

Suspect MG

Refer to → NEUROLOGY DEPT | Dr Philcox/Dr Eastman

1. Admit neurology ward
2. Confirm diagnosis by
   - History
   - Clinical features
   - Tensilon test
   - EMG Study
   - Antibody levels
   - Therapeutic test
3. Evaluate thymoma
   - X-Rays
   - CT Scan
4. Identify associated disorders
5. Classify type of MG

OCULAR MG

1. Try anticholinesterases only
2. Refer MG clinic for monitoring for development of generalized MG (40%)

GENERALIZED MG

1. Anticholinesterases (Mestinon)
   Start with 60 mg hourly.
   Increase to max 120 mg 6 hourly
2. Steroids
   Start with 20 mg daily.
   Increasing to max 60 mg daily.
   Monitor for myopathy, weight gain, hypertension, diabetes.
   Reduce very slowly when stable over months to 20 mg alt. days.
   Once on steroids continue for at least 2 years if no complications.
3. Azothioprine
   Initially used only if steroids contra-indicated or if plasma exchange performed.
   Start with 100 mg daily.
   Increase by 50 mg/day after a month to 6/52 if inadequate response.
   Monitor FBC for optimum effect on WBC, platelets & MCHC.
4. Plan thymectomy

FULMINATING MG WITH RESP. FAILURE

1. Refer Respiratory ICU
2. Indications for ventilation
   - VC < 15 mls/kg
   - MEP < 30 cm H_2O
   - $PaCO_2O$ > 6 kPa
   - Inability to cough and clear secrections
3. Weaning
   - Clear of infection
   - VC > 15 mls/kg
   - MEP > 30 cm H_2O
   - Adequate cough
   - IMV + PEEP ---> CPAP
4. Therapeutic options
   - Appropriate antibiotics
   - Anticholinesterases N/G
   - Immunosuppression
     - steroids
     - azothioprine
   - Plasma exchange

MG CLINIC

Dr Philcox — Dr Eastman
Dr Thompson — Dr Linton
First Tuesday of month
Neuro. OPD, D-Floor, 2 pm

1. Patients seen monthly till stable, then 3 monthly till off immunosuppression, then 6 monthly or p.r.n.
2. Monitoring includes:
   - Progess (strength & response)
   - Complications
   - Therapy
   - Weight
3. Liaison with other departments
   - Obstetrics
   - Ophthalmology
   - Respiratory
   - Haematology
4. Objective measurements of lung function by Respiratory Clinic E16.

THYMECTOMY

1. Median sternotomy
2. Complete removal of thymic tissue and surrounding fat
3. Peri-operative management in Respiratory Unit

PLASMA EXCHANGE

1. Refer haematology
2. Protocol for exchanges
3. Commence immunosuppression with azathioprine
4. If patient not in hosptial - to attend either Neurology or Respiratory Clinics weekly until stable

ANNEXURE IV

RESPIRATORY ICU COMPUTERISED RECORDS

Code: RESREC

Uses: DBase IV

Facilities:

A - Enter new records

B - Alter existing records

C - View individual records

D - Compare records

E - Search records

F - Utilities

Q - Quit

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GROOTE SCHUUR HOSPITAL - RECORD SYSTEM:

RUN <R>ESPIRATORY RECORDS OR <M>YASTHENIA GRAVIS STUDY?

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GSH - RESPIRATORY RECORDS
- MAIN MENU -

A -- ENTER NEW RECORDS

B -- ALTER EXISTING RECORDS

C -- VIEW INDIVIDUAL RECORDS

D -- COMPARE RECORDS

E -- SEARCH RECORDS

F -- UTILITIES

Q -- QUIT

MMMMMMMMMMMMMMMMMMMMMMMMMMMMMM
MMMMMMMMMMMMMM
YEAR -> 1990
MMMMMMMMMMMMMM

MMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMM

V I E W I N G   A   R E C O R D
==============================

IDENTIFY RECORD BY:

<1> NAME
<2> FOLDER NUMBER
<3> HELP
<4> EXIT TO MAIN MENU

ENTER CHOICE (1-4): 3

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INDIVIDUAL PATIENT RECORD

Name: SOLON R
Folder: 71880967
Race/Sex: Coloured female
Birthdate: 29/07/75
Age: 15
Ward: A1
Specialty: Medical
Apache: 12

Admission date: 27/03/90
Discharge date: 02/04/90
Admitted from: General Ward
Discharged to: General Ward
Duration: 6 days

Primary diagnosis: Myasthenia gravis
Associated diseases: Nil
Nil
Nil
Nil
Nil

Surgery: No

Organs failed: day 1 - 0
day 2 - 0
day 3 - 0
day 4 - 0
day 5 - 0

Inf. pres. on adm.: No
No

Adm. infection only: No
No

Sec. Organism isol.: No
No
No

Special Investigation: No
No
No

S.G.Catheter: No
Route: No data

Compl. of S.G.C.: Nil
Nil

Ventilatory therapy:

Conservative only	- No
CPAP - Mask	- No
- Tube	- No
ETT	- Yes
IPPV w/o PEEP	- No
with PEEP	- Yes
> 15cms	- No
Tracheostomy	- No
Minitrac	- No
HFPPV	- No
Double lumen tube	- No
Indep.lung vent.	- No

Duration in days:

ETT	- 2
Tracheostomy	- 0
CPAP	- 0
IPPV	- 2
Maximum PEEP (cm)	- 5

Indication for ETT: Respiratory failure
Indication for Trach: No data

Other Therapy: No
No
No

Procedures: Peripheral I/V
No
No

Drugs: Cefotaxime
Steroids
Choline - esterase inhibitors
Other drugs

Complications in ICU: Nil
Nil
Nil
Nil
Nil
Nil

Cause of Death: Does not apply (Patient survived)
Act. tr. discont.: No

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                    IMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMM;
                    : GSH RESPIRATORY RECORDS - SEARCH ROUTINE    :
                    HMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMMM<

    1:  YEAR                          ->   1987, 1988, 1989

    2:  CONDITIONS              1     ->   PRIMARY DIAGNOSIS = 55
                                2     ->    AND SECONDARY DIAGNOSES = 8
                                3     ->
                                4     ->
                                5     ->

    3:  DISPLAY                       ->   STANDARD DISPLAY

    4:  RECORD NUMBERS                ->   YES

    5:  STATISTICAL ANALYSIS          ->   YES

    6:  PRINTER OUTPUT                ->   YES

    9:  PERFORM SEARCH...

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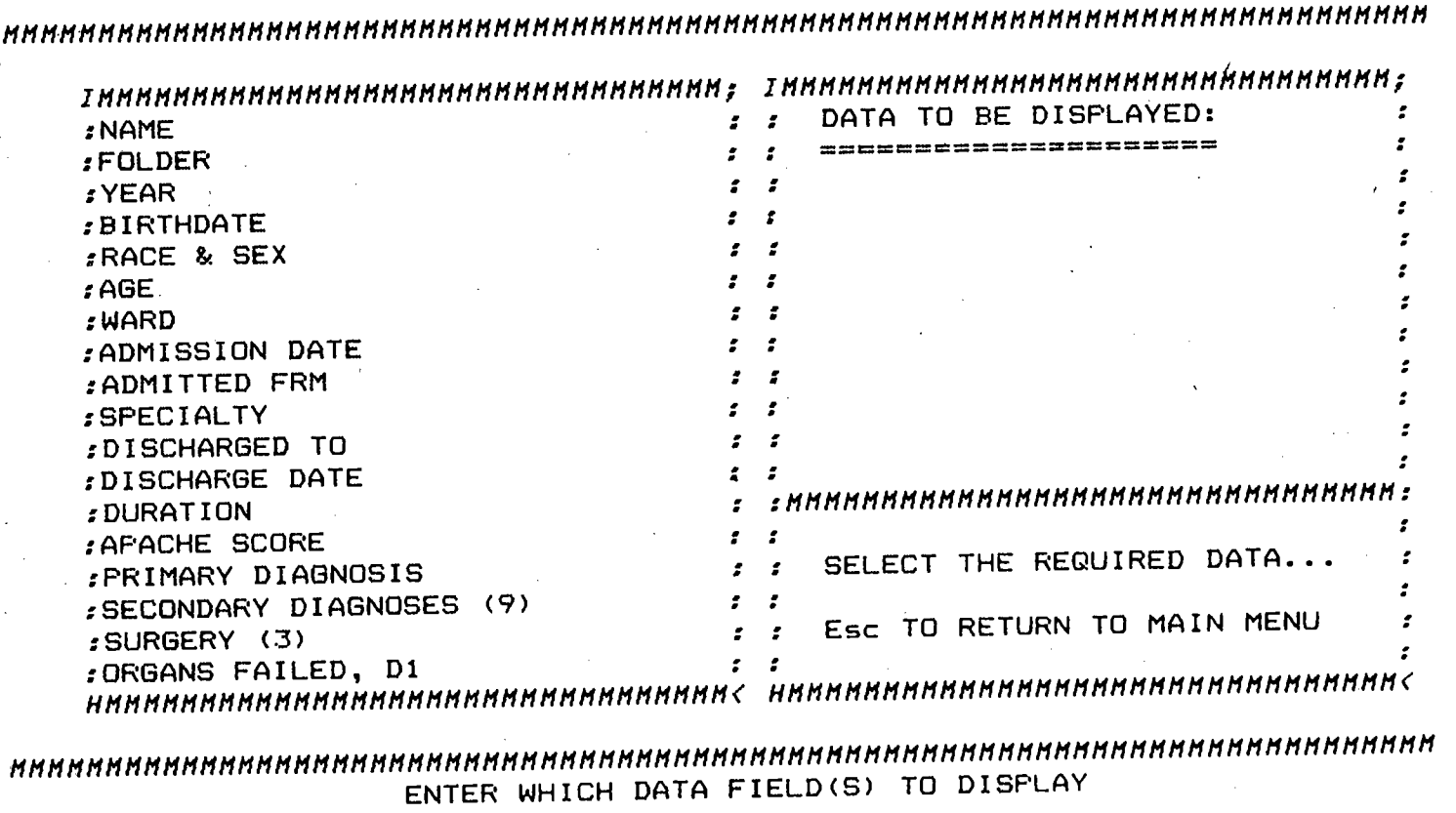
```


NAME
FOLDER
YEAR
BIRTHDATE
RACE & SEX
AGE
WARD
ADMISSION DATE
ADMITTED FRM
SPECIALTY
DISCHARGED TO
DISCHARGE DATE
DURATION
APACHE SCORE
PRIMARY DIAGNOSIS
SECONDARY DIAGNOSES (9)
SURGERY (3)
ORGANS FAILED, D1
DATA TO BE DISPLAYED:
SELECT THE REQUIRED DATA...
Esc TO RETURN TO MAIN MENU
ENTER WHICH DATA FIELD(S) TO DISPLAY

SEARCH CONSTRAINT: (DIAG1 = 55)
YEAR = 89

ATKINSON K	71125728
SOLON R	71880967
RISPEL R	52659885
VAN BREDA A	73230112

TOTAL NO. OF PATIENTS MEETING CONSTRAINT --> 4

SEARCH CONSTRAINT: (DIAG1 = 55)
YEAR = 88

ATKINSON K	71125728
PETERSEN N	60196052
SIHLALA M	52358884
ATKINSON K \2	71125728
MACKRIEL S	71571764
RISPEL R	52659885
WILKINSON J	71938682
GCABA L	72193113

TOTAL NO. OF PATIENTS MEETING CONSTRAINT --> 8