

Myasthenia Gravis Association



INFORMATION PACK

Volume 2

A Medical Guide for Patients with LEMS or Congenital Myasthenia

Sponsored by





2nd Edition

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 available 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 printing, 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 families. 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 Internet, 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 2

A Medical Guide for Patients with LEMS or Congenital Myasthenia

About this Guide

THE OTHER MYASTHENIAS: THE LEMS AND CONGENITAL MYASTHENIA

The Myasthenias come in three main types. In all of them, the main problem is painless weakness of voluntary muscle caused by *faults in nerve to muscle triggering* – (see Figure 1 on page 4). Beyond that, they are very different. Much the most common of the three is Myasthenia Gravis (MG), which is covered in Volume 1. The subjects of this Volume are the two rarer forms, the **Lambert-Eaton Myasthenic Syndrome (LEMS)**, where there is an immune attack by antibodies, this time against the nerve endings, and the Congenital Myasthenias, where the faults are *inherited*.

As each person's experience of LEMS and the Congenital Myasthenias 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 with LEMS or Congenital Myasthenia, 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 May 2003, but is not the only view possible.

To assist the reader, italics have been used to emphasise important points and useful phrases which are repeated have been set in bold.

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.

FOR THE NEW PATIENT; WHAT IT MEANS TO HAVE THE LEMS OR CONGENITAL MYASTHENIA

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

Starting on the bright side: -

- Mostly, these Myasthenias can be brought under good enough control to allow a reasonably normal life.
- If you must have a neurological disorder, the Myasthenias are among the more treatable ones, with the least pain and the fewest major long-term snags; they rarely cause death by themselves.
- 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.

Try not to let it take over your life.

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

- Your Myasthenia may well be with you for many years. Don't wait around for a remission – see an expert Neurologist and get treated soon.
- You will probably have to plan your day to make the most of prime time when your strength is greatest.
- People may misunderstand you, especially at the first meeting, for example misreading even your best efforts at a smile.
- You will almost certainly need some drugs, and may well have to adapt to their side-effects. On the other hand, these drugs are more patient-friendly than in many similar diseases.

NB Patients with the LEMS **or** Congenital Myasthenia vary a lot, and it is difficult to make general rules.

2

THE CONGENITAL MYASTHENIAS

These account for about one Myasthenic patient in 40 (2-3%) and are caused by **inherited faults** in nerve to muscle ignition. *They do not involve the immune system at all* (unlike MG and the LEMS). Inherited faults (mutations) can occur at random in any of our (roughly) 35,000 genes, so they vary greatly and can affect any system in the body. Those causing Congenital Myasthenia can affect the nerve endings, the AChE or the AChRs (the ignition locks; see Figure 1); most of those identified so far are in the AChR and fall into two main groups [see best known faults, (a) and (c)], but faults are now being found in other nearby triggering proteins.

Thus these patients are a mixed bunch, ranging from mild cases, mainly with droopy eyelids, to wheelchair users. In unusual cases the Myasthenia becomes obvious only in the teens. However, ‘congenital’ strictly means ‘evident from birth’ – and that applies in most cases; some of whom improve later, for unknown reasons. Typically, patients have obvious weakness in movements of the eyes, eyelids, face, throat and/or chest. It is often made worse by crying in babies and by effort at any age, because of limited staying power. In infancy, they are often slow in reaching the normal milestones for movement. Occasionally, they also have bouts when their breathing becomes very shallow or even stops altogether (apnoea) for short periods. Parents and other carers can be trained to cope with that. Obviously, it is vital that the risk is recognised so that they are suitably forearmed. These episodes are rare after the age of about 6 years, and the other disabilities often get milder in the teens.

The best known faults

Currently (mid-2003) these fall into four main groups:-

(a) Not enough AChRs is the main effect of most of the faults. In general, our genes are in pairs and we get one copy of each from our mother and one from our father. Typically, these affected babies have inherited a faulty gene from each parent; mum and dad are usually not affected, because they each have only one faulty gene (which is ‘recessive’), and their other good gene is enough to keep them fit. For these parents, there is a 1 in 4 chance of each subsequent child having

Myasthenia. Because mum and dad are more likely to share the same fault if they are related, these faults are much more likely to show up in marriages between cousins.

These patients are often helped by Mestinon[®] which gives the ACh a better chance of triggering, or '3,4-diamino-pyridine' (**DAP**) which boosts the release of ACh (see Figure 1). DAP is only available through special centres (i.e. Oxford in the UK), and has to be used with care (see section 5, page 10).

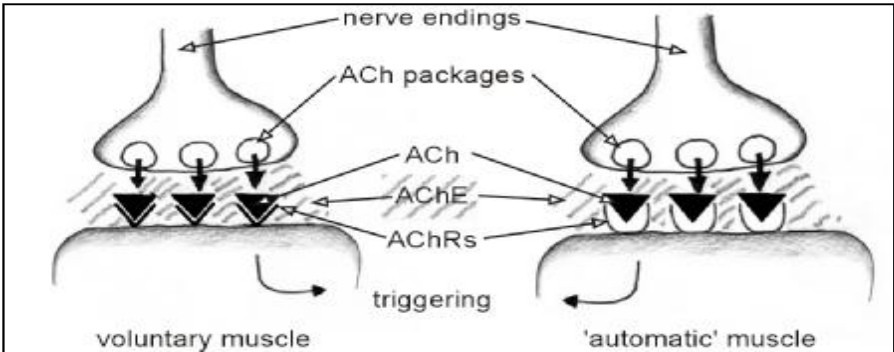


Figure 1

Diagram of nerve → muscle junctions

Key

ACh = acetylcholine

AChR = ACh Receptor

AChE = ACh Esterase (which destroys spare ACh)

When an electrical impulse arrives from the brain, it causes release of packages of ACh – the *ignition keys*. These cross the short gap and latch into the special *ignition locks* – the ACh receptors (AChR) which they then trigger. The spare ACh is broken down by AChE and the resulting fragments are re-cycled (by an enzyme, ChAT) to produce new ACh in the nerve terminals.

The AChRs are completely different in the voluntary and 'automatic' muscles (so we've given them V and U shapes). However, the nerve endings (and ACh) are similar. Their Calcium channels – which are attacked by the auto-antibodies in LEMS patients – are located right at the point of ACh release on the nerve endings.

(b) Not enough ACh. In some cases the fault is in the production of ACh in the nerve endings (i.e. in a protein called ChAT). These patients are particularly prone to breathing difficulties in early life.

(c) Over-choking the ignition. Other cases inherit a *single faulty AChR gene* ('*dominant*') from only one of the parents – who is usually affected too. Where this happens, there is a 50% chance of each subsequent child having Myasthenia. These faults are actively harmful because the AChR stays open for too long during triggering, the abnormal AChR allows too much salt (including calcium) into the muscle (this is the '**slow channel syndrome**'). Gradually, that damages the muscle and eventually causes weakness, which is often experienced when the child is in its teens. A similar picture also results from (*recessive*) faults in the AChE (see **d** below). In either case, Mestinon[®] may actually be harmful because it causes even more calcium damage. Blocking the faulty AChRs with quinidine can be tried instead – this underlines the value of seeking expert advice and having an exact diagnosis. Quinidine acts by encouraging the AChR to close, and so cuts down the long-term damage; alas, it can cause heart problems.

(d) Too much ACh. As we saw in the diagram, any spare ACh should be broken down by the enzyme AChE, which helps the AChR – and thus the muscle – to relax; that normally also prevents the calcium damage mentioned in (c). Patients with faulty AChE seem very similar to those with the slow channel syndrome, but, at present, they can only be treated with general support, unfortunately. Again, Mestinon[®] can make them worse.

Assessment

Patients with any of these very unusual Myasthenias need to go to a specialist centre. Electrical testing of nerve to muscle ignition (EMG) is often particularly useful for sorting them out there and then, but finding the faulty gene is the definitive test (see below). Exact diagnosis helps in giving advice to the parents about the chances of similar trouble in later children, and about their current care and **treatment** – which needs to be tailored according to the particular fault, as we saw in (c).

Because the Congenital Myasthenias do not affect the immune system, *immune suppression and thymectomy are quite unsuitable treatments.*

On the other hand, vaccinations can proceed as in any normal subject, and may be especially important (for example against 'flu or pneumonia) in children who are at risk of breathing problems.

Finding the faulty genes

The Department of Health is now providing ring-fenced funding to the Oxford NHS Trust for a specialist clinical and diagnostic service for these very rare patients. Dr David Beeson and colleagues have started a new (2002) diagnostic lab which tries to identify the genetic faults in the DNA (from blood samples). Obviously, with so many genes at risk, that can take time. David's team is also researching possible new treatments:-

- (i) Selectively to turn off the damaging genes in the dominant forms.
- (ii) The AChR is built up from five different **protein** chains and one of these (gamma) is active only in the unborn baby. Normally, the 'adult' (epsilon) chain replaces it shortly before birth; it is very often the chain at fault in the AChR-deficient cases. These patients seem to depend on their remaining gamma – which Dr Beeson is now trying to boost to help them get even stronger.

3

THE LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

The LEMS is at least ten times less common than MG. Although muscle weakness is again the main problem, it fluctuates less than in MG. Whereas MG particularly affects the eye, face, neck and chest movements, the LEMS shows a more '**bottom** ↑ upwards' pattern; the legs feel heavy – almost like walking through treacle. It can affect the arms, but less commonly the muscles of speech, swallowing, eyes or breathing. Very often, there are also problems with 'automatic' bodily functions [see (ii), page 7].

There are two forms of the LEMS. About half of the patients have a 'small cell' lung cancer, which is found only in smokers; the LEMS is an unusual reaction against the tumour cells (see page 7), and usually starts after age 40 years. In the others, there is no tumour; their LEMS

can even start as young as 9 years old but more often after 30 years, and the reasons are completely unknown.

Like MG, the LEMS is also caused by auto-antibodies, but these **ones cut down the release of ACh** from nerve endings (see Fig 1, page 4). So it also differs from MG in two other ways: -

- (i) LEMS patients often get a bit stronger as they try harder.
- (ii) Because the nerve endings are similar in the guts and the bladder etc, they too get attacked by the same antibodies, so there is usually also some trouble with ‘automatic’ bodily functions, for example causing a dry mouth, constipation or impotence, again unlike in MG.

Diagnosis can be confirmed by checking both for the typical changes in the EMG and for the damaging antibodies in a blood test; these are directed against calcium channels in the nerve endings and are found in almost every case. It is also very important to check for lung tumours, especially in smokers. The cancer cells have rather similar calcium channels and somehow immunise the patients against their own nerve endings. When 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.

Treatment

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 the feeble ACh release – the key defect in the LEMS. DAP is only available through special centres (i.e. Oxford in the UK), and has to be used carefully (see section 5, page 10); it is sometimes combined with Mestinon[®].

Being auto-immune, the LEMS responds well to the same plasma exchange, IvIg and immune-suppressing treatments as MG (section 5, page 10), though the benefits of plasma exchange take longer to kick-in (best after 2 - 3 weeks) than in MG (3 - 5 days). With both, they gradually tail off after 6 - 8 weeks. Thymectomy is not used because we think the thymus isn’t involved. In patients with tumours, treatment of the cancer must take priority; if it can be removed or destroyed, the LEMS often gets better or even disappears.

Drug interactions

The target for the damaging antibodies in the LEMS is a calcium channel in the nerve endings; drugs like Verapamil and Diltiazem block these channels. They are used often to treat high blood pressure, and occasionally by anaesthetists, but should be avoided in the LEMS as they can make it worse.

4

HISTORY

Breakthroughs in MG have often paved the way for subsequent progress for the other Myasthenias. MG was first clearly described in the 17th century but it has probably always affected human beings. Indeed, since it also occurs in dogs and cats it must be ancient.

The term ‘myasthenia gravis’ comes from Greek (myasthenia = muscle weakness) and Latin (gravis = severe). It was recognised as a disorder of nerve to muscle ignition 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 MG 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 5).

The differences between the LEMS and MG were clearly recognised only in the 1950s, when the American physiologist **Dr Ed Lambert** (at the Mayo Clinic) noted that too little ACh is released from the nerve endings – sometimes about half-normal amounts. However, it can build up with repeated stimulation; as many patients notice, the harder they try, the stronger they get – the exact opposite of MG.

Noting that LEMS patients often also have other auto-immune disorders, Professor John Newsom-Davis and his team tried **plasma exchange** in about 1981; to general delight, the LEMS got better.

Moreover, the plasma produced similar electrical and structural defects in the muscle ignition system when transferred to mice; the damaging antibodies were first shown to recognise Calcium channels in the mid 1980s by Dr Bethan Lang in the same team.

Families with **inherited myasthenias** began to be noticed in the 1930s. A key breakthrough was the identification of the AChR genes, first in animals and then (by Dr David Beeson, with MGA support) in humans in the 1980s. Finding the first faults took several years, both in David's lab and by Dr Andrew Engel's team in the Mayo Clinic (USA). Luckily, the methods improved dramatically in the early 1990s. Faults in other nearby proteins were first defined only in the late 1990s.

5

MORE ABOUT TREATMENTS

General common-sense things can be very effective in coping with the Myasthenias. 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 (for example mornings). While that may sound obvious, fellow-sufferers in MGA have lots of other valuable hints along similar lines (see Volumes 3 and 4).

Specific treatments: Broadly, most Myasthenias can be treated by:

- (i) souping-up nerve to muscle ignition;
- (ii) reducing the damaging antibodies or their production, *but only in the auto-immune types*.

(i) DAP AND MESTINON® (properly called *pyridostigmine*) are front-line weapons; a bit like the choke in a car, they give the (handicapped) ignition system a better chance of firing, so providing a temporary boost (see figure 1, page 4). They may strengthen some muscles much more than others, *but they don't 'clean the plugs' – therefore they don't cure the underlying immune or inherited faults*. So many LEMS (or MG) patients need more fundamental treatment to reduce the damaging antibodies.

DAP acts on the nerves; it makes their electrical messages last longer so that more ACh is released, and the chances of successful muscle triggering increase. At normal doses, it can cause short-term tingling around the mouth or in the fingers and toes. At excessive doses (not recommended), it can also affect the brain, causing anxiety, over-excitement and even epileptic fits, but that is very rare below 100 mg per day. For most patients, DAP is more effective than Mestinon[®], but sometimes combining the two is even better.

Mestinon[®] blocks the enzyme AChE that breaks down the ACh, and so the ACh lasts longer and again has a better chance of triggering the muscle. Since Mestinon's[®] effects last only a few hours, it is more important to take it often (for example 5 times daily). The exact dose 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 (that is 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). Mestinon[®] sometimes causes stomach cramps and diarrhoea, so it 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.

(ii) IMMUNOLOGICAL TREATMENTS are important in the LEMS (as in MG) for reducing the levels of the damaging antibodies. First, plasma exchange and IvIg are used in the short-term when benefits are needed *urgently*, for example if the weakness is rapidly getting worse, before surgery, or while waiting for steroids to take effect. While they are both very useful for that, neither is curative; alas, the cells obstinately go on making the antibodies, so extra immuno-suppressive drugs are very often needed.

Intravenous Immunoglobulin (Iv Ig) is the easier to use and is particularly effective in LEMS patients. It means infusing the total antibodies (**Ig**) pooled from huge numbers of healthy blood donors, into a *vein* (**Iv**). It clearly does help, though *only for about 8 weeks*, alas. We don't know *how* it works; there are more theories than hard facts. (It may simply water-down the damaging antibodies or sidetrack the bystander amplifying mechanisms they recruit). It is slightly cheaper than plasma exchange, but it also 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.

Plasma exchange is a helpful alternative, but needs more complicated machinery; the antibodies are simply washed out of the blood and replaced with a plasma substitute. During a thorough 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. That means being in a special hospital ward for 5 days connected by an intravenous line (often in the groin) to and from the separator for around 4 hours per day. After around 2 - 3 weeks, strength reliably improves for another 6 weeks or so, but then the benefits wear off as the antibodies are gradually replaced. It is safe, if slightly uncomfortable.

LONG-TERM IMMUNO-SUPPRESSION (to ‘clean the plugs’)

1. Prednisolone: The first choice drug is usually a synthetic *steroid* called ‘Prednisolone’, which is taken by mouth. It generally improves the LEMS after a delay of a month or more. It lowers the damaging antibodies, and probably has many other immune-suppressing effects too.

You probably already know that steroids can be a mixed blessing. Do remember that, in most 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 1 patient in 10 has to give them up because of the side-effects. You can find out more about them and other immuno-suppressants in Volume 5 or from your doctors, but here is a very quick run-down.

In general, as you know, *people vary greatly*: so do their responses to steroids – both the benefits and the side-effects. The normal procedure for LEMS patients is to start with a relatively high dose and then, when the weakness has been brought under control, to cut down to the

minimum needed to keep up the patient's strength. 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 (for instance by avoiding big crowds), you can usually keep that risk low without spoiling your social life.
- 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** (for example injury or appendicitis). Because the doses given to patients are so unnaturally high, they shut their adrenal glands off. So they are no longer cushioned against these stresses, and may collapse suddenly. That problem can be partly prevented by giving the steroids every other day, to keep their adrenals on their toes. Even so, *cutting down the dose always has to be done in small 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 most of which can be treated. They include: weight-gain, mood changes, sleeping troubles, diabetes and high blood pressure, skin changes (including thinning, easy bruising, slow healing and unwanted hair growth), bone-thinning (which can be prevented with other drugs), stomach ulcers, glaucoma and lens cataracts.

2. Azathioprine (Imuran[®]). This drug also reduces antibody production, but that takes at least a year to 'kick in'. It is sometimes used by itself for patients who can't quite manage on DAP or Mestison[®] alone. More often, it is used to enhance the benefits of steroids, and/or to get away with lower doses thereof ('steroid-sparing'). After that, the dose of Azathioprine itself is tapered down to the minimum needed to control the symptoms. For several reasons, steroids may be used alone, without Azathioprine, if the LEMS is associated with a lung tumour.

Azathioprine's 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 3 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, skin cancers are somewhat more common in people taking Azathioprine, *so they should be careful about sun-exposure*. There may also be a very low risk of a lymphoma in any patient on Azathioprine, *but usually the benefits far outweigh these hazards*.

3. We can use other immuno-suppressants if need be. Cyclosporin A may help if Azathioprine hasn't been a success even after being given a fair chance (for instance after at least one year). Other alternatives include mycophenolate mofetil (Cellcept[®]), methotrexate and cyclophosphamide, 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 than steroids, especially in the LEMS, and have their own side-effects too, partly because they are more powerful immuno-suppressants.

Vaccines

Two warnings for people taking significant amounts of immune-suppressing drugs (more than 20 mg prednisone on alternate days):-

1. Remember always to mention what you are taking before you are given any vaccines; a good rule of thumb is that live attenuated vaccines should be avoided, while the other (killed) types are safe:
2. It may be wise to discuss with your doctor whether you should be immunised against 'flu (and even pneumonia) each autumn.

6

DENTISTRY AND MYASTHENIA

If the Myasthenia is under good control, there is no reason why patients can't have normal dental care. Good communication between patient and dentist is vital. The patient must know exactly what the dentist is going to do. The dentist needs to know the patient's limitations, and to be prepared for them. That should help the patient to relax and co-operate more fully. It is vital that the dentist consults with the 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 strength is greatest, and to keep them short. If there are difficulties in opening and closing the mouth, in holding the head up, or in swallowing, *the dentist needs to know* so as to prevent problems. A mouth prop may help for keeping the mouth open; thorough suction (perhaps controlled by the patients themselves) helps to avoid drooling or choking problems.

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

Local anaesthetics are preferable; general anaesthesia should **never** be used outside the hospital setting.

Prevention is vital to avoid dental emergencies; they are most stressful and can aggravate the Myasthenia. 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 the teeth free of plaque.

The gums are liable to infections, and the patient may not even be aware of them; if severe, they can have knock-on effects on the Myasthenia and/or lower 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 the teeth. That, in turn, can create extra stresses or even pain.

ANAESTHETICS AND THE MYASTHENIAS

The Myasthenias used to pose challenges for anaesthetists. Nowadays, they are so well aware of them that that they rarely cause problems any more. Thanks to better awareness, preparation, monitoring and treatment, you should forget the out-of-date horror stories. However, Congenital Myasthenia patients, in particular, are such a mixed bunch and so unusual that no one specialist has much experience of anaesthetising them. They should each ask in advance for personalised advice from their own specialist. The following is therefore for the LEMS patients; again, **it is vital that the anaesthetists know about your LEMS**, and it may help for them to talk to your Neurologist in advance.

As you know, you can have either a **local or a general anaesthetic**. **Local anaesthetics** (for example lignocaine, bupivacaine or carbocaine which is shorter-acting and has fewer side-effects) 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 (for example into the jaw nerve) **or** around their spinal cord roots (as for spinal and epidural anaesthetics). These are suitable for many operations below the waist, for instance on hips, knees, varicose veins, hernias, some in gynaecology and even some on the chest. So many of you prefer them – both to avoid the feeble breathing caused by some general anaesthetics, and also to allow your treatment to continue normally. Light sedation given in advance helps you to ‘chill out’ – a bit like a sleeping tablet or an extra tipple!

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

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, such as gall bladders. 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, deeper anaesthesia was used instead, with more depression of blood pressure and breathing, longer recovery times, and more vomiting).

With their lower reserve of muscle-triggering power, LEMS (and MG) 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 by injecting a short-acting Mestion[®] cousin, Neostigmine, and DAP which works well too. Very occasionally, an unsuspected LEMS patient may need more Neostigmine than expected to perk them up – that is **one** of the roundabout ways in which LEMS can be first diagnosed.

NB some operations don't need any muscle relaxants; in that case, you can breathe by yourself or with assistance.

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

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 weakness 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.

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** (for example table salt, consisting of sodium and chloride atoms). Some 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 raw egg white, containing various salts, sugars and small building blocks that are combined to form proteins, fats and sugary carbohydrates. Inside this solution is the nucleus, the ‘brain’ of the cell; here the inherited blue-prints or genes (made of DNA), that code 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 35,000 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, in all our cells; they can transport molecules like oxygen, as does the red protein haemoglobin in our blood; they can transport food substances (for example glucose) into our cells from outside; 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 (as muscle proteins do); 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 – and order – 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.

Appendix 1

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 (for instance 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 (that are woven together); when triggered, they shorten ('contract'), so pulling bones ('voluntary' muscles), or narrowing tubes (for example 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 just ratchet the screw a bit tighter or looser.

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 to 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 Volume 1, page 6).

The immune system

To protect us against germs, we have several co-operating 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 auto-immune 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 4]. 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 4]. 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 4].

Anti-choline esterases are drugs that block AChE, so that any ACh lasts longer and so has a better chance of triggering [see Figure 1, page 4]. 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 immune cells or antibodies that sometimes attack our own tissues or cell products.

Azathioprine (Imuran[®]) is a drug that generally suppresses immune responses [see section 5, page 12].

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.

ChAT, the enzyme that produces ACh in the nerve endings.

Congenital, evident from birth.

Appendix 2

Congenital MG, This strictly means MG that can be seen at birth. In fact, some of these inherited faults in nerve to muscle triggering can start even in the teens [see section 2, page 3]. 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 [see section 5, page 13].

Cyclosporin A is a drug that generally suppresses immune responses, especially of 'T cells' [see section 5, page 13].

DAP, 3,4-diamino-pyridine, is a drug that makes the nerve impulses last longer, leading to more ACh release from their endings [see section 5, page 10].

Diplopia, double vision.

Diuretic, causing an increased output of urine.

Dominant, an inherited feature like brown eyes that shows itself even when you have only one copy of the gene, and is evident in about half of your offspring.

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 Myasthenias and LEMS from 'immune' MG.

Gene, inherited blueprint for one of our natural proteins; genes are made of DNA.

Imuran[®], see Azathioprine.

IvIg, intravenous immunoglobulin, Injecting (slowly into a vein) the pooled antibody fraction from normal blood. For unknown reasons, that improves many autoimmune conditions [see section 5, page 10].

Appendix 2

LEMS, Lambert-Eaton Myasthenic Syndrome, is caused by antibodies against nerve endings [see section 3 page 6, section 5, page 9 and Volumes 1 and 5].

Mestinon[®] is the commercial name for Pyridostigmine, an anti-choline esterase.

Methotrexate is a drug that generally suppresses immune responses, used in patients who can't take more standard immuno-suppressants [see section 5, page 13].

Muscles are long tubes of proteins woven together; when triggered, they shorten ('contract'), so pulling bones ('voluntary' muscles), or narrowing tubes (for example 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 change in a gene; can lead to loss, or to some abnormal function, of its product.

Myasthenia. Disorders causing fatiguable muscle weakness.

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

Neonatal MG is the term used when MG in a newborn baby is caused by antibodies from its mum [see, Volume 1, sections 1 and 5, and Volume 5]. Luckily, it only happens with about 10% of MG mums.

Nerves relay electrical impulses from sense organs (for example 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.

Appendix 2

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

Pyridostigmine is an anti-choline esterase also called Mestinon[®].

Recessive, refers to an inherited feature like blue eyes that shows itself only when you inherit it from both parents.

Quinidine is a drug that partly blocks the AChR and is used to limit the harmful effects of some Congenital Myasthenias. 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) is 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 4].

Thymus, This is 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 MG patients, that may somehow auto-immunise in MG [see Volume 5].

Vaccine, This is 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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