

Myasthenia Gravis Association



INFORMATION PACK Volume 1 A Medical Guide for Patients with Myasthenia Gravis

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Acknowledgements

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THE INFORMATION PACK

The Board of Trustees of the Myasthenia Gravis Association has approved the following publications, for supply, free of charge, to sufferers of Myasthenia Gravis and to the medical practitioners and professionals who look after them. Copies may be obtained from the MGA Headquarters at the address on the back cover. The pack comprises six volumes:

Volume 1 - A Medical Guide for Patients with MG

Medical Information on Myasthenia Gravis for those people who have been diagnosed with the condition.

Volume 2 - A Medical Guide for Patients with LEMS or Congenital Myasthenia

Medical Information on LEMS and Congenital Myasthenia for those people who have been diagnosed with these conditions.

Volume 3 - Additional Information for Myasthenic Patients

Information on complementary treatments.

Volume 4 - General Information for Myasthenic Patients

Information of general assistance to people with Myasthenia, including Driving and the DVLA, the DSS, prescription charges, insurance and other helpful organizations and Charities.

Volume 5 - Medical Information (Medical Professionals)

Information for people working in the medical profession. Details of Myasthenia Gravis, LEMS and Congenital Myasthenia with a greater emphasis on the neurological effects and drug information.

Volume 6 - Medical Articles

Extracts from medical articles published in the MGA Newsletters.

The Association does its best to ensure that the information contained in these publications is complete and up to date at the time of publication, but cannot accept any legal liability whether for any inaccuracy or otherwise.

INFORMATION ABOUT MYASTHENIA GRAVIS AND RELATED DISORDERS

The Myasthenia Gravis Association (MGA) has now updated the leaflets providing information about the different types of myasthenia: Myasthenia Gravis, the Lambert-Eaton Myasthenic syndrome and the Inherited (congenital) Myasthenias. Many patients want to be fully informed about the nature of their disorder, and such knowledge can be very helpful not only to the patient themselves but also to their family. It also makes it easier for the patient to understand what the doctor is trying to do to help them.

Although information about the myasthenias is available on the Web, it is not always presented in a form that is easily understood by a lay person. A number of us have contributed to this new edition, and we hope that the information in these leaflets will be easy to understand. But I am sure there will be room for improvement, and for this reason we would be very grateful for feedback that will be used when we come to prepare the next edition.

For those of you who have not heard about MGA, you might like to know that the Association was formed in 1968, became independent in 1976, and was incorporated as a company in 1995. The aims of the Association are to provide a care and support network for myasthenia patients and their families, and to promote research aimed at understanding what causes these disorders and at developing better treatments.

The Association wants to foster close links within the patient/member community, and also with the caring professions and the researchers. We do that through our local Branches, through Branch, Regional and National meetings (often with an expert speaker), through MGA News and through our information leaflets. Our membership is now nearly 1,500.

We hope you find the information helpful, and please let MGA have your views.

John Newsom-Davis MD
President

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Volume 1

A Medical Guide For the Patient with Myasthenia Gravis

ABOUT THIS GUIDE

As each person's experience of Myasthenia Gravis (MG) is unique, this guide can approach the topic only in a general way. It is one view of a complicated subject that we don't fully understand. It has been written to provide information and guidance, not only to those suffering from MG, but also their families, friends and anyone interested in finding out a little more about the condition. It is one team's most up-to-date view as of Jan 2003, but is not the only view possible.

This volume deals with Myasthenia Gravis. Information on Lambert Eaton Myasthenic Syndrome and the Congenital Myasthenias is contained in Volume 2 of this information Pack.

As a newly diagnosed myasthenic patient or the relative and or carer of one, you may find the science and medical terms unfamiliar. If so then please make use of appendix 1, 'Some simple science for the terrified beginner' (page A1), and the Glossary in appendix 2, (page A3), before you read on.

This revised edition now includes sections on Dentistry (section 10) and Ocular Myasthenia (section 11).

AN INTRODUCTION TO MG

What is MG?

The term ‘myasthenia gravis’ comes from Greek (myasthenia = muscle weakness) and Latin (gravis = severe). Mercifully, the myasthenias are rare and the muscle weakness is **painless**. It is caused by problems with nerve → muscle (nerve to muscle) transmission – the ‘*ignition system*’ of our muscles (see section 2, page 6). The myasthenias come in three quite separate forms:

- **Myasthenia gravis (MG)** is by far the commonest. Here, an immune attack damages the ignition locks of our ‘voluntary’ muscles only. The weakness typically fluctuates and is ‘*fatiguable*’ – the more you try, the worse it gets. So patients are often strongest in the mornings and get weaker during the day.
- **Congenital myasthenias** (less than one in twenty of all myasthenias). Here, inherited faults make the ignition system less efficient (see Volume 2).
- **The Lambert-Eaton Myasthenic Syndrome (LEMS)** (around one in twenty of the total). Here, a similar immune attack damages the nerve endings in both the voluntary and the ‘automatic’ muscles (e.g. in the blood vessels, bowels and bladder; see Volume 2).

None of these directly affects sensation (e.g. sense of touch or temperature) or causes pain, though overstrain can cause aches (e.g. in the neck or the back).

For the new patient; what it means to have MG

We don’t want you to find the next few pages scary.

Starting on the bright side: -

- MG can nearly always be brought under such good control that most patients can lead a full life.
- If you must have one of these ‘autoimmune’ disorders, MG is one of the most treatable, with the least pain and the fewest major long-term snags. Very few people actually die of their myasthenia.

- Treatments are improving all the time; with your help, we are determined that this should continue.
- Every myasthenic patient should be their own best doctor, and work out their own ways of keeping their myasthenia in its place.
- You must not let it take over your life.

On the other hand, you should be forewarned that: -

- Your MG may well be with you for many years. Don't wait around for a remission; only about one MG patient in 20 achieves a remission in a year, without treatment.
- You will probably have to plan your day to make the most of prime time when your strength is greatest.
- MG often affects the muscles of the face and the voice, so people may not always understand you, especially at the first meeting; e.g. misreading even your best efforts at a smile, (a myasthenic smile can come over more like a snarl, despite your best efforts).
- You will almost certainly need some drugs, and may well have to adapt to their side-effects. For most people, the benefits far outweigh the side-effects.

What are the symptoms?

No two patients show exactly the same symptoms, either in kind or severity. The onset can be sudden; much more commonly, it starts so gradually and insidiously that it is easily missed or diagnosed only after a delay.

Very often, it starts in muscles that we use all the time – e.g. with drooping eyelids and double vision – i.e. with the movements (but not the focusing) of the eyes. Sometimes these eye muscles are the only ones affected. Frequently also, weakness of the face muscles causes a ‘snarling’ smile, and/or the voice becomes nasal, and may even fade or become slurred and hard to understand. MG often affects the muscles of the throat, neck and trunk; sometimes also the hands, arms and legs, weakening the grip or the gait, but

that is less common, so MG has a ‘head downwards’ bias – the nearer the feet, the milder it is and the less likely muscles are to be affected.

If the weakness affects swallowing or chewing, eating may be slow and there is a risk of choking or inhaling small bits of food, which can cause chest infections. Still more seriously, the patient may have difficulty in breathing and even become gravely ill – hence the ‘gravis’: MG used to cause many deaths until the 1930s. If the breathing troubles are serious, the patient is in ‘crisis’ and needs mechanical ventilation in a hospital.

Now, with greatly improved treatments, MG rarely shortens life and most patients can lead an active life, despite a few side-effects from the treatments. It usually reaches its worst within three to five years and then levels off. Unfortunately, only around one patient in five ‘grows out’ of their MG permanently (i.e. goes into ‘*remission*’), and most have to learn to keep it in its place.

What makes MG worse?

Many things increase the weakness, including infections (such as colds, pneumonia, or a tooth abscess), fever, heat, over-exertion and emotional stress. Some women notice worsening of their MG during a particular time of the monthly cycle, during pregnancy or after delivery. Either too little or too much thyroid activity can worsen MG; so can salt depletion brought on by diuretic drugs or frequent vomiting; also the stress of surgery or radiation therapy.

Who gets MG?

MG can occur from the cradle to the grave, affecting all races and both sexes. While it often affects young females (ages 10-40), the number of elderly myasthenic patients, particularly men, seems to be increasing, and so does our awareness of them. The ‘immune’ form is **not** inherited. It *rarely* affects more than one family member, even though some risk factors do run in families. For example, when one identical twin develops MG, the other is more likely to do so than in non-identical twins but, even then, the risk is

less than 1 in 5. There is absolutely no sign that MG can be caught from another person with Myasthenia Gravis. While it may seem to start after infections, no one germ is under strong suspicion.

MG occurs in all races, but the pattern of the disease can vary. For example, MG confined to eye muscles ('ocular MG') is more frequent in young Chinese and Japanese patients, especially before the age of ten – when it is very uncommon in Europeans.

Patient subgroups

About 10% of patients have persistently pure 'ocular' MG. Those with generalised weakness are usually further subdivided into about 10% with a thymic tumour ('thymoma'), 25 % with 'early-onset MG' (starting before age 40, mostly female) and 50% with 'later-onset' (with a slight male bias). The thymus looks abnormal in 'early-onset MG', but there is no tumour (see section 2).

Finally, the babies of about one in eight mothers with MG may be weak for the first 2 to 3 weeks after birth (see section 4); they usually respond well to treatment and soon get back to normal.

Why do only some people get these disorders?

We know very little. However, one of the inherited risk factors for 'early-onset MG' also predisposes to other autoimmune disorders, so thyroid disease and 'young-onset' diabetes are slightly commoner in myasthenic patients – and also in their blood relatives – than in the national average. But autoimmune MG only strikes twice in the same family in about 1 % of cases.

We suspect there must also be other inherited and external risk factors such as infections but very few are known. Occasional patients taking the drug D(-) penicillamine for rheumatoid arthritis get typical myasthenic antibodies plus MG; both usually fade away when the drug is stopped. Internal factors include thymic tumours ('thymomas') in about one myasthenic patient in ten, and the thymic changes in 'young-onset' myasthenic patients (see section 2).

2

WHAT GOES WRONG AND WHY ?

Normal muscle 'ignition' and how it goes wrong

When an electrical impulse arrives from the brain, the nerve endings release a shower of a chemical transmitter – acetylcholine (ACh) – the 'ignition keys' (the black triangles ▼ in figure 1). These travel across a narrow gap and latch into the tailor-made 'locks' – the ACh receptors (AChRs) on the muscle surface – which then trigger the muscle to contract via complicated electrical and biochemical mechanisms. The surplus ACh is destroyed by a special protein – AChE (ACh Esterase) – which allows the muscle to relax again. The drugs neo-stigmine and pyrido-stigmine (*Mestinon*[®]) **block this AChE**, so that the transmitter lasts longer and has a better chance of triggering. As ACh also normally

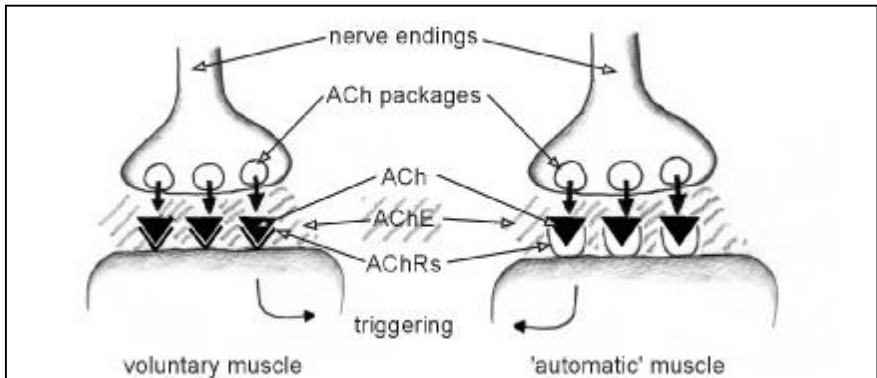


Figure 1

Diagram of nerve → muscle junctions:

In the two muscle types, the AChRs are completely different (V and U shapes). Luckily therefore, the immune attack on the AChRs in the voluntary ones does not affect the 'automatic' muscles in the guts, heart, blood vessels, bladder and glands. **But** the nerve endings and the AChE are similar in both, so **Mestinon**[®] soups up ignition in both types.

Key

ACh = acetylcholine;

AChR = ACh Receptor;

AChE = ACh Esterase (which destroys spare ACh);

stimulates the ‘automatic’ muscles in the guts, these drugs often make them over-active, causing bowel looseness. To prevent that, these ‘automatic receptors’ can be blocked with the drug Propantheline.

In typical **autoimmune MG**, there are too few AChRs because they have been destroyed by antibodies. They are produced by over enthusiastic immune cells as if the AChRs were invading germs (see next section). These antibodies against the AChR are found in most (but not all) typical MG patients (see section 3).

The immune system and how it goes wrong

We have two groups of white blood cells that help to protect us against ‘invaders’ such as bacteria and viruses. The ‘B cells’ come from the bone marrow, and make **antibodies**. These proteins are tailor-made for each target. For example, if you are immunised against tetanus, you make antibodies that only recognise tetanus and not ‘flu virus’ (and *vice versa* if you have a ‘flu jab’). Antibodies travel around in the body fluids and latch onto their particular target. They then activate other amplifying cells and proteins to destroy that target.

Other white cells called ‘T cells’ come from the thymus and are the ‘control freaks’ of the immune system. They too are tailor-made for each target; when they recognise it, they turn on any ‘specific’ B cells that recognise the same target to make their antibodies. T cells can also switch on other cells to fight infections. Because both T and B cells include thousands of different ‘families’ – each recognising different targets – the immune system is a hugely complicated mix.

In MG, alas, a few immune families start to attack their own AChR just as if they were foreign invaders. These immune ‘vandals’ are probably only a tiny minority, and the many other T and B cell families continue trying to fight infections. Their great specificity offers hope of devising smart weapons for selectively turning off only the damaging families without clobbering the whole defence system with steroids etc.

The thymus is where the T cells first develop, and it sits just behind the breastbone. It is most active during childhood, and exports T cells

in vast numbers which then travel around the body looking for invaders. When they find them, many settle in lymph glands where they multiply and send some of their offspring away on further travels.

In ‘early-onset MG’, the thymus gets colonised by lymph gland-like ‘factories’ for antibody production. This may be sparked off by rare muscle-like cells, which are found in the normal thymus too. It may be in these factories that the antibodies evolve to bind and attack the AChR even more strongly. Removing the thymus (thymectomy) **may** cut this evolution short, but there are other theories to explain its benefits in MG.

Thymomas are tumours of the ‘framework’ cells of the thymus. Mercifully, many are benign, but they do need to be removed because they can invade locally (e.g. into the lungs). What is more, having MG is a valuable early warning to check for a thymoma; thanks to the usual X-rays and scans, they are often nipped in the bud. However, some might have already started spreading before they are diagnosed. Even at worst, they respond much better to radio- and chemo- therapy than many other tumours. Unfortunately, removing thymomas doesn’t usually seem to improve the myasthenia much.

Thymomas often look a bit like normal thymus gone crazy, generating *vastly* too many T cells, for example. Roughly one thymoma patient in three gets MG, and another few get autoimmune bone marrow failures. We *think* thymomas must somehow immunise against AChR, but that is less clear than in the lung tumours in the LEMS (see section 9, page 19, also Volume 2, A Medical Guide for Patients with LEMS or Congenital Myasthenia). These are fascinating clues to processes that are otherwise very hard to study in humans.

3

HOW IS MG DIAGNOSED?

Whereas MG is quite rare, weakness and fatigue are so common, and have such varied causes, that the diagnosis of Myasthenia Gravis is easily missed, especially if it is mild or localised. However, the patient's account of their symptoms, and the visible telltale pattern of weakness, will ring bells with most doctors who are familiar with MG. Once suspected, it can be confirmed in several ways:

One is to test for *fatigue* by repetitive movements of the eyes, arms or legs. This can be done without equipment, or it can be done electrically by recording the responses of a muscle to stimulation of its nerve with harmless electrical needles – electromyography (**EMG**). In MG, the response often gets smaller over the first few stimuli; 'single fibre EMG' provides the most sensitive test. EMG also helps to sort out confusions with LEMS and congenital myasthenias that may need different treatments.

A second approach is to inject a short-acting anti-cholinesterase drug like 'Tensilon[®]' ('Edrophonium' – a cousin of Mestinon[®]) and measure strength beforehand and afterwards in the worst affected muscle groups (usually two of them). This '*Tensilon[®] test*' is used less often nowadays because it carries slight risks and needs to be done in a hospital with equipment ready in case of emergency. Alternatively, the patient's general improvement on anti-cholinesterase drug treatment is useful supporting evidence.

The most specific diagnostic test is a blood test for the typical antibodies to the AChR (see above); around 85% of all MG patients have them, whereas patients with other muscle diseases almost never do. Nearly another 10% of typical MG patients have other antibodies to a different target next to the ignition locks called MuSK; a new test for them has now been developed in Oxford.

4

HOW IS MG TREATED?

There are five main sorts of treatment; most patients end up with their own individual blend of them.

1. Many common-sense things can be very effective in coping with MG. Plenty of rest and a well-balanced diet actually help. If possible, one should try to avoid exposure to infections, some drugs and all forms of stress, though, of course, that's easier said than done. Patients should try to pace their activities so that they don't exhaust themselves, and tackle the harder jobs when they expect to be at their strongest (e.g. mornings). While that may sound obvious, fellow-sufferers in MGA have lots of other valuable hints along similar lines (Volume 4).

2. Mestinon[®] is a front-line weapon (see diagram page 6; it is properly called Pyridostigmine); a bit like the choke in a car, it gives the handicapped ignition system a better chance of firing, so providing a temporary boost; it may strengthen some muscles much more than others. *But it doesn't clean the plugs – i.e. it doesn't cure the underlying immune or inherited faults in MG* (see section 4, page 12).

Since Mestinon's[®] effects last only a few hours, it is more important to take it often than to worry about the exact dose, which varies a lot between patients and from time to time in the same one. Generally it helps to keep the dose between a half and one and a half of the 60 mg Mestinon[®] tablets (i.e. 30 - 90 mg) every three or four waking hours; always keep on the low side to avoid both side-effects on the one hand and tolerance on the other (when it becomes less effective with time). These medicines sometimes cause stomach cramps and diarrhoea, so they should be taken with bland food such as crackers or milk to minimise that. These side-effects can be prevented by taking Propantheline about 30 minutes in advance.

Overdosing with Mestinon[®] can lead to a 'cholinergic crisis', with worsening of the myasthenic weakness. That almost never happens in people taking fewer than six 60 mg tablets per day. Obviously, it is important to distinguish that from a myasthenic crisis, which needs completely different treatment (e.g. more Mestinon[®]). If you suspect

that either type is coming on, you should seek immediate advice from your GP or Consultant. Too much Mestinon[®] can cause muscle twitching, increases in sweating, in salivation (drooling) and in lung secretions (→ phlegm), and tightening of the pupils.

3. Plasma exchange. To treat the underlying *immune faults* in MG, there are two short-term measures. In the first, the damaging antibodies are simply washed out of the bloodstream; during a thorough plasma exchange ('plasmapheresis'), several litres of blood are removed one by one, spun in a separator, and the red blood cells are returned in an artificial substitute (albumin and saline solution) without the antibodies. After about three days, that reliably improves strength for up to around four weeks, but then the benefits wear off as the antibodies are gradually replaced. It is used most when benefits are needed *urgently*, e.g. if a respiratory crisis is looming, before surgery, or to cover the start of steroid drug treatment. It is very safe.

Plasma exchange must be done under close medical supervision, which means being in a special hospital ward for 5 days connected by an intravenous line (usually in the groin) to and from the separator, for around 4 hours per day.

Nowadays, an alternative is '**Iv Ig**', which means infusing the total antibodies (**Ig**), pooled from huge numbers of healthy blood donors, into a *vein* (**Iv**). It clearly does help, though again *only for 6 to 8 weeks*, alas. We don't know *how* it works; there are more theories than hard facts. (It may simply water-down the damaging MG antibodies or sidetrack the bystander amplifying mechanisms they recruit). It is slightly cheaper than plasma exchange, but again it means being in a special hospital ward for 5 days running; the Ig has to be given very slowly into a small arm vein for about 5 hours each day. Patients sometimes get a headache, a rash or rise in blood pressure; blood tests are used to monitor for possible effects on the kidneys. By their nature, human blood products inevitably carry low-level risks. Though very carefully screened for the known viruses (hepatitis and HIV), there is obviously a remote possibility of some new unsuspected agent.

4. Thymectomy is almost always done for thymic tumours (thymomas) to prevent them from spreading. Unfortunately, that seldom improves the myasthenia as it seems to do in ‘early-onset’ MG patients. Even in them, the benefits have not been completely proved*, but we believe that about a quarter of them eventually go into complete drug-free remission and another half have a marked improvement. It is often done in the hope of saving them from steroids, but that doesn't always work. The improvements don't usually occur immediately after surgery, but may take up to 2 years to reach their maximum*; even after benefits occur, there is still a small possibility of relapses later. Alas, we can't predict beforehand who will benefit from thymectomy*. However, thymectomy itself doesn't worsen the course of MG. Whether it also helps the over 45s is far less clear*.

*[*We **hope** that some of these queries may be answered in a forthcoming clinical trial.]*

Thymectomy is a safe procedure. Being a major operation, it is only done when the patient's MG is well controlled. It is best done in a specialist centre (see section 5, page 16).

5. Long-term immuno-suppression.

a. Prednisone

The first choice drugs are usually synthetic *steroids* called ‘Prednisone’ or ‘Prednisolone’, which are taken by mouth. They reliably improve the myasthenia after a delay of around 2 - 6 weeks. They lower the damaging antibodies, and probably have many other immune-suppressing effects too.

You probably already know that steroids can be a mixed blessing. Do remember that, in most myasthenic patients, **their benefits far outweigh their snags, so don't be put off** by what follows. Obviously, the choice between steroids and other treatments needs careful thought. Only about one myasthenic patient in ten has to give them up because of the side-effects. Your doctors will tell you about them in detail, but here is a very quick run-down.

In general, as you know, *people vary greatly*: so they do in their responses to steroids – both the benefits and the side-effects. At the

outset, steroids can even make the MG worse for a few days, so their dose is usually built up gradually to flatten the MG, and then lowered as far as we dare. In the end, most people reach a steady level, with a good balance between benefits and snags. Again, the best dose varies a lot between patients. Alas, very few manage to cut them out altogether.

The snags fall into three main groups:-

i. Because they are suppressing immunity, steroids are bound to raise the risk of infections. By taking reasonable care (e.g. avoiding big crowds), you can usually keep that risk low without isolating yourself completely.

ii. Steroids are produced naturally at carefully controlled levels by our own ‘adrenal’ glands. One of their main jobs is to tune us up for the day, and to tide us over times of physical **stress** (e.g. injury or appendicitis). Because the doses given to patients are so unnaturally high, they shut our adrenal glands off. So we are no longer cushioned against these stresses, and may collapse suddenly in a crisis. That problem can be partly prevented by giving the steroids every other day, to keep our adrenals on their toes. Even so, whenever we drop the dose, it has to be done in very gradual steps. Therefore, everyone on steroids must carry a card to alert others.

iii. Steroids lower activity in many cells. For this and other reasons, they can also cause many other side-effects including: weight-gain, mood changes, sleeping troubles, diabetes and high blood pressure; skin changes including thinning, easy bruising and unwanted hair growth; bone-thinning, which can be prevented with other drugs; stomach ulcers, glaucoma, and lens cataracts.

More detailed information on steroids may be found in Volume 5.

b. Azathioprine (Imuran[®])

This drug also reduces antibody production, but that takes at least a year to ‘kick in’. It is sometimes used by itself with patients who can’t quite manage on Mestinon[®] alone. More often, it is used to enhance the benefits of steroids, and/or to get away with lower doses thereof.

Its side-effects include allergies; also liver damage and bone marrow suppression, for which regular blood tests are needed around every week at the start and every 2 months for ever more (done by the GP). Some patients react to it in the first few weeks, with fever, nausea, vomiting, loss of appetite or tummy pain, and the drug must then be stopped. In pregnancy, one should ideally avoid most drugs as far as possible; however, many healthy babies have been born to mums who needed to take Azathioprine and/or steroids to keep up their strength while pregnant. In the long-term there may be an increased risk of a type of cancer called lymphoma, *but the absolute risk is still very low. As with steroids, the benefits usually far outweigh these hazards.*

c. Other immunosuppressants

There are other immunosuppressants, such as Cyclosporin A, Methotrexate and Mycophenolate Mofetil (Cell-Sept[®]), which are usually kept in reserve for people who can't take the above front-line drugs. These others are less well tried-and-tested in MG, and have their own side-effects too, partly because they are more powerful immunosuppressants.

5

ANAESTHETICS AND MG

Myasthenia used to pose challenges for anaesthetists. Nowadays, they are so well aware of them that that it rarely causes problems any more. Thanks to better awareness, preparation, monitoring and treatment, you should forget all the out-of-date horror stories.

As you know, you can have either a **local** or a **general anaesthetic**.

Local anaesthetics (e.g. lignocaine, bupivacaine) are injected around the nerves and 'freeze' them by blocking their electrical conduction. So all feeling from their territory is wiped out for some hours. That works just the same whether they are injected near the nerve endings (e.g. into the jaw nerve) or around their spinal cord roots (as for spinal and epidural anaesthetics). Spinal and epidural anaesthetics are suitable for many operations below the waist, e.g. on hips, knees, varicose veins, hernias, and even some in gynaecology. So many of you prefer

them – both to avoid the feeble breathing caused by some general anaesthetics, and also to allow your MG treatment to continue normally. Light sedation given in advance helps you to ‘chill out’ – a bit like a sleeping tablet or an extra tippie!

Before any **general anaesthetic**, it is vastly better if the myasthenia is under the best possible control. This may mean tuning up with plasma exchange or IvIg a week or so beforehand. Then, it should be just as safe in myasthenic patients as in anyone else, as long as care is taken over the following:-

A Muscle relaxants

These drugs paralyse all the voluntary muscles (by blocking muscle ignition). They are given to help the surgeons get easier access for ‘deep’ operations, e.g. on gall bladders (etc). Because they also paralyse the breathing muscles, we must connect you to a breathing machine (ventilator) via a tube in your windpipe. (In the old days, we had to use deep anaesthesia instead, with more depression of blood pressure and breathing, longer recovery times, and more vomiting). NB some operations don’t need any muscle relaxants; in that case, you can breathe by yourself or with assistance.

With their lower reserve of muscle-triggering power, myasthenic patients are extra-sensitive to muscle relaxants, and need 5 or even 10 times lower doses. The resulting paralysis can easily be monitored in any operating theatre. It is normally stopped after the operation by injecting a short-acting Mestinon[®] cousin, Neostigmine. Very occasionally, an unsuspected myasthenic patient may need more Neostigmine than expected to perk them up – that is one of the roundabout ways in which MG is sometimes first diagnosed.

B Mestinon[®]

Should it be stopped beforehand? No, but Mestinon[®] counter-acts the muscle relaxants, so that they may need to be given at slightly higher doses if you have recently taken your Mestinon[®]. That should not be a problem, and may even help if you find it reassuring to take it regularly. Afterwards, it can be given into a stomach tube if you have trouble swallowing it.

C Steroids

Should the doses change? Yes: you naturally produce extra steroids to tide you over the stress of surgery. Prior steroid treatment shuts that response off, so we normally boost your body's own efforts with extra steroids by injection before, during and after the operation.

D Talk to the Anaesthetist

Finally, meeting the anaesthetist in advance helps both sides. (You should be able to find out who it will be from either your surgeon or the hospital anaesthetic department). If you do, the anaesthetist can explore with you the various options, assess the severity of your MG and your overall fitness for anaesthesia and surgery, and arrange for an intensive care bed for recovery if need be. Importantly, too, it gives you confidence and courage, which is ideal for everyone.

E Thymectomy

The rules are exactly the same as above. The thymus lies just behind the breastbone, which has to be split open. So a general anaesthetic is essential. Although a major operation, it usually takes only around 1½ hours. Most patients don't need any blood transfusion, and perk up quickly afterwards, though they may need to spend 1-3 days in the intensive care unit. Surprisingly, it is not very painful; many patients are home within a week .

6

FAMILY AND WOMEN'S ISSUES

Many women notice their weakness is worse around the time of their monthly periods, and others for a few months during the menopause ('change of life'). There is no objection to Hormone Replacement Therapy ('HRT') in patients with MG, nor to the contraceptive 'pill'. Moreover, MG very rarely affects the outcome of pregnancy; there is almost no extra risk of miscarriage or stillbirth. While Myasthenia occasionally gets worse during pregnancy, it more often does so for a few months afterwards.

Prednisone and Azathioprine should only be used in pregnancy when they are essential, although historical evidence suggests that they are not harmful to the unborn baby. That is probably also true for Cyclosporin, but **not** for Methotrexate and Mycophenolate which should definitely not be used in pregnancy.

With around one MG mother in eight, the new-born babies have a short-term weakness, but they usually recover fully in the first 3 weeks or so. This ‘neonatal myasthenia’ is due to transfer of the mother's damaging antibodies across the placenta (along with her protective ones) which then affect the baby's muscles (just like mum's). Unfortunately, the antibodies are also transferred through the milk, so, if the baby is affected, breast-feeding should be avoided. Mercifully, since the babies do not make anti-AChR antibodies of their own, they recover as those from mum gradually decline, and their muscles get back to normal. Each mum tends to stick to the same pattern – i.e. later babies usually show similar weakness (or not) to that in the first. Neonatal myasthenia may be getting rarer with improved treatments for MG. Very rarely, babies can have joint deformities (‘arthrogryposis’). If so, that is because mum's antibodies particularly attack the baby's AChR (which is slightly different from the adult's); subsequent pregnancies can be protected by prior immunosuppression.

7

WHAT IS THE OUTLOOK?

With improved treatments, MG rarely shortens life and the outlook now is good. Most patients can expect a marked improvement in their symptoms, which may well disappear altogether, though they may have to continue to take some drugs. However, these treatments sometimes have troublesome side-effects that can lessen their usefulness.

In general, it is very important to keep your MG in its place, and try not to let it take over your life. Also, there is a lot of truth in the old saying that everyone is their own best doctor, because they can usually find ways of handling their own MG, not all of which may suit every other myasthenic patient.

For the researchers, a lot remains to be done. We need to know why some people get MG and, perhaps more importantly, why others don't. What triggers it? Why does it appear to be becoming commoner in older people, especially men? How, exactly, do steroids help? We need to find more selective ways of treating the disorder, ideally stopping only the damaging immune reaction in its tracks and avoiding any side-effects. The answers to such questions will need further research, which the MGA is striving hard to fund and encourage. Valuable clues may well come from observant patients, so we welcome your queries, however much some of them may fox us. As the enormous advances in understanding and treating MG over the last 25 years strongly suggest, the future is bright for myasthenic patients.

8

HISTORY

Myasthenia gravis (MG) was first clearly described in the 17th century, although it has probably always affected human beings. Indeed, it also occurs in dogs and cats, for example. The term 'myasthenia gravis' comes from Greek (myasthenia = muscle weakness) and Latin (gravis = severe). It was recognised as a disorder of the nerve-muscle junction in the early part of the 20th century; only in the mid 1930s did (British) doctors discover the benefits of physostigmine (an early version of Mestinon[®]). *Thymectomy* was first used in many patients from 1940 onwards; we still don't fully understand why it works.

An 'autoimmune' origin for MG was suggested by our Vice-president, Prof. Ian Simpson, in 1960. It was only proved, however, in 1973, when Drs Jim Patrick and John Lindstrom (in the USA) showed that antibodies *can* cause MG. Much subsequent research has focussed on how they cause weakness, and on how their production is controlled. *Steroids* began to be prescribed regularly as treatment in the 1960s and plasma exchange was first used in the mid-1970s (see section 4, page11).

THE OTHER MYASTHENIAS

This Volume is concerned with Myasthenia Gravis, but the following brief description of the two other forms of Myasthenia has been included for completeness. More detailed information may be found in Volume 2.

The Lambert-Eaton Myasthenic Syndrome (LEMS)

The LEMS was first recognised in the early 1950s. The damaging antibodies (which are different from those in MG) were first identified in the early 1980s.

The LEMS is rare and usually starts after age 30 years. It is also caused by auto-antibodies, but these ones cut down the **release of ACh** from nerve endings. Therefore, it differs from MG in several ways. LEMS patients get *stronger* as they try harder, and their weakness also affects the limbs more than the head, neck and trunk. Because the nerve endings are similar in the guts and the bladder etc (see figure 1), these too get attacked by the same antibodies, so there is usually also some trouble with ‘automatic’ bodily functions, e.g. a dry mouth, constipation or impotence.

We can confirm the diagnosis by checking for the typical changes in the electromyography (EMG) and for the damaging antibodies in a blood test. It is also very important to watch any smokers for lung tumours, which are found in around half of LEMS patients. The cancer cells somehow immunise the patients against their own nerve endings. If they do, the LEMS is often a valuable early warning of the tumour; what is more, the immune reaction even seems to slow its growth, so having the LEMS isn’t all bad (see Volume 2).

Treatment with Mestinon[®] is often less helpful than in MG, but another drug – ‘3,4-diamino-pyridine’ (DAP) – works better in LEMS patients; it acts by boosting ACh release. It is available only through special centres (i.e. Oxford in the UK), and has to be used cautiously.

Being autoimmune, the LEMS responds well to the same plasma exchange, IvIg and immune-suppressing treatments as MG, though plasma exchange takes longer to kick-in (2-3 weeks) than in MG. Thymectomy is not used, partly because the patients are older. In patients with tumours, treatment of the cancer must take priority.

Congenital myasthenias

These account for about one myasthenic patient in 40 (2-3%) and are caused by **inherited faults** in nerve → muscle triggering. Such faults occur at random in any gene, so they can affect any system in the body, and vary greatly. So congenital myasthenic patients are a mixed bunch, ranging from mild cases, mainly with droopy eyelids, to wheelchair users. In most, the AChRs are just too few in number, but, in some, they are overactive and cause muscle damage that builds up over the years. ‘Congenital’ strictly means evident at birth, but some of these latter cases are only diagnosed in their teens.

For assessment, these patients need to go to a specialist centre; EMG is often particularly useful for sorting them out. These myasthenias *do run in families*, especially in those with cousin marriages, where the same genetic fault can be passed down from both sides. The Oxford lab now runs a service for identifying the exact faults. It is not possible to test for all of them instantly, since there are so many possible target genes.

The specialist assessment helps for advising the parents about the chances of further children having the same problem, and about care and treatment for this one. That is especially important because good treatment for one subgroup may even make others worse; one patient's tonic may be another one's poison. For example, some need Mestinon[®] or 3,4-DAP to boost ignition, whereas blocking that with quinidine may help those with overactive AChRs.

Because there is no autoimmune problem, *none of the immune treatments is suitable in any way for the congenital myasthenias.*

DENTISTRY AND MYASTHENIA GRAVIS

As explained below, taking good care of your teeth, and preparing yourself for dentistry, may save you a lot of trouble.

Excellent home care habits are crucial, however difficult they may be. They include **regular** brushing, daily flossing, cleaning between teeth, and oral cleanliness; also regular dental visits and cleaning, to keep your teeth free of plaque.

Prevention is vital to avoid dental emergencies; they are most stressful and can aggravate your myasthenia.

Your gums are liable to infections; you may not always be aware of them. If severe, they can have knock-on effects on your myasthenia and or lower your resistance, so proper care is vital. With immuno-suppressants, infections are more likely, and healing may take longer than expected. Finally, weakness of jaw muscles can affect the closing of your teeth. That, in turn, can create extra stresses or even pain.

If your myasthenia is under good control, there is no reason why you can't have normal dental care. Excellent communication between you and your dentist is vital, so that you know exactly what is going to be done. The dentist needs to know what your limitations are, and to be prepared for them. That should help you to relax and co-operate more fully. It is vital that the dentist consults with your Neurologist at the planning stage if surgery is necessary, and it may also help even for normal care.

It helps to book appointments for the morning or whenever your strength is greatest, and to keep them short. If you have difficulties in opening and closing your mouth, in holding your head up, or in swallowing, *the dentist needs to know* so as to prevent problems. A mouth prop may help for keeping your mouth open; thorough suction (perhaps controlled by you) helps to avoid drooling or choking problems.

Even root canal work need not be traumatic. A rubber dam may be needed to prevent worries about choking. If you can't close off your throat, or tend to regurgitate fluids into your nose, you may prefer to sit more upright in the dental chair.

If you have to have an anaesthetic, local anaesthetics are preferable to general. General anaesthesia should **never** be used outside the hospital setting.

11

EYE WEAKNESS IN MG (OCULAR MYASTHENIA)

MG can affect one group of muscles much more than others, for example just one small muscle that moves one eye in one direction; or just one of the larger muscles involved in face, limb or breathing movements, sometimes only on one side. Weakness of eye movements is particularly common in MG: indeed, it may be the only problem in some patients, whereas it is often an early sign of a more general picture in others. So opticians and eye specialists are important allies for the MG community for two reasons. They are often the first to suspect MG. Secondly, in both community and private practice, they are increasingly involved in the shared care of MG patients and can sometimes offer them practical help.

Strictly speaking, we only label myasthenia as '*Ocular MG*' if the weakness is still restricted to eye movements at least two years after the very first symptom. We do that because *generalised MG* begins with *ocular weakness* in around three quarters of all myasthenics (and affects about 9 in 10 eventually); it may start to affect other muscles only after 6 months (in about a quarter of them), or even longer (in about an eighth). So, if the MG remains purely ocular for two years, there is only about a 1 in 20 chance that it will 'generalise' after that.

Just as with any muscles in MG, those that move the eyes may be quite strong when you are well rested. However, they can tire easily as you use your eyes or when you are subject to emotional strain. For example, after looking upwards or sideways for along time, your

eyelids may gradually start drooping or you may see double as one of the muscles weakens. Your eyes may even refuse to move altogether. These signs can easily be mistaken for other medical conditions with similar effects, e.g. strokes, tumours, thyroid eye disease, infections or multiple sclerosis. So MG is often first suspected by opticians or eye specialists.

Why are the eye muscles so commonly involved in MG? As you know from watching people nodding off, *the eye muscles are especially vulnerable to tiredness*, probably for several reasons:-

- a) they need to be much more precise than most other muscles;
- b) they are very small and have less reserve capacity;
- (c) there are subtle differences (from other muscles) in their nerve endings and possibly in their AChRs;
- (d) they get less rest, even during sleep.

What makes eye weakness worse? Bright sunlight, emotional stress, viral illness, surgery, menstruation, pregnancy, immunisations and other factors may all provoke changes in the ocular weakness, although not in predictable directions.

DIAGNOSIS

The diagnosis depends on your story and physical condition, and on a blood test for the anti-AChR (positive in about 60% of patients with pure Ocular MG). If it is negative, a very sensitive electrical test (single fibre EMG) can be done on the eyelid muscles; in a few cases, we need to test the response to an injection of Tensilon (edrophonium). This test would be carried out in a hospital.

DRUG TREATMENTS

As with most forms of MG Mestinon® (pyridostigmine) is usually the first-line treatment. With careful use, it often helps, but may not eliminate all ocular weakness.

Again if Mestinon® is not enough, then immuno-suppressive drugs may be tried.

OTHER MEASURES

For double vision, you can tilt your head or turn your face to bring your relatively stronger eye muscles into play. If looking upwards is the main problem, then you tilt your head back, thus bringing your gaze downwards out of the area of the weakened muscle.

If drugs work poorly or cause side-effects, other methods may be effective in relieving your double vision. Fresnel (stick-on) prisms, for instance, can be attached to your eyeglasses to relieve double vision; if helpful, they can then be incorporated into the lenses. By optically ‘bending light’, they enable you comfortably to look straight ahead or downwards and read with both eyes open. Sometimes, a pirate’s eye patch, a frosted lens, or simply sticking a piece of tissue paper over one lens in the spectacles is an easy short-term way of stopping double vision to allow more comfortable reading or TV-watching. Very rarely, surgical correction can be useful for long-term deviations that don’t vary.

For droopy eyelids (ptosis), some patients use sticky tape to hold them up. **Ptosis props** are sometimes useful if drug treatments are not successful, but are not widely used. They come in two forms:-

Lundie Loops act as a spring-based support for the upper lid and are fitted to the spectacle frame, which needs to be thick enough along its top rim to support them. Details of the loop can be obtained from the MGA

Traditional **bar ptosis props** can be fitted by most glazing houses; their projection, length and size are specified by the optometrist. Rubber tubing can be used to cushion the bar. A few patients find them a tolerable long-term solution.

Rarely, surgical correction may be considered if the ptosis is stable and other measures are not working. NB before recommending either surgery or props, it is particularly important *to ensure a good capacity for eye closure*, which is often weak in MG. Otherwise, defects in the normal protective reflexes may confer a risk of damage to the cornea.

SOME SIMPLE SCIENCE FOR THE TERRIFIED BEGINNER

The building blocks of life

Protons, neutrons and electrons are assembled into the smallest chemical units called atoms. **Atoms**, in turn, can assemble into **molecules** (e.g. table salt, consisting of sodium and chloride atoms). Many molecules in living things are much bigger than salt, indeed so big that they can be seen on the strongest (electron) microscopes.

Different kinds of molecules collect together and are built up into cells, which can quite easily be seen on normal (light) microscopes. In general, our cells are composed of a thin outer surface membrane made of fat, a bit like a soap bubble. Inside that is a jelly-like solution a bit like egg white, containing various salts, sugars and small building blocks that get put together into proteins and fats and sugary carbohydrates. Inside that is the nucleus, the ‘brain’ of the cell; here the inherited blue-prints or genes (made of DNA) that code for our proteins, are stored and copied. Each of us inherits one copy of each gene from our mother and one from our father. They number around 30,000 in all.

Proteins are incredibly variable and versatile molecules; they can be structural, as in wool and silk and ligaments; those called enzymes speed up chemical reactions as in yeast and in all our cells; they can transport molecules like oxygen, as does the red protein haemoglobin in our blood; they can transport food substances into our cells from outside (e.g. glucose); they can act as surface receptors for outside signals, as does the AChR, the key target molecule in MG; they can themselves act as messengers (as insulin does when it binds to insulin receptors); they can move other cells; they can even turn chemical energy into light. In general, they are highly specialised, and often recognise other chemicals very specifically.

The difference between one protein and another lies in its exact combination of different building blocks. These come in twenty different shapes, and are strung together in an exact order (sequence); nearly every link in the chain has to be just right. A single mistake at one key point can be a matter of life or death. Inherited mistakes are called mutations, and occur randomly anywhere in any gene.

The cells involved in the myasthenias

Muscles and nerves are made up of huge numbers of (much smaller) cells.

Nerve cells relay electrical impulses from sense organs (e.g. eyes and skin) to the brain and spinal cord or from there to muscles and glands. They relay signals to other nerves or muscles or glands at special junctions (synapses), and switch them either on or off. Sometimes, they act more like dimmer switches or thermostats, telling other cells to work harder or slower.

Muscle cells are long tubes of interlocking proteins (i.e. woven together); when triggered, they shorten ('contract'), so pulling bones ('voluntary' muscles), or narrowing tubes (e.g. the involuntary muscles in the guts, bladder, blood vessels and heart). In voluntary muscles, the nerve provides a short sharp trigger. In involuntary ones, different nerves may turn the thermostat up or down.

A Synapse is a junction between a nerve and another nerve, or a muscle or a gland. Signals are usually passed by chemical transmitters like ACh, but sometimes by direct electrical triggering. The nerve → muscle synapse is where things go wrong in the myasthenias, and is described in Volume 1, 'Normal Muscle Ignition and how it goes wrong' (see page 6).

The immune system

To protect us against germs, we have several cooperating systems. 'General' ones include blood proteins that help to destroy either germs, rubbish or our own normal cells as they die (which happens all the time). These proteins are helped by cells ('phagocytes') that eat up rubbish. 'Specific' defences include 'T cells' and 'B cells' which are each tailor-made to recognise only one target – usually a foreign germ but occasionally (alas) our own molecules or cells in autoimmune diseases like MG, thyroid disease and young-onset diabetes. The B cells' main job is to release antibodies, proteins that travel around in the blood and specifically latch onto their targets so that they get destroyed quickly.

GLOSSARY

Acetyl-Choline (ACh) is a chemical transmitter released from nerve endings = ‘ignition key’(s) [see Figure 1, page 6]. It is far too small to be seen on any microscope.

Acetyl-Choline Receptor (AChR) is the ‘ignition lock’ on the nearby muscle surface [see Figure 1, page 6]. When ACh binds to it, it opens up channels into the muscles, allowing salt (Na⁺) to enter and trigger the muscle into action. Like other large proteins, AChRs can just be seen on the most powerful (electron) microscopes.

Acetyl-Choline Esterase (AChE) is a protein near the AChRs that destroys any spare ACh [see Figure 1, page 6].

Anti-choline esterases are drugs that block AChE, so that any ACh lasts longer/has a better chance of triggering [see Figure 1, page 6]. These drugs include Mestinon[®] (long-acting; proper name Pyridostigmine) and Tensilon[®] (short-acting; Edrophonium).

Antibodies are proteins tailor-made to destroy germs or block toxins. They are made by ‘B cells’ (from the bone marrow) and travel around in the blood and tissue fluids. [see Volume 5].

Antibody negative MG is a bad name, because these patients do have typical MG, and it is caused by antibodies, but not against the AChR. In about half of them, antibodies instead recognise another muscle target called MuSK [see Volume 5].

Apnoea/apnoeic attack, the sudden stopping of breathing.

Autoimmune diseases are caused by cells or antibodies that can attack our own tissues or cell products.

Azathioprine (Imuran[®]) is a drug that generally suppresses immune responses [see section 4, page 13].

B cell(s) are immune cells from the bone marrow [see Volume 5]. When their surface-bound antibodies recognise their particular target or germ, they release more of these antibodies to destroy it.

Appendix 2

Bulbar applies to the movements of chewing, swallowing, speech and breathing controlled by the lower brain stem.

Congenital MG strictly means MG that can be seen at birth. In fact, some of these inherited faults in nerve → muscle triggering can start even in the teens [see, section 9 and Volume 2]. While many faults are in the AChR, others are in other genes involved in triggering.

Cyclophosphamide is a drug that generally suppresses immune responses, used in patients who can't take more standard immuno-suppressants.

Cyclosporin A is a drug that generally suppresses immune responses, especially of 'T cells' [see, section 4, page 14].

DAP, '3,4 diamino-pyridine' is a drug used to boost ACh release from nerve endings in LEMS and some congenital MGs [see Volume 5].

Diplopia, double vision.

Diuretic, causing an increased output of urine.

Dysarthria, difficulty in getting words out – i.e. in the movements of speech rather than in finding the right word in your brain.

Dysphagia, difficulty in chewing/swallowing.

Dyspnoea, difficulty in breathing.

EMG = electromyography, where nerves are stimulated electrically, and the resulting (electrical) impulses are measured in the muscles they supply. EMG helps Neurologists to sort out different congenital MGs and LEMS from 'immune' MG [see, section 3, page 9].

Imuran®, see Azathioprine.

IvIg, intravenous immunoglobulin: i.e. injecting (slowly into a vein) the pooled antibody fraction from normal blood. For unknown reasons, that improves many autoimmune conditions [see section 4, page 11].

LEMS, Lambert-Eaton Myasthenic Syndrome, is caused by antibodies against nerve endings [see page 19 and Volumes 2 and 5].

Appendix 2

Mestinon[®] is the commercial name for Pyridostigmine.

Methotrexate is a drug that generally suppresses immune responses, used in patients who can't take more standard immunosuppressants [see, section 4, page 14].

Muscles are long tubes of proteins woven together; when triggered, they shorten ('contract'), so pulling bones ('voluntary' muscles), or narrowing tubes (e.g. the involuntary muscles in the guts, bladder, blood vessels and heart). Muscles and nerves are made up of huge numbers of (much smaller) cells.

Mutation, an inherited fault in any gene.

Myasthenia, any form of muscle weakness.

Mycophenolate Mofetil is a drug like Cyclosporin A that generally suppresses immune responses, especially of 'T cells'; also called Cell-Cept[®].

'**Neonatal MG**' the term used when MG in a newborn baby is caused by antibodies from its mum [see, sections 1 and 5 and Volume 5]. Luckily, it only happens with about one in eight of MG mums.

Nerves relay electrical impulses from sense organs (e.g. eyes and skin) to the brain and spinal cord or from there to muscles and glands. They relay the signals to other nerves or muscles at special junctions, and switch them either on or off. Sometimes, they act more like dimmer switches, telling things to work harder or slower.

Ocular MG is MG affecting only the eye movements, and not other muscles (nor eye focussing).

Plasmapheresis or **plasma exchange**, means washing the liquid fraction out of the blood, to remove the antibodies, and then giving the red cells back in an artificial fluid.

Prednisone, **Prednisolone**, synthetic steroid drugs (like those from the adrenal glands) that generally suppress immune responses.

Propantheline is a drug like atropine that cuts down the side-effects of Mestinon[®] on the guts.

Appendix 2

Quinidine is a drug that partly blocks the AChR, and is used to limit the harmful effects of some congenital MGs. It is related to quinine (from a tree bark) that was used to treat malaria (and is still in tonic water).

Strabismus, squint.

Synapse, any junction between a nerve and another nerve, a muscle or a gland. Signals can be passed either by chemical transmitters like ACh, or by direct electrical triggering.

T cell(s) are immune cells (from the thymus). Like antibodies, they also recognise foreign germs; they can either directly attack infected cells or recruit other cells to do that instead ('inflammation'). They are also needed to help switch 'B cells' on [see Volume 5].

Tensilon[®] (Edrophonium), a short-acting anti-AChE drug; for diagnosing myasthenia, it is injected into a vein and the resulting increase in muscle strength is measured [see AChE and Figure 1, page 6].

Thymus, a 'factory' that produces immune 'T cells', especially before age 40, and exports them to the rest of the body. It lies between the breast-bone and the heart. It may be involved in starting the immune reaction against the AChR [see Volume 5]; removing it – thymectomy – seems to improve the MG in some young-onset patients.

Thymoma, a tumour of the thymus found in around 10% of myasthenics. It may somehow auto-immunise in MG [see Volume 5].

Vaccine, a germ (or germ product) made harmless. Still recognisable by 'T and B cells', it can be injected in advance, so stimulating these cells to multiply and forearm us before the real menace comes along.



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