Clinical electrophysiology in myasthenia gravis

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Summary Effective diagnostic methods are of great importance in order to recognise myasthenic patients among those with muscle fatigability. Intracellular recordings are useful for research work within the field and for detailed description of the motor end-plate’s physiology in the individual case. The method is not used for the routine diagnosis of myasthenia gravis. The decrement of the electrical muscle response with nerve stimulation is the most commonly used method. The diagnostic yield is higher in proximal muscles, in warmed muscles, after exercise, and after ischaemia. A significant number of patients may be undiagnosed with this technique. The mechanical response with nerve stimulation shows the same type of decrement but also an abnormal response to long stimulation. The diagnostic value of this is under dispute. Single fibre EMG needs more patient cooperation than do these tests. The diagnostic yield is significantly higher. Some patients considered to have myasthenia gravis do not show any abnormalities with this technique, particularly those with the pure ocular form. Conventional EMG is not useful for the diagnosis of myasthenia, but may be indicated in these patients when concurrent nerve or muscle disease is in question. Tests for eye movement fatigue have not proved useful. Stapedius reflex fatigability is demonstrated in about the same proportion of patients as have positive SFEMG findings. The technique is not comfortable for the patient and requires minimal cooperation. The general usefulness must be assessed by further routine use. Even with the advent of immunological tests, neurophysiological investigations are indispensable in helping establish the diagnosis of myasthenia gravis. Discrepancies between the results comparing electrophysiological and immunological tests may indicate that myasthenia gravis is a heterogenous entity within which subgroups may be identified.

Neurophysiological methods have been used in the investigation of myasthenic patients for two main reasons. The diagnostic value of different methods have been demonstrated since the early reports of changes in muscle response to repetitive nerve stimulation. Over the decades these methods have also been used to help understand the pathophysiological mechanisms of myasthenia gravis (MG) and, in spite of the recent recognition of the immunological defect in MG, neurophysiological methods still have to be used to demonstrate the functional effects of the morphological or molecular changes demonstrated with other techniques. This paper will deal with some clinical neurophysiological methods for the diagnosis of disturbed neuromuscular transmission, both those commonly used and others at present used only in certain laboratories.

MG has attracted considerable attention out of proportion to the actual number of patients with the disease. This is mainly due to the early report of positive therapeutic effects of cholinesterase inhibitors, thymectomy, lymph drainage, corticosteroids, 4-aminopyridine, and other drugs as well as exciting new knowledge about the pathogenesis, including the development of a useful animal model. The disease may also provide a model for the further understanding of other immunologically induced diseases.

Efficient diagnostic methods are of great importance in order to recognise myasthenic patients among those with muscle fatigability and to follow the effect of different therapeutic measures. Over the years Ian Simpson has contributed much to the knowledge of MG and has inspired enthusiasm among those working with these problems. As a clinical scientist he acknowledged and used neurophysiological methods in the battery of tests of neuromuscular transmission. He was the first to draw attention to the correlation of MG with autoimmune disorders. As editor of the Journal of Neurology, Neurosurgery and Psychiatry he has always been receptive to papers concerning neuromuscular
transmission and so promoted the reporting of new methods and new findings in this field.

The first neurophysiological investigation of MG was published in 1895 by Jolly who used submaximal faradic stimulation of the nerve and voluntary activation to study fatigability of muscle. He observed a continuous decrease in muscle response during faradisation with recovery after rest. After voluntary exercise the muscle gave less response to subsequent stimulation and conversely, gave less voluntary force after faradisation. A similar technique is used today when we test the muscle response with repetitive nerve stimulation and which is sometimes called the Jolly test, although we use another stimulation pattern and usually a supramaximal stimulation strength.

In 1941 Harvey and Masland reported that the EMG potential recorded with concentric needle electrodes varied in amplitude with consecutive discharges during voluntary activation in myasthenia gravis, a phenomenon which still is used as an indication of disturbed neuromuscular transmission. We now know that this depends on intermittent disappearance or increased temporal variability of the individual spike components constituting the so called motor unit potential. Their other finding was the decrementing muscle response with repetitive nerve stimulation. This method has been modified but is probably the single most widely used method for the diagnosis of myasthenia today. Attempts have been made to use the method of repetitive nerve stimulation to differentiate presynaptic and postsynaptic defects, particularly together with pharmacological tests. It was used by Grob et al in their studies of pathophysiological mechanism in MG.

The similarity between the decremental response in MG and that of the curarised normal muscle, the worsening in MG after intra-arterial injection of acetylcholine (ACh), and the abnormal response to other depolarising agents was taken as evidence that MG was due to a postsynaptic defect. Desmedt et al using the same techniques found greater similarity between MG and the effects of hemicholinium which inhibits the uptake of choline producing a presynaptic block due to reduced ACh synthesis, and therefore considered MG to be a presynaptic disorder.

Since the decrement method does not allow localisation of the defect in greater detail a more direct method was necessary. This came when the technique of intracellular recordings from human intercostal muscles was introduced for the study of myasthenic motor end-plates.

Intracellular recordings are used in some laboratories for diagnosis of MG but the method is complicated and has its main use in research. It has been the most important method for understanding the pathophysiology of MG and has helped in explaining the results obtained with many other neurophysiological methods.

With the tip of the recording glass capillary electrode inside the muscle fibre at the end plate region small sub-threshold depolarisations are recorded which are too small to elicit a muscle fibre action potential. These are called miniature end-plate potentials (mepps) and have amplitudes of about 1 mV. They represent the quantal release of ACh from the nerve terminal, and occur spontaneously in the resting state. After depolarisation of the nerve terminal a large number of quanta are released and their mepps summate to produce an end-plate potential (EPP) with an amplitude which would reach 70–80 mV in the normal muscle if it was developed undisturbed. This exceeds the threshold for firing a muscle action potential and the EPP can therefore normally not be examined since it is transformed into a large propagated action potential. To study the EPP its amplitude must be reduced to subthreshold levels. This is obtained by decreasing the production of release of ACh (usually by magnesium) or the postsynaptic sensitivity (usually by curare). In the latter case the mepp amplitude is diminished to the same extent.

From mepp frequency, mepp amplitude, and EPP amplitude, information is gained about storage and release of ACh and about postsynaptic conditions. In the curarised preparation of a normal motor end-plate the amplitude of EPPs decrease during the first few of a train of stimuli. This is seen even at 2 Hz stimulation rate but is more pronounced at higher frequencies. When tested directly after a period of high frequency stimulation (50–200 Hz) the decrement with low frequency stimulation is initially less than before, and the amplitude is higher, a change known as posttetanic facilitation. After a few minutes there is an even more pronounced posttetanic exhaustion. In the motor end-plate treated with magnesium (which causes a presynaptic block), the amplitude of successive EPPs shows a great variability at stimulation rates below 10 Hz since they are composed of a reduced but variable number of normal sized quanta. At higher stimulation rates the EPP amplitude increases and shows less variability owing to an increased quantal content of the EPP.

The myasthenic motor end-plate was reported to have reduced EPP amplitudes. Amplitudes were sometimes too low to reach the threshold for
firing a muscle fibre action potential and so gave impulse blocking. The same authors also found reduced amplitudes of the mepps but normal number of mepps in each EPP, ie normal quantal content. The reduced mepp amplitude could either be due to a presynaptic or a postsynaptic defect. Normal sensitivity to application of ACh analogues was found and the reduced mepp amplitude was interpreted as indicating a presynaptic defect, probably defective synthesis of ACh since release was normal, tested with increased potassium in the bath. Later investigations by others have confirmed the EPP and mepp changes but they showed a reduced sensitivity to applied ACh in the experimentally induced MG probably due to reduced or physiologically blocked cholinergic receptors in accordance with a postsynaptic defect, also shown with other techniques in human myasthenic muscles and now considered to be the principal site of lesion in MG.

These are the basic phenomena behind the typical findings in the routine repetitive nerve stimulation tests in disorders of neuromuscular transmission.

Repetitive nerve stimulation

General findings  The change in muscle response to repetitive nerve stimulation has become the most commonly used test for the diagnosis of MG. It has shown to be a useful diagnostic technique provided it is used correctly and to its full capability. It has also given additional knowledge about MG.

A minimal programme for an investigation with this method could be as follows. Surface electrodes are used, one over the belly of the muscle, the other at a position remote from the muscle. Low frequency stimulation is given by a surface electrode on the corresponding nerve at a rate of 2–3 Hz. Movements induced by the muscle contraction have to be prevented by convenient fixation. The negative amplitude of the first response is measured together with the relative difference between the fourth (or fifth) and first response (fig 1). In our department we use a computer for the analysis and have also included measurements of the area between the signal envelope and base-line, also used by others. The change in this value is usually close to the amplitude change. If not, recording artefacts have first to be suspected. With these excluded the difference may then be due to so called pseudo-facilitation, an increase in the amplitude of the summated action potential due to “synchronisation.” Here the area is a better indication of the changes. In the normal muscle the amplitude and area measures exceed certain minimal values, varying with different muscles and different ages. The amplitude and area normally change less than 5% with repetitive nerve stimulation but in MG they decrease more than that. As mentioned earlier there is a normal reduction in end-plate potential (EPP) amplitudes during the first stimuli after a period of rest but due to a high safety factor in the normal muscle this does not lead to impulse blocking and is therefore not detected with a recording of the gross muscle response. In MG or any condition with reduced safety factor, that is, having low EPPs (Eaton-Lambert or other myasthenic syndromes, botulism, curare), this physiological decrease in EPP amplitude is unmasked and causes blocking in successively increasing number of motor end-plates, giving a decremental response.

Fig 1  Computer printout of two decrement investigations from the deltoid muscle before (upper) and after (lower) 20 s of maximal voluntary activation. Black bars indicate the negative amplitude of the first four responses. The first (dotted) and fourth (full line) responses are displayed in detail. 

A=amplitude of the first response.

DA=decrement in amplitude of the fourth relative to the first.

DS=decrement in surface of the fourth relative to the first.

Note the facilitation with increased amplitude and reduced decrement after activation.
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After a period of maximal activation or high frequency repetitive stimulation (the latter is not used in our department since it is uncomfortable for the patient although it is considered to be a better controlled activation) the amplitude and area are mainly unchanged in the normal muscle. In the myasthenic muscle (not overtreated with cholinesterase inhibitors) the decrement becomes less pronounced or disappears and an eventually reduced resting amplitude is increased towards normal values, an effect seen only during the first 20–30 seconds after the activation.

This is again the normal phenomenon of facilitation of ACh release in the motor end-plates. It is unmasked in situations where the increase in ACh may contribute positively to restoration of transmission. In conditions where disturbed neuromuscular transmission is mainly caused by impaired release, typically in Eaton-Lambert syndrome, the effect of this facilitation is particularly pronounced. On the other hand in conditions where an over-exposure to ACh is causing the dysfunction (such as overtreatment with cholinesterase inhibitors,17 intoxication with organophosphorus compounds,18) there is no increase of the recorded response but rather a reduced amplitude directly after maximal voluntary contraction or tetanic stimulation. The amplitude of the response at the height of the facilitation gives an indication of the total number of motor end-plates that can be activated, that is, not irreversibly blocked or destroyed and the measure is thus of practical value.

After this short period of facilitation in the myasthenic muscle the amplitude decreases and the decrement becomes more pronounced. This is called the postactivation exhaustion and was first described by Desmedt.19 This parameter seems physiologically closer to the fairly reversible myasthenic fatigue after exercise than the decrement. The cause of the postactivation exhaustion is not yet clear. The receptors are known to show "desensitisation" experimentally after even a short exposure to ACh18 and this may play a role but further investigations are necessary.

In all tests it should be remembered that facilitation and exhaustion are two separate phenomena acting at the same time but with different time scales, and that the observed response is determined by the summated effect of the two.9 This affects the results of the routine electrophysiological testing. In a patient with pronounced MG a period with maximal voluntary activity of 20 seconds may be too long to show facilitation since more pronounced exhaustion is already dominating after this time. Here a shorter period may shown facilitation. In a patient with myasthenia of moderate degree a 20 second period may be enough to give facilitation but too short to show any significant exhaustion. One has to be aware of these effects of activity when testing patients. To compare results from different occasions the same basic conditions must be present. We rest the patient for 30 minutes before the test. In long term studies it is important to have the patient comfortably positioned and completely relaxed. The effect of activity on base-line conditions is particularly pronounced in severely affected muscles.

Neuromuscular transmission can be quantified by means of a similar technique using different stimulation patterns. By using double pulse stimulation and testing the relative amplitude of the second response a recovery curve of the neuromuscular transmission is obtained.20,21 In the MG there is a depression of the second response not seen in the normal muscle at intervals of 0.1 to 10 seconds, correlated to the severity of the disease.

By using repetitive nerve stimulation (1–8 Hz) for 10 to 40 minutes other aspects of the dynamics of neuromuscular transmission can be tested.22–24 The area of the action potential reaches a plateau level after the initial decrement and a transient facilitation. Bergmans et al.25–28 assumed that this level represents a steady state of emptying and refilling the transmitter store and used the information from the prolonged stimulation experiments to study the kinetics of the transmitter. New knowledge about the postsynaptic defects in MG may to some extent change the interpretation of the above mentioned special tests which therefore are not described in detail here.

Difference between muscles In the clinical examination MG usually shows a proximal distribution. This must also be noted when making electrophysiological tests. The decrement is as a rule lower in hand muscles (properly warmed) than in proximal muscles in the same patient. The diagnostic yield of the method is significantly lower for distal than for proximal muscles. This was shown in a study of 80 MG patients. The decremental pattern was obtained in 82% in deltoid muscle, 50% in abductor digit minimi (ADM) muscle, 62.5% in orbicularis oculi muscle and 52% in the wrist flexors. When all these muscles were considered together 95% of the patients showed abnormalities. In our cases (table) we have not seen a single case where the hand muscles have shown a decrement and the proximal muscles have been normal at the same time. This may not necessarily indicate that the immunological attack to the motor end-plates is more pronounced proximally but may indicate different safety factors in different muscle groups or reflect other differences. From Single Fibre EMG (SFEMG) studies it has
been reported\textsuperscript{28} that in ADM muscles with minimal or no decrement some individual motor end-plates showed impulse blockings and some of them facilitation even at low stimulation rates (2 Hz) which more or less effectively compensated for the drop-out in the others and explained the small net effect measured as the decremental response with surface electrodes.

**Effect of temperature** The effect of temperature on myasthenic muscle has been discussed by Simpson\textsuperscript{27} and others.\textsuperscript{28} In our decrement studies deterioration with increasing temperature is a constant finding. With a change from 26 to 35\degreeCelsius intramuscularly, decrement may increase from 0\% to 29\% (fig 2B). This is also the case in patients that do not report any subjective worsening with increasing temperature. The effect of temperature on neuromuscular transmission has been studied in animals.\textsuperscript{29-30} The cause for the impaired neuromuscular transmission at higher temperatures is not known in detail. Intracellular recordings show a dramatic increase in miniature end-plate potentials (mepp) frequency. In the magnesium blocked motor end-plate the EPP amplitude decreases with increasing temperature probably due to decreased quantum content (presynaptic effect); in curarised muscle the EPP amplitude is seen to increase but is dramatically shortened, most likely due to postsynaptic membrane effects, and increased cholinesterase activity.

Because of a high safety factor the normal muscle does not show any neuromuscular block within the physiological temperature range. In cases with disturbed neuromuscular transmission this factor may have considerable influence. In order to compare the results of one investigation with another in the same patient it is therefore of greatest importance to make the test at a standardised temperature. A thermostatically controlled lamp is recommended. Intramuscular temperature in the hand decreases normally to below 30\degreeCelsius (26\degreeCelsius is not uncommonly seen) within 30 minutes of rest in a warm laboratory room. Proximal muscles show less change and a temperature reduction of 2\degreeCelsius (from 36 to 34\degreeCelsius) is more commonly seen. This parameter must always be checked in long term investigations, for example when following the effect of intravenously injected or per orally administered cholinesterase inhibitors or other drugs over more than 30 minutes.

**Provocative tests** The easiest way of increasing the myasthenic defect temporarily is to fatigue the muscle by activity, either by voluntary exercise or by a more standardised electrical stimulation, for example 3 Hz for five minutes. The effect can be stronger if the muscle temperature is slightly increased.

The neuromuscular transmission is sensitive to ischaemia. Therefore, a combination of exercise and ischaemia is reported\textsuperscript{9} to be effective. The test has been made in two steps, first 3 Hz stimulation for five minutes with free blood circulation, then the same activation under ischaemia. With this a decrement can be seen in cases of mild MG that do not show any significant abnormality with standard testing before provocation.
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Based on the increased sensitivity of patients with MG to curare, this drug has been used to reveal a neuromuscular disturbance. In order to reduce the risk the test is made after regional intravenous administration. A diagnostic yield of up to 96% in generalised MG is reported. A curare test is considered potentially hazardous and its use has therefore been discouraged in most laboratories.

Staircase phenomenon Decrement of the electrical response as described above is usually the commonly used test of the MG defect but it can be measured from the mechanical response as well. In this situation not only is neuromuscular transmission tested but also the contractile characteristics of the muscle fibres. With low frequency stimulation (2 Hz) normal muscle shows a slow increase in twitch amplitude during the first minutes of stimulation. This is assumed to be an effect of intensified excitation-contraction process. In myasthenia this so called staircase phenomenon was reported to be abnormally weak or by some authors absent whereas others reported that the staircase phenomenon was usually within normal limits. If it is abnormal, after the amplitude reduction in the electrical response caused by neuromuscular transmission is considered, it should suggest defects in MG other than those located at the motor end-plate.

This should be tested further. Today the value of testing the staircase phenomenon for the diagnosis of myasthenia gravis is still uncertain.

Single fibre EMG

With the development of a technique called Single Fibre EMG (SFEMG) it has become possible to study the microphysiology of the motor unit in humans including the functional status of individual motor end-plates in situ. A needle electrode with a recording surface of 25 μm in diameter in a side port of the cannula is positioned in the voluntarily activated muscle to record activity from a few adjacent muscle fibres. For the study of neuromuscular transmission an electrode position is sought where activity from two muscle fibres belonging to the same motor unit is recorded as a potential pair. There is usually a time interval between the two action potentials depending on the difference in propagation time from the common branching point along the nerve twig to the recording electrode. With consecutive discharges there is a variability in the interpotential intervals called the jitter. When expressed as the mean value of consecutive differences of these time intervals (MCD), this jitter is of the order of 5–50 μs in the normal muscle. The jitter increases in situations with disturbed neuromuscular transmission such as after a small dose of curare; when the disturbance is

Fig 3 SFEMG jitter recordings from EDC muscle of a patient with myasthenia gravis and malignancy. Symptoms were only present during periods of fever. The oscilloscope sweep is triggered by the first action potential, delayed by 1–2 ms. The jitter is seen as a variable position of the second and in C also a third action potential. Upper tracings: 20 superimposed sweeps, lower tracings: sweeps moved downwards. Within the same muscle one can see normal jitter (A), increased jitter but no blockings (B) and increased jitter and intermittent blockings (second potential in C). C demonstrates different degree of abnormality among motor end-plates in the same motor unit. Jitter A = 29 μs, B = 65 μs, C = 81 μs and 49 μs.
more pronounced partial or total impulse blocking is seen. The jitter expresses a varying neuromuscular delay time which may be due to a variable rise time of consecutive EPPs, which has not been seen with intracellular recordings in the normal muscle. It is more likely due to a slight variation of the threshold at which the EPP initiates a muscle action potential. The EPP will therefore reach the threshold after different times from initiation. When the EPP is changed in shape, for example after curare reaching the threshold under a less steep slope, the effect of the threshold fluctuations will be more pronounced and give rise to a larger jitter. If the EPP is too low to reach the threshold, impulse blocking occurs.

The jitter value is different for motor end-plates even within the same motor unit. Different muscles have a different mean jitter value within the same subject and the mean value for one particular muscle differs between subjects. After a small standard dose of curare the jitter value increases less in those motor end-plates with an initially low value than in those with an initially high jitter value. It seems that the jitter value in a motor end-plate is an indicator of its safety factor expressed as sensitivity to curare, that is, low jitter suggests less sensitivity. In myasthenia gravis the jitter is typically increased. The degree of abnormality in one muscle shows a range from normal motor end-plates to those with pronounced changes including partial or total blocking (fig 3). This range of abnormality is also seen within the same motor unit (fig 3C). When using the SFEMG method it is therefore necessary to make recordings from at least 20 different electrode positions. The jitter mean value varies for different muscles in the myasthenic patient. Usually we start recording from the extensor digitorum communis (EDC) muscle. It is easy to activate and shows abnormalities even in slight MG, clinically as well as neurophysiologically. If this muscle is normal, recordings are made from other muscles depending upon the symptoms, usually deltoid, frontalis or orbicularis oculi muscles. The findings are quantified as jitter value and degree of blocking for each individual potential pair, often summarised for the whole recording as a percentage of recordings with normal potential pairs, those with increased jitter, and those showing partial impulse blockings (fig 4). The mean jitter value for all recordings is given as well. The criterion for abnormality in individual recordings is a jitter value exceeding an upper limit determined from the normal material (about 50μs but different for different muscles). The investigation in one muscle of at least 20 recordings is abnormal if more than two individual recordings show abnormal jitter or if the mean jitter exceeds a certain value obtained from the normal material.

The abnormal jitter and degree of blocking usually decrease after the injection of Tensilon in patients with untreated myasthenia gravis. Normal motor end-plates in myasthenia do not change after the injection of Tensilon. In patients receiving cholinesterase inhibitors the effect of Tensilon may vary for different motor end-plates. Some of them may show improvement, others in the same muscle may not change their abnormality, while others at the same occasion may show even increase in jitter and degree of blocking. These findings indicate the varying degree of myasthenic defect and sensitivity to treatment. Some motor end-plates are undertreated, others are optimally or even overtreated. This is certainly true not only for individual motor end-plates but for muscle groups. In the clinical situation some muscles may be undertreated while others may be overtreated. In these situations the optimum response has to be judged from the clinical situation with particular regard to vital muscle groups, such as those concerned with respiration or swallowing. The effect of temperature is principally the same as indicated by the findings in repetitive nerve stimulation. With increasing temperature the abnormality in a motor end-plate increases. During continuous and steady activity the jitter may increase during the first few seconds but will then usually remain relatively constant. With decreasing mean firing frequency the jitter may decrease and at increasing rate the jitter increases.

![Graph showing distribution of jitter values](https://example.com/graph.png)
In Eaton-Lambert syndrome the jitter is increased. It has the same characteristics as jitter in MG except for the reaction to increased firing rate. In MG the jitter and degree of blocking increases, in Eaton-Lambert syndrome they decrease when the innervation rate is increased.

In some clinically diagnosed patients with MG a proportion of the abnormal motor end-plates show, in contrast to the larger part of the motor end-plates, a slight improvement during continuous voluntary activation as described for the Eaton-Lambert syndrome. Thus patients with clinical myasthenia may have a mixture of motor end-plate defects, some typical for MG, some similar to those found in the myasthenic syndrome. This intermediate form is sometimes seen also with decrement testing in these patients.37

SFEMG has been performed in 164 of our patients with MG diagnosed on clinical grounds. The jitter values have been abnormal in 94% of the cases. The degree of neuromuscular disturbances expressed in terms of jitter and impulse blocking is grossly correlated to the degree of clinical involvement. When the patients are sub grouped into those ocular, moderate generalised and severe generalised MG the degree of abnormality is successively more pronounced for each group when the extensor digitorum communis muscle is tested. The SFEMG abnormalities in two groups have been compared,38 one with and the other without clinical involvement of the tested muscle, the extensor digitorum communis muscle. The jitter was significantly more abnormal in the group where clinical symptoms were present, 114±8-5 μs than in the nonsymptomatic group, 47±2.5 μs. In the symptomatic group abnormalities were found in 63 of 64 and in the nonsymptomatic group in 56 of 74 patients.

In a few cases we have made SFEMG investigations before and after complete remission, that is disappearance of clinical signs and symptoms and on no medication. The average jitter decreased but some motor end-plates still showed abnormalities. In none of these cases did SFEMG normalise completely (fig 5). In another study38 7 out of 9 patients with clinical remission after corticosteroids showed abnormal SFEMG values.

A comparison between the diagnostic yield of repetitive nerve stimulation (temperature-controlled proximal muscle), antibody titre against acetylcholine receptors, and SFEMG results are summarised in the table. It is seen that the SFEMG investigations have the highest proportion of positive tests. In no case was a decrement present where SFEMG was negative. The titre of receptor antibodies was abnormal in all seven tested cases out of the 10 SFEMG negative cases. On the other hand SFEMG was abnormal in all 17 cases with normal antibody titre. In patients with ocular myasthenia,38 all three tests in general had the lowest percentage of positive findings, 28% for repetitive nerve stimulation, 67% for SFEMG in EDC and 86% when also a facial muscle is investigated, and 67% for antibodies.

It should be stressed that increased jitter and partial impulse blockings are not pathognomonic for MG, but indicate disturbed neuromuscular transmission or sometimes an abnormal impulse propagation in the terminal nerves. Increased jitter and blocking are also seen during early stages of reinnervation,35 for example, posttraumatic, lower motor neurone disorders, polynuropathies, also in pronounced electrolyte disturbances, and to some extent in myopathies, particularly in polymyositis. Other SFEMG parameters such as fibre density and duration usually typify these disorders. They are rarely a problem in the differential diagnosis from MG clinically electrophysiologically.

Fibre Density The arrangement of muscle fibres within the motor unit can also be determined by SFEMG.

The average number of muscle fibres belonging to the same motor unit is determined from 20 different
electrode positions and the local fibre density (FD) is measured. The FD differs for different normal muscles but is of the order of 1.3 to 1.5. From other studies we know that the FD is increased in conditions with reinnervation and in situations of verified fibre type grouping.

In our total material or patients with MG the FD is increased on average. Statistical analysis has not revealed any correlation with severity or duration of the disease but there is a statistically significant difference between patients treated and not treated with cholinesterase inhibitors.

In the patients where the treatment had been used for more than one month the FD was increased from the normal mean by 2.2 SD (p<0.01) in the biceps brachii muscle compared to 1.2 SD in the untreated patients. The difference was most pronounced in older treated patients. In the cases where EMG has been taken the degree of fibre type grouping was correlated to the FD. The increased fibre density most likely reflects reinnervation caused by the cholinesterase inhibitors. Signs of denervation can also be induced in animals. The slight increase in average fibre density in the nontreated group as compared to a normal value is statistically significant (p<0.01). This may be due to the morphological changes of the myasthenic motor end-plate which sometimes may be pronounced leading to denervation. Reinnervation by axonal sprouts from adjacent motor units will produce remodelling indicated by abnormal fibre density values for the motor unit. Morphological abnormalities of the motor end-plate have been discussed by Simpson earlier.

Conventional electromyography
Conventional electromyography (EMG) is performed in MG mainly for two reasons: one is to find signs of this particular disease, the other and more important is to exclude or detect other diseases which clinically may have similar symptoms. Some of these may occur concurrently with MG such as thyroid myopathy and polymyositis; others may be induced by the steroid treatment.

The typical finding in conventional needle EMG is varying shape of the motor unit potential. Harvey and Masland reported amplitude variation as a characteristic sign in MG. This is due to increased variability in the time dispersion between individual spike components constituting the motor unit potential, that is increased jitter. Owing to drop out of individual fibres in more pronounced MG the number of muscle fibres in the active motor unit may be reduced which give motor unit potentials of decreased amplitude and short duration, the same as is seen in primary myopathies. This is particularly seen during activity. After a period of rest the motor unit potential may regain a normal shape. This EMG sign should not be misinterpreted as an indication of "myopathic" changes in MG. This phenomenon has to be taken into consideration when an EMG investigation is made to evaluate the presence of a myopathy in MG, eg induced steroid myopathy.

The conventional needle EMG has thus not turned out to be very useful in the diagnosis of MG but is of value for the study of concomitant muscular disorders.

Other tests
Muscle fatigability in myasthenia gravis can be seen in most, perhaps all, skeletal muscles in patients with definite symptoms, more frequently in severe cases. Other tests than repetitive nerve stimulation can be used to quantify this.

One such test concerns the extraocular muscles. The patient is asked to follow with his eyes a dot moving on a screen in front of him. The eye movements are recorded with surface electrodes lateral to the eye similarly to the technique used in nystagmography. In cases of MG the eye movement will progressively become slower and the amplitude of the excursion smaller. The test has been used to a limited extent for special studies. The value of this test for the diagnosis of MG as compared to others has not been evaluated so far but the yield is probably less than with repetitive nerve stimulation.

Another measure of muscular fatigue is obtained by measuring fatigue of the stapedius reflex. The stapedius muscle controls the tension of the ear drum and reacts reflexly to sound stimuli. The contraction developed by the muscle can be inferred by measuring the acoustic impedance of the tympanic membrane. It is used in many audiology departments in routine neuroaudiological investigations. When a continuous tone is given to the ear the muscle contracts and remains so until the sound is removed. The measured impedance is increased to a constant value during the stimulation. In MG there is a continuous decrease of the acoustic impedance due to a fatigue of the stapedius muscle. Owing to base-line shifts it is sometimes difficult to measure the impedance over many seconds of stimulation. The technique was modified to a stimulation with a pulsating 500 Hz tone where the duration of the pulses were 200 or 500 ms (sound pulse stimulation SPS 200 and SPS 500) separated by an equal duration "off line". In this way the muscle is repetitively stimulated in a similar way used in nerve stimulation tests. When the change in impedance is measured between the responses obtained during the first and last 10 seconds of a stimulation period of 300 seconds the normal subject
shows a slight increment for the 500 ms pulses and a slight decrement for the 200 ms pulses. In MG there is a decrementing response to this stimulation that improves after cholinesterase inhibitors. With SPS 500 stimulation, 83% of MG patients showed abnormal responses and with SPS 200 77% were abnormal. At least one of the stimulation patterns was abnormal in 96% of the cases tested. The technique is easy to apply in places where the audiometry department is equipped for stapedius reflex testing. The test is painless for the patient and the diagnostic yield seems to be very high, comparable to SFEMG. Experience so far is limited and it is recommended that control values be obtained before using this test for the routine diagnosis of MG.

Comparison of techniques

The diagnosis of MG is mainly based on clinical symptoms and signs. Laboratory investigations are however important to confirm the diagnosis or to make it unlikely. These tests are also indispensable to describe the status of the neuromuscular transmission in atypical cases. Many of the myasthenic syndromes simulate MG clinically in many, though not all, respects. New subgroups of myasthenia will certainly be described by means of combined electrophysiological and immunological testing. Usually it suffices to use only one of the electrophysiological tests when it reveals a neuromuscular defect. When the first used method fails to demonstrate an abnormality other tests must be utilised. Their accessibility in the individual situation, the diagnostic yield of the method, and discomfort for the patient are factors of importance for the choice.

Decrement studies are commonly available in most EMG laboratories; they are technically simple although technical pitfalls can easily ruin the results. Studies of the hand muscles are tolerated by most patients, but even with warming the hand before testing and with measurements after exercise the diagnostic yield is relatively low. Ischaemia and high frequency long term nerve stimulation may provoke abnormalities but are more painful for the patient and may require local anaesthesia. Decrement studies in proximal muscles, eg biceps, deltoid or facial muscles, are somewhat more painful than hand muscles but usually tolerated by the patients, including children. The tests in these muscles are more prone to artefactual changes; however the neuromuscular abnormalities are much more demonstrable. A decrement test is incomplete if only hand muscles are studied and the results obtained are negative. SFEMG measurements are still only available in a few laboratories. It requires minimal changes in routine EMG equipment with some extra training and experience by the electro-

myographer. The patients’ cooperation is needed and a complete test can usually not be performed in patients below the age of seven years. For the patient the test gives the same discomfort as an ordinary EMG investigation; some patients find this test less uncomfortable than repetitive nerve stimulation. The diagnostic yield is very high and is particularly valuable in cases with mild forms of myasthenia gravis and in cases with the ocular form. Usually only one muscle has to be tested. If SFEMG in EDC muscle is normal in a patient with ocular symptoms the frontalis or orbicularis oculi muscles should be tested. If a complete investigation gives normal results in a clinically weak muscle the diagnosis of myasthenia is very unlikely.

Tests of stapedius reflex and eye movements are painless and require minimal patient cooperation. The test can be performed in any well equipped audiological and ENT department respectively but their clinical applicability for the diagnosis of myasthenia remains to be assessed by further routine use.

In this paper the value of measuring the antibody titre against acetylcholine receptor has not been discussed. This test demonstrates the immunological abnormality and has obvious advantages. So far the test is not correlated to the clinical severity of the disease and has unfortunately, like the other tests, the lowest yield in ocular myasthenia.

The discrepancies in the results when using the different electrophysiological and immunological tests may indicate that myasthenia gravis is a heterogenous entity within which subgroups may be identified. It is a challenge for further studies of myasthenia gravis and the myasthenic syndromes.

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