Further motor unit studies in Duchenne muscular dystrophy¹

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SUMMARY Numbers of functioning motor units have been estimated in 124 muscles of boys with Duchenne dystrophy; some of the patients were studied on several occasions. In the distal muscles examined (extensor digitorum brevis, thenar, and hypothenar muscles) the losses of units were probably present at birth and did not decrease with age. In contrast, the numbers of units and of excitable muscle fibres in the soleus muscles declined significantly, especially between the ages of 9 and 12 years.

In 1970 we reported a new type of neurophysiological study on patients with Duchenne muscular dystrophy (McComas *et al.*, 1970); it was shown that reductions in the numbers of functioning motor units in extensor digitorum brevis (EDB) muscles were frequently encountered. In two subsequent investigations involving the same muscle but different modifications of the counting technique these results were not confirmed (Ballantyne and Hansen, 1974; Panayiotopoulos *et al.*, 1974); limited support was obtained in a third study (Brown *et al.*, 1975). It is not the purpose of the present paper to analyse the possible reasons for these discrepancies; the matter has been dealt with elsewhere (McComas 1975, 1977) and will be considered in a further paper. Instead we wish to present the results of our further experience in Duchenne muscular dystrophy, using the same basic methodology as that of McComas *et al.* (1971a). Apart from the increased number of patients studied, the present investigation includes observations on the thenar, hypothenar, and soleus muscles; part of this work has been described previously (McComas *et al.*, 1974). A feature of this study has been the repetition of the motor unit estimates in some patients over a period of four years.

Methods

One hundred and eighty-eight examinations were made on 124 different muscles of 63 males with Duchenne muscular dystrophy. Twenty-seven patients lived in the Hamilton-Toronto area, and in 10 of these the same muscles were examined on more than one occasion. The observations were made during the course of routine neurophysiological assessments requested by referring physicians. Results from studies of 19 EDB muscles in Newcastle, England, and of 17 EDB and 12 soleus muscles in Buenos Aires have also been included. The motor unit estimates were performed by the methods of McComas *et al.* (1971a) and Sica *et al.* (1974); the placement of the recording electrodes for the experiments on soleus were as illustrated by McComas *et al.* (1973) and McComas (1977). For the serial studies, the motor unit estimates were performed without the observer being informed of the previous year's findings.

Results

In Fig. 1 the numbers of excitable motor units in 124 EDB, thenar, hypothenar, and soleus muscles of 63 patients are shown as a function of age. In those patients studied on more than one occasion, only the results from the initial investigations have been included. The results show that the greatest proportional losses of functioning motor units were present in the thenar, EDB, and soleus muscles, the populations of hypothenar units being com-

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Fig. 1 Numbers of functioning motor units in 124 EDB, thenar, hypothenar, and soleus muscles of 63 patients with Duchenne dystrophy. Values are shown against ages of patients at time of initial examinations and have been expressed as percentages of mean values for control muscles (see McComas, 1977). ---- = lower limits for controls.

paratively well preserved (Table). Only among the soleus muscles was there a significant decline in motor unit population with age ($r = -0.45$, $P < 0.001$). It is interesting that loss of EDB units could be demonstrated in the youngest patient studied, aged 14 months.

In view of the considerable differences existing between patients for the same muscle preparation, particular importance is attached to successive observations on the same individuals. Such investigations were performed on four boys aged 8 to 9 years; further examinations were carried out after one and a half, three, and four years. The motor unit results are shown in Fig. 2 together with the corresponding maximum evoked muscle responses; the four values for the same preparation have been averaged for each year and shown with the standard deviation of the mean.

Table Mean numbers ($\pm$ SD) of functioning motor units in patients with Duchenne dystrophy and in male controls of similar ages. Numbers of muscles investigated are shown in parentheses. All differences between patients and controls are significant at the $P < 0.001$ level.

	Soleus	Thenar	Hypothenar	EDB
Controls	1037 $\pm$ 227 (30)	401 $\pm$ 111 (23)	413 $\pm$ 86 (15)	206 $\pm$ 65 (50)
Patients	337 $\pm$ 203 (31)	137 $\pm$ 54 (22)	228 $\pm$ 91 (21)	68 $\pm$ 46 (50)

The results of motor unit counting in these last experiments are consistent with the population survey shown in Fig. 1; thus in the EDB, thenar, and hypothenar muscles no further losses of units took place over the four year period of observation whereas a significant loss of units occurred in the soleus. In this last muscle the M wave amplitude showed an even greater percentage reduction but in each of the intrinsic muscles of the hands and feet no significant changes were observed.

Finally, Fig. 3 shows serial results for three of these muscles; they have been chosen to illustrate the extremes of motor unit behaviour. In the EDB muscle (Fig. 3, top, left) there is a remarkable constancy of motor unit function. In contrast the loss of motor units and of excitable muscle fibres in the soleus is well shown in Fig. 3 (bottom, left). The rapidity of these degenerative changes is striking and was similar to that found in two of the other three soleus muscles studied serially. In two of the 12 intrinsic muscles investigated there were temporary fluctuations in the numbers of motor units; comparisons with control observations (Fig. 3, right) revealed that these changes in the dystrophic muscles were too large to be attributable to inaccuracies in the counting technique itself.

Discussion

The present study confirms earlier findings (McComas *et al.*, 1971b, 1974) in showing that there is frequently

Fig. 2 Mean numbers (+1 SD) of functioning units and amplitudes of maximum evoked muscle responses (M waves) in four muscles of four patients (ages 8 to 9 years) studied over period of four years. The unequal column widths reflect mean intervals between successive examinations. Symbols indicate values significantly different from the initial means (★, $P < 0.01$; *, $P < 0.001$).

Fig. 3 Serial observations on three muscles chosen to illustrate (a) stability of EDB results (top left), (b) temporary improvement in EDB results, particularly in the number of units (top right), and (c) deterioration in soleus potentials and units (bottom left). At bottom right are 10 pairs of observations made twice weekly on a normal EDB to show the degree of methodological error anticipated in this type of study.

a loss of functioning motor units in muscles of patients with Duchenne muscular dystrophy. To answer criticisms of methodology (Ballantyne and Hansen, 1974), we have shown previously that such losses can still be demonstrated if measurements are made of potential area (voltage $\times$ time) rather than of

potential amplitude alone. The new findings are in agreement with the earlier work of McComas *et al.* (1971b) in showing no correlation between the number of functioning motor units in EDB muscles and the age of the patient. A similar lack of correlation has now been shown to apply to the other distal limb

muscles studied, namely those of the thenar and hypothenar muscle groups. These findings suggest that the losses of motor units may already be present at birth. We have no direct evidence that this is so, though losses were already demonstrable in the two youngest patients studied, aged 14 months and 2 years respectively. Similarly, no further losses of EDB units could be shown in a three year old child when studied four years later. Although the number of units in the distal muscles does not show a permanent reduction over the period of observation, significant fluctuations were occasionally observed. This last finding would suggest that previously quiescent motoneurons may sometimes develop excitable neuromuscular connections with muscle fibres. Setting aside these rather unexpected findings, the study of maximum evoked responses suggests that surviving units in the intrinsic muscles suffer only slight losses of muscle fibres with increasing age.

Fig. 4 Summary of motor unit findings in the four muscle types. Motoneurons having no excitable synaptic connections to muscle fibres are indicated by dark cell bodies; stippling indicates motoneurone innervating normal or diminished populations of fibres; third type of motoneurone is normal and may adopt fibres by axonal sprouting (interrupted line).

It is an invariable clinical observation that in Duchenne muscular dystrophy the proximal muscles show a greater reduction in strength than distal ones. Unfortunately, and despite several attempts, it has not been possible to apply the motor unit counting technique successfully to muscles above the knee or elbow. Nevertheless, the soleus, occupying an intermediate position in the axis of the leg, has shown a striking loss of excitable muscle fibres with age. In the four boys aged 8 to 9 years who were

studied serially the mean loss of fibres, estimated from the maximum evoked muscle responses, amounted to 67% of the respective initial values over the three years of study. This pronounced decline in evoked response is unlikely to have reflected muscle fibre atrophy from disuse since it was present in a further boy who was still walking at the age of 12 years. Our observations on these five children indicate that 9 to 12 years is a critical age period for the development of weakness in soleus. Once the marked reduction in function has taken place the muscles appear to enter a new equilibrium. In Fig. 4 an attempt has been made to summarise the experimental findings in the different muscles in terms of three types of motoneurone-muscle fibre relationship. In one type there are no excitable connections between motor axons and muscle fibres; this situation is responsible for the loss of functioning motor units observed with the counting technique. In the second type the motoneurone innervates a normal or diminished muscle fibre population. The third relationship possible involves a small but variable proportion of motor units and consists of an enlargement of the muscle fibre populations, presumably through collateral reinnervation. The Figure also demonstrates the change in the soleus motor units with advancing age. The implications of these findings for pathogenetic hypotheses of muscular dystrophy will be discussed in a subsequent paper.

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