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A new method for the estimation of the number of motor units in a muscle

1. Control subjects and patients with myasthenia gravis

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SYNOPSIS A new method, incorporating on-line computer analysis, is described for the estimation of the numbers of motor units in human muscle. The results obtained in the extensor digitorum brevis muscle in normal subjects and patients with myasthenia gravis are presented. These indicate that the numbers of motor units in that muscle in patients with myasthenia gravis are within the normal range, in contrast with the reduction in numbers reported by other workers using a different technique. Evidence is presented to suggest that the discrepancy in these results is due to increased sensitivity and discrimination of the computerized method. Several hypotheses on the aetiology of a number of neuromuscular diseases, based on the results of the other method, may require re-evaluation.

The recent introduction of an electrophysiological method for the estimation of the numbers of motor units in the human extensor digitorum brevis muscle (EDB) derived from the amplitudes of the compound muscle action potentials evoked by stimulation of its motor nerve, has added a new dimension to the investigation and detection of neuromuscular disease (McComas *et al.*, 1971b). The application of this technique to a number of diseases has been interpreted as indicating a possible neurogenic influence in the aetiology of Duchenne type muscular dystrophy (McComas *et al.*, 1971d), limb-girdle dystrophy (Sica and McComas, 1971), myotonic dystrophy (McComas *et al.*, 1971a), myasthenia gravis (McComas *et al.*, 1971c, 1973a) and in the neuromuscular disorder in thyrotoxicosis (McComas *et al.*, 1973b). Similar studies may indicate the presence of transynaptic degeneration of lower motor neurones in hemiplegic patients (McComas *et al.*, 1973c) and in Parkinson's disease (Sica *et al.*, 1973).

Brown (1972, 1973) has used a somewhat similar method to count the number of motor units in the thenar muscles in healthy subjects and in patients with the carpal tunnel syndrome. In conditions accompanied by denervation, the absence of electrophysiological evidence of an increase in the amplitudes of the action potentials of surviving motor units has led to the concept of 'sick' motoneurones (McComas *et al.*, 1971c, 1973a).

The results obtained by the use of this technique and the conclusions drawn therefrom have not received universal support. Both histochemical (Jennekens *et al.*, 1972) and electrophysiological (Rosselle and Stevens, 1973) evidence is available which demonstrates the occurrence of denervation in the EDB muscles of normal subjects of all ages, so that this muscle may not be representative of the body musculature in general. The method has been further and more seriously criticized on the grounds that it cannot distinguish the small motor unit potentials that occur in dystrophic disorders of muscle (Scarpalezos and Panayiotopoulos, 1973). Certainly, the claim that there is a reduction in the

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total number of motor units in Duchenne dystrophy (McComas *et al.*, 1971d) is difficult to reconcile with the generally agreed interpretation of needle electromyography that motor unit potentials are present in normal numbers but with decreased amplitudes and durations (Richardson and Barwick, 1969; Lenman and Ritchie, 1970). We too have reservations on the reliability of amplitude measurements for the recognition and quantitation of evoked motor unit responses, particularly those potentials of reduced or otherwise altered electrophysiological dimensions that may occur in neuromuscular diseases.

The purpose of this paper is to describe a computer aided method for the detection and estimation of the number of motor units in intact human EDB muscle of normal subjects and patients with myasthenia gravis. The technique has also been applied to the frontalis muscle and the results of that study will be the subject of a further paper.

METHODS

Thirty-nine healthy volunteers aged 35 ± 14 years were obtained from among the staff of the Department of Neurology. They had no history or clinical evidence of neurological disease.

Twenty patients with myasthenia gravis aged 38 ± 16 years were studied. Three patients were asymptomatic, 17 were symptomatic and/or had evidence of a decrementing response to tetanization. The duration of the myasthenia gravis ranged from two months to 50 years. Ten of the patients had undergone thymectomy six months to 14 years before this study. In none of the patients was there evidence of any other neurological disorder.

All subjects were investigated in a thermostatically controlled room and limb temperature was maintained at $33°C \pm 1°C$.

For stimulation of the anterior tibial nerve at the ankle a pair of gauze padded, saline soaked silver electrodes were used. The electrodes were 25 mm apart and fixed in position with an elasticated strap. The recording and earth electrodes consisted of silver foil strips 6 cm long and 5 mm wide. These were coated with electrode jelly and held in place with insulating tape. The stigmatic electrode was placed over the motor points of the EDB muscle (McComas *et al.*, 1971b). The indifferent electrode was applied over the base of the small toe and the earth electrode between the stigmatic and the stimulating electrodes.

The instrumentation is represented schematically in Fig. 1. Electrical stimuli consisting of rectangular

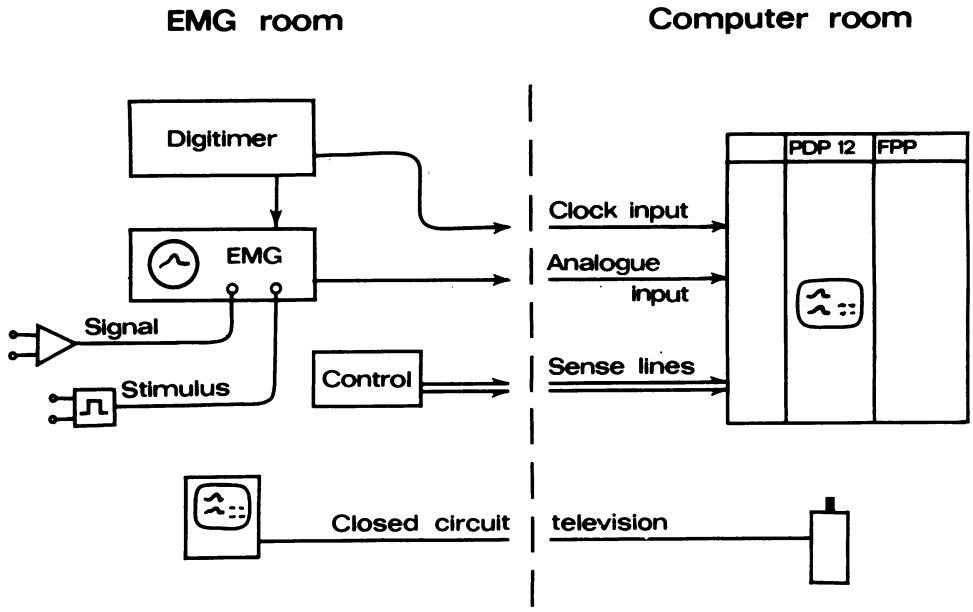

FIG. 1. *Schematic representation of apparatus.*

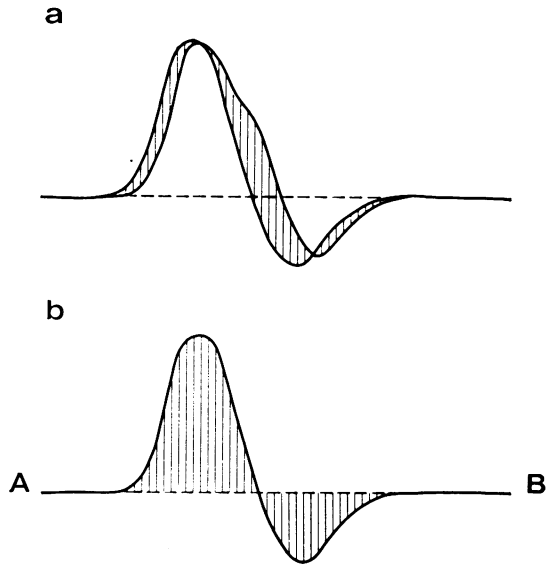

FIG. 2. *Area of difference potential.* a: *used to compare two potentials,* b: *used to obtain the absolute area of a potential.*

voltage pulses of 0·1 ms duration with a repetition rate of one per three seconds are delivered from an isolated stimulator. The stimulus intensity can be finely adjusted by means of a 10-turns potentiometer. The muscle potential is fed through a differential input probe (Hewlett Packard type 21305B), amplified by the electromyograph (Hewlett Packard type 1051A), and displayed on its variable persistence oscilloscope. The lower and upper frequency limits (−3 dB points) are 15 Hz and 1 kHz respectively. An output voltage proportional to the displayed signal is led from the electromyograph (EMG) and fed into the analogue to digital converter of the computer. The oscilloscope sweep and the stimulator are triggered simultaneously by a Digitimer clock generator (Devices, type 3290).

Data processing is handled on-line by a PDP 12 computer with 8K of core memory, a KW 12A real time clock, and a Floating Point Processor (FPP 12). The FPP 12 can multiply and divide some 100 times faster than the PDP 12. The two processors work in parallel; the FPP 12 is used for arithmetical operations while the PDP 12 handles sampling, display, and the control of the FPP 12.

The KW 12A clock is triggered after a delay by the pulse from the Digitimer and the computer

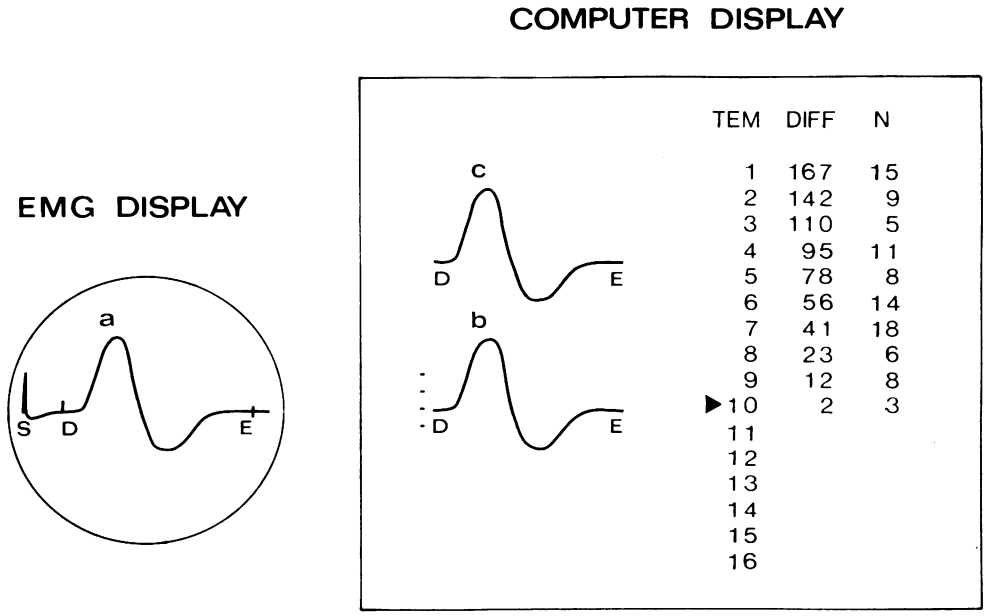

FIG. 3. *A typical display during a motor unit count.* a: *Evoked potential,* b: 'a' *sampled by computer,* c: *stored potential (template 10).* S=*Stimulus artefact, DE=analysis interval, SD=pre-analysis delay, TEM=templates (1–16), DIFF=area of difference potential,* N=*number of potentials averaged to form the template.*

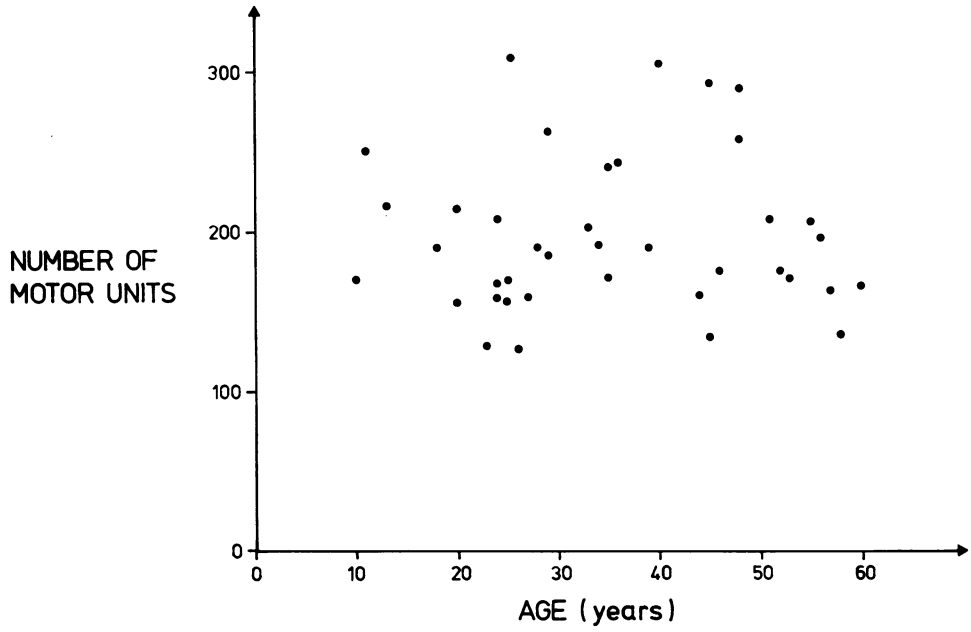

FIG. 4. *Motor unit counts in EDB muscles: normal subjects.*

samples the evoked muscle action potential. The delay can be adjusted relative to the stimulus so that a wide range of peripheral latencies—that is, the time intervals between the application of the stimulus and the onset of the muscle action potential—can be accommodated. The sampling time required is determined by the duration of the longest potential. The sampling time available is 17 ms, which has been of adequate duration in all studies to date. In this time 128 points are sampled. The computer has the capacity to retain 16 potentials in its memory stores. These memory stores are hereafter called 'templates'. The operator can pass instructions to the computer via the control box by changing the logic level of the computer sense lines. The computer output is displayed on its own cathode ray screen and relayed to the EMG room by closed circuit television. The investigation can thus take place in a relatively quiet environment.

COMPUTER ANALYSIS OF RESPONSES

1. RECOGNITION AND IDENTIFICATION OF MOTOR UNIT POTENTIALS When two responses are compared, each is analysed at 128 fixed points. Each point is fixed in time relative to the end of the pre-analysis interval. The voltages at corresponding points are measured in both potentials and the magnitudes of the differences between them are obtained (the difference potentials). The difference potentials at all the points are summated and expressed as 'the area of the difference potential' (Fig. 2a). It is apparent that any change in latency, duration, amplitude, or contour between the responses will produce a change in this area. Only when all five parameters are identical will the potentials be recognized as the same by the computer.

2. CALCULATION OF ABSOLUTE AREAS OF RESPONSES These values are similarly calculated by measurement of the areas of the difference potentials between the motor unit responses and a sweep of zero potential, obtained by shorting the input to the amplifier (Fig. 2b). Occasionally, the stimulus artefact has been large with potentials superimposed upon it. In these circumstances, the absolute area is derived relative to the stimulus artefact instead of to zero potential.

3. RECORDING AND CALCULATION OF NUMBERS OF MOTOR UNITS Successive motor units are recruited singly by the application of finely graded stimuli to the anterior tibial nerve (McComas *et al.*, 1971b). The first motor unit potential is displayed on the oscilloscope of the electromyograph and recognized as such by the operator. He instructs the computer to

store this potential in template 1. The stimulus intensity is gradually increased to recruit further motor units one by one. The potential corresponding to units 1 and 2 is stored in template 2, that corresponding to units 1, 2, and 3 in template 3, and so on, until up to 15 templates are filled.

A typical display from a motor unit count is shown on Fig. 3. The lower trace shows the most recently sampled potential. This sample is compared with all stored templates in terms of the areas of the difference potentials. The values so obtained are displayed in the DIFF column. That template (in this case number 10) having the smallest area of difference potential from the sample is indicated by a marker and is simultaneously displayed on the computer screen (top trace). This trace can be displaced vertically by the operator to facilitate visual comparison of the complexes. On repetitive sampling of the same unit, the area of the difference potential is usually less than 5 units of area. When a given potential has been so analysed the operator can instruct the computer to handle it in one of three ways. He can: (1) define the sample as a new template, or (2) incorporate the sample into the template which is displayed. The number of samples thus averaged to form the template is displayed in the 'N' column. Or he can (3) delete the last template—for example, if the potential contained therein is thought to be spurious. Should none of these options be chosen, the sample will be replaced by a new sample on the receipt of a trigger pulse and the analysis repeated.

When 10 to 15 templates have been filled in this manner, the supramaximally evoked muscle action potential is sampled and stored in the final template. The absolute area of the potential in each template is derived as described above and the value displayed in the DIFF column. The number of motor units is calculated from the formula: nA(max)/A(n), where n is the number of motor unit potentials in the penultimate template, A(max) is the absolute area of the supramaximally evoked muscle action potential and A(n) is the absolute area of the potential composed of n units.

The information contained in each template is stored on magnetic tape for further analysis. The configuration of the potentials of individual motor units can be obtained by serial subtraction of templates.

RESULTS

All values are expressed as the mean ± 1 standard deviation.

NORMAL SUBJECTS (39) The number of motor units estimated in the EDB muscle was 197 ± 49 (Fig. 4). This result was uninfluenced by either sex or age or whether the left or right EDB was studied. The reproducibility of the method in the same subject was evaluated by the mean of 10 estimations on different days and gave a value of 163 ± 19.

PATIENTS WITH MYASTHENIA GRAVIS (20) The

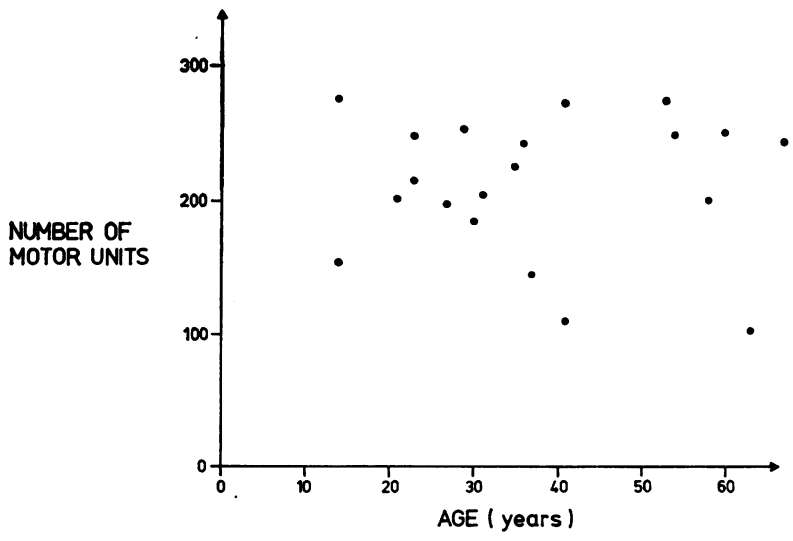

FIG. 5. *Motor unit counts in EDB muscles: patients with myasthenia gravis.*

mean value of the motor unit counts in this group was 212 ± 51 (Fig. 5). By Student's t test, this is not significantly different from the results in the control group. While the numbers in the series are small, there is no evidence to suggest that the duration of the myasthenia gravis, or previous thymectomy has affected the results. Similarly, no significant difference was found between symptomatic and asymptomatic patients.

DISCUSSION

AREA VERSUS AMPLITUDE METHOD Each motor unit potential evoked by stimulation of the motor nerve to the muscle and displayed on an oscilloscope can be defined absolutely in terms of five parameters—latency, duration, amplitude, area, and number of phases. A given motor unit is likely to differ from every other unit in at least one of these variables. In the comparison of any two units all five parameters will influence the area of the difference potential between them (Fig. 2a). Two units, therefore, that have identical durations, amplitudes, absolute areas, and number of phases but different latencies are recognized as distinct. Alteration in any one or more of the other parameters between two units is identified in the same way. Consequently, a given motor unit potential or the recruitment of an additional potential may not be recognized if fewer than these five parameters are evaluated. In these circumstances, the number of motor units contained in the potential from which the total number of units is eventually derived—for example, $B^1D^1C^1$ (Fig. 6)—will be erroneously low. Examination of other criteria that must be established if amplitude is to be taken as a representative measure of (n) motor unit potential reveals a further source of error. These criteria are as follows:

1. All motor units must be of approximately the same duration as the maximal response.
2. All motor units must be of approximately the same latency.
3. There must be temporal coincidence of the potential maxima of individual units.

The method is therefore reliable only if there is

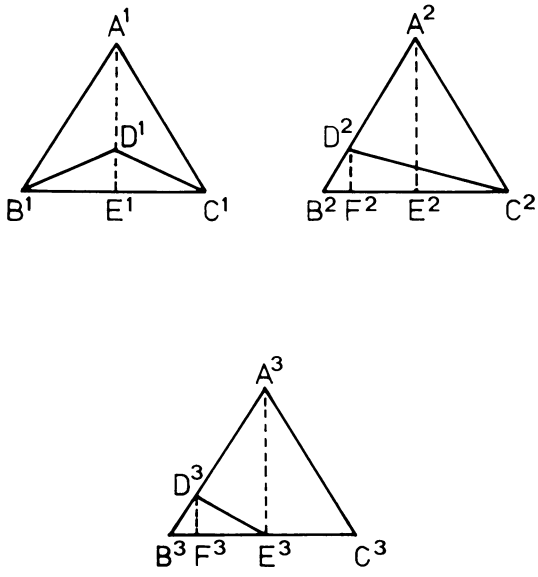

FIG. 6. *Large triangles represent supramaximally evoked muscle action potential. Small triangles represent the potential corresponding to n motor units.*

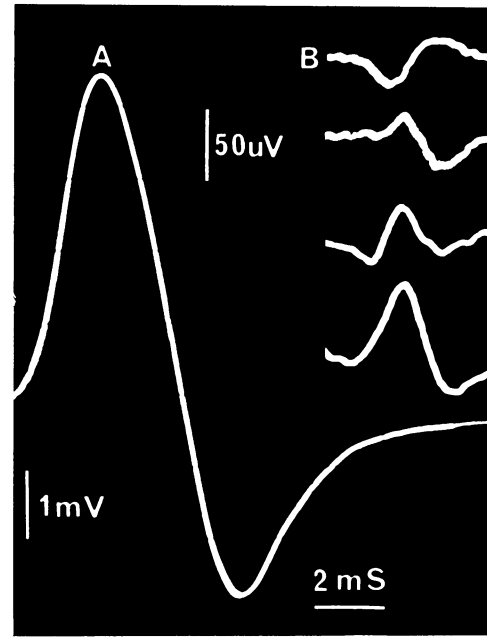

FIG. 7. *Supramaximally evoked muscle action potential* (A) *and potentials of individual motor units* (B) *recorded from the EDB muscle in patient with myasthenia gravis. The pick-up electrodes were not disturbed between the recordings.*

negligible variation in these parameters. Figure 6 illustrates the inaccuracy that arises using the amplitude with particular regard to the first criterion. By both methods the number of motor units in complex $A^1B^1C^1$ is the same and derived from the formula: $n(A^1E^1/D^1E^1)$. Similarly, both methods give the same value in complex $A^2B^2C^2$. However, evaluation of complex $A^3B^3C^3$, where $D^3B^3E^3$ contains units of reduced duration, gives a motor unit count equal to: $n(A^3E^3/D^3F^3)$ by the amplitude method, whereas the correct value is obtained by the area method—that is, $2n(A^3E^3/D^3F^3)$. The amplitude method of McComas has underestimated the number of motor units by 100%. The percentage error will be even greater if, as we have already postulated, the units contained in complex $D^3B^3E^3$ are not all identified. That units of duration considerably shorter than the duration of the maximal response do occur is shown in Fig. 7 from one of our patients with myasthenia gravis.

NORMAL SUBJECTS In our group of normal subjects, motor unit counts in the EDB muscles are similar to those obtained by McComas *et al.* (1971b). We have confirmed all of the major observations made by those authors. There is no significant loss of motor units up to the age of 60 years. We too have found a considerable scatter of values within the population. That this is not entirely due to the error of the method is shown by the close reproducibility of the results from the same muscle at different times. Like McComas, we believe that the figure indicates a true variation in the number of motor units in the EDB muscle in normal subjects.

The histochemical and electrophysiological evidence (Jennikens *et al.*, 1972; Rosselle and Stevens, 1973) that denervation occurs in the EDB muscles of young normal subjects and our results indicating no corresponding loss of motor units with time are not incompatible if interpreted in terms of the following hypothesis. Engel and Warmolts (1973) consider that denervation in muscle may be of either '*in portio*' or '*in toto*' types. *In portio* denervation is present when some of the fine terminal nerve fibres within the peripheral territory of the motor unit lose functional contact with their muscle fibres. We suggest that a degree of *in portio* denervation is part of the normal dynamic process of wear, tear, and repair that occurs in muscle. Motor units are continuously losing and gaining small numbers of muscle fibres within their own and the overlapping territories of other units. This process continues in motor units throughout the life of the patient so that muscle fibre densities and total numbers in individual units may vary somewhat from time to time but the distribution of these parameters within the total population of units in that muscle may be expected to remain statistically unchanged—that is, denervation (wear) and reinnervation (repair) are balanced. The balance may be disturbed by extraneous factors—for example, trauma and disease. Age may also exert some influence. Depending upon its severity, trauma will have a temporary or permanent effect. It has been claimed that pressure from footwear may damage some of the axons in the anterior tibial nerve at the ankle (Gairns *et al.*, 1960; Rosselle and Stevens, 1973). If such damage occurs, histological evidence suggests that it does not lead to degeneration and loss of axons (Arnold and Harriman, 1970). Such damage is likely therefore to be temporary but recurrent. In these circumstances, a number of motor units served by these axons may undergo a more marked *in portio* denervation. A greater number of their muscle fibres will be lost and reinnervated by adjacent overlapping units. The latter will become larger and the former smaller than before. This may explain the increased type grouping of fibres found in the EDB and other muscles in normal subjects (Hennekens *et al.*, 1972). When the damaged motor axons recover from the trauma the normal dynamic process of remodelling of units will have an averaging effect, tending to return the dimensions of the population of units to normal. In these circumstances, and perhaps at particular times, it will be possible to find evidence of denervation without cumulative loss of motor units. The electrophysiological signs of denervation noted by Rosselle and Stevens (1973) may also be explicable on this basis, although their figure of an 87% incidence of denervation in young, normal subjects has surprised us. In our experience of over 1,000 routine EMG examinations involving the EDB muscle we have found such changes infrequently.

PATIENTS WITH MYASTHENIA GRAVIS In our group of myasthenic patients, the number of motor units in the EDB muscle is not significantly different from that in normal subjects. McComas, using the amplitude method, has shown a reduction in motor unit numbers in that condition (McComas *et al.*, 1973a). We consider that this discrepancy arises because of the inability of the amplitude method adequately to recognize and quantify the abnormalities that occur in motor unit action potentials in pathological states—in this case, myasthenia gravis. It is a corollary of this statement and a consequence of our results that we believe that there is a qualitative difference in motor unit potentials in myasthenia gravis. Reduction in the durations of the motor unit potentials in that condition has been reported by Simpson (1969) and Oosterhuis *et al.* (1972). The dimensions of units in myasthenia gravis obtained by template subtraction (see Methods section) will be the subject of a further paper.

We would not conclude from our results that denervation is absent in myasthenia gravis, only that such is not accompanied by loss of motor neurones. Indeed, the qualitative changes occurring in motor units are possibly the result of a pathological *in portio* type of denervation. This could occur in both pre- and post-synaptic disorders (Engel and Warmolts, 1973).

We have found no indication of a reduction in the numbers of motor units with increase in the duration of myasthenia gravis, nor does thymectomy appear to influence the motor unit count. Histological studies (Brownell *et al.*, 1972; Engel and Warmolts, 1973; Oosterhuis and Bethlem, 1973) have shown the presence of denervation in myasthenia gravis. Brownell *et al.* (1972) noted the 'remarkable' terminal nerve fibre branching both in the presence and absence of neurogenic atrophy, suggesting 'a physiological response of healthy neurones to the presence of diseased muscle fibres'. These authors were unable to find any change in the morphology or numbers of motor neurones of the anterior horns or in the axons in intramuscular nerve bundles. Our findings would support the thesis that the primary abnormality in myasthenia gravis lies in the periphery and not in the soma or axon of the motor neurone (Simpson, 1969).

Surviving motor units in neurogenic disease of greater than normal amplitude have been classed as healthy, while units of less than normal amplitude are 'sick' (McComas *et al.*, 1971c, 1973a). Our results and the questionable validity of amplitude measurements in neuromuscular disease indicate that this hypothesis must be reappraised. The usefulness of this concept depends on the accuracy of the method from which it is derived. The underestimation of motor unit numbers by that method must also result in an overestimation of their individual amplitudes. The motor units of increased amplitude described by McComas in myasthenia gravis are probably compounded of two or more units.

In conclusion, we have presented evidence which indicates a serious deficiency in the amplitude method of McComas when applied to the estimation of the number of motor units in the EDB muscle in neuromuscular pathology. The validity of the results and concepts so derived is open to question and requires re-examination.

The theoretical advantages of the computer assisted method for the detection and estimation of motor unit numbers in neuromuscular disease are considerable and are supported in practice by the demonstration of normal numbers of motor units in the EDB muscles in a group of patients with myasthenia gravis.

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