The Neural Hypothesis of Muscular Dystrophy

A review of recent experimental evidence with particular reference to the Duchenne form

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SUMMARY: *Recent observations are considered to provide further evidence for an abnormality involving motoneurones in DMD. The dystrophic process appears to take place in two stages of which the first occurs during early embryonic life. This stage is thought to involve faulty inductive actions of the neural tube upon mesoderm and upon itself. The neural consequences vary among individuals and are manifested as mental retardation, EEG abnormalities and losses of functioning motor units. While the first two abnormalities are non-progressive, a further loss of motor units, associated with striking reductions in the numbers of excitable muscle fibers, takes place in trunk and large limb muscles at 9-12 years. The latter process, the cause of which is uncertain, constitutes the second stage of DMD.*

RÉSUMÉ: *Des observations récentes semblent fournir de nouveaux arguments en faveur d'une anomalie des motoneurones dans la dystrophie musculaire — forme Duchenne (DMD). Le processus dystrophique semble se produire en deux étapes dont la première se déroule lors du début de la vie embryonnaire. Nous croyons que cette étape implique une action inductive fautive du tube neural sur le mésoderme et sur lui méme. Les conséquences neurologiques varient selon les individus et peuvent se manifester par un retard mental, des anomalies à l'EEG ou la perte d'unités motrices fonctionnelles. Alors que les deux premières anomalies sont non-progressives, une nouvelle perte d'unités motrices, associée à des réductions importantes dans le nombre de fibres musculaires excitables, se produit de 9 à 12 ans dans les muscles du tronc et les gros muscles des membres. Ce dernier processus, dont la cause est incertaine, serait la deuxième étape du DMD.*

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INTRODUCTION

The aim of this paper is to review the neural hypothesis of muscular dystrophy (McComas, Sica and Campbell, 1971) in the light of recent evidence from this and other laboratories. This hypothesis proposed that the muscle changes in each of the four main types of dystrophy (Duchenne, myotonic, limb-girdle and facioscapulohumeral) were secondary to abnormal trophic influences exerted by motoneurones. Although several types of evidence for a neural mechanism in dystrophy were considered (McComas, Sica and Currie, 1970; McComas, 1975, 1977), the observations considered to carry most weight were those involving estimates of numbers of functioning motor units in dystrophic extensor digitorum brevis muscles. These observations were made possible by the application of a new electrophysiological method for estimating motor units, the principle of which was to compare the amplitudes of the potentials evoked by single motor units with that of the whole muscle (McComas, Fawcett, Campbell and Sica, 1971). In each type of dystrophy most patients were found to have losses of functioning motor units (McComas, Campbell and Sica, 1971; McComas, Sica and Currie, 1971; Sica and McComas, 1971).

One of the main reasons for a review of the neural hypothesis has been reports of conflicting experimental data. Perhaps the most important of these was the finding of normal numbers of units in Duchenne muscular dystrophy (DMD) and limb-girdle dystrophy by two groups of workers using modifi-

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cations of the original counting technique (Ballantyne and Hansen, 1974; Panayiotopoulos, Papapetropoulos and Scarpalezos, 1974). Also to be explained were the findings of normal ultra-structure of nerve endings on dystrophic muscle fibers in DMD (Jerusalem, Engel and Gomez, 1974), normal numbers of axons in myotonic dystrophy (Pollock and Dyck, 1976) and the absence of a spread of acetylcholine receptors in myotonic dystrophy (Drachman and Fambrough, 1976). Direct evidence against a neurotrophic abnormality in some forms of mammalian dystrophy came from animal experiments employing parabiosis with cross-innervation. Neither in the mouse (Douglas and Cosmos, 1975; Montgomery. 1975; Law et al, 1976) nor in the hamster (Johnson and Montgomery, 1976) were normal or dystrophic muscles altered as a result of their new innervation. At the same time that the neural hypothesis was losing ground, an impressive body of evidence was emerging which pointed to the existence of a primary membrane defect in dystrophic muscle fibers (see Rowland, 1976, for review).

In spite of the negative findings cited above, the argument in favor of a neuropathic component in dystrophy deserves consideration on the basis of more recent experience with the motor unit counting technique. In this paper only the new results for DMD will be presented, largely since it is this form which has attracted most attention in recent debates on the pathogenesis of dystrophy. By including observations of motor unit function in the soleus, the study overcomes the criticism that the earlier investigation (McComas et al, 1970, 1971d) was confined to a comparatively small and unimportant distal muscle, the extensor digitorum brevis (EDB).

The soleus, together with the gastrocnemii, is of particular interest not only because of the severe weakness which it incurs in later stages of DMD, but also because it exhibits two other characteristic features of that disorder, namely the early muscular pseudohypertrophy and the later shortening contractures. It will be shown that the EDB and soleus muscles, although showing similar electrophysiological abnormalities in early DMD, follow quite distinct courses in their later development. The contribution of these observations to a reassessment of the neural hypothesis will be considered subsequently.

METHODS

Subjects

Observations were made on 45 soleus muscles in 41 males aged 3 to 23 years. The findings in these muscles were compared with those in 50 EDB muscles (45 patients); of the latter population 19 muscles were those investigated in Newcastle in 1970 and the others in either Hamilton or in Buenos Aires using identical techniques (see below and McComas, 1977). Control observations were made on 54 EDB and 34 soleus muscles from 53 and 32 subjects, respectively. The controls were males aged 5 months to 23 years; in all cases they (or their parents) had given informed consent. The examinations of patients had been performed at the request of referring physicians.

Stimulating and recording systems

Recordings were made with thin strips of silver foil, 6 mm wide, attached to the skin overlying the muscles. For EDB the stigmatic electrode was placed over the end-plate zone (see McComas et al, 1971b) and the reference electrode was fastened over the inferomedial aspect of the foot at a similar distance from the heel (see Fig. 6.2 in McComas, 1977). To record an evoked response which was predominantly that of soleus, the stigmatic electrode was placed transversely at the junction of the upper and middle thirds of a line joining the lower margins of the gastrocnemii to the heel; the reference electrode was attached to the heel. The lengths of the silver strips varied according to the size of the subject, ranging from2 cm for infants to 5 cm for adults. The evoked activity was amplified and displayed on a variable persistence storage oscilloscope (Hewlett-Packard type 141B) from which measurements of peak-to-peak amplitude were made. With a 3 db cut at 1kHz, the signal-to-noise ratio enabled potentials larger than 3 uV to be detected by superimposition (see McComas, 1977; Fig. A6.1). Two silver disc electrodes, mounted in a Plexiglass holder, were used to stimulate the peroneal nerve at the ankle and the tibial nerve in the popliteal fossa.

		NUMBER OF UNITS			M-WAVE (mV)		
		Mean ± S.D.	Range	Coeff.	Mean ± S.D.	Range	Coeff.
H.F.	Soleus	949 ± 90	826 - 1138	9.5	18.7 ± 0.8	17.8 - 20.0	4.2
	EDB	287 ± 36	240 - 356	12.5	8.3 ± 0.7	7.5 - 9.4	8.9
J.M.	Soleus	1061 ± 75	900 - 1157	7.1	21.7 ± 1.32	19.0 - 23.0	6.1
	EDB	166 ± 17	144 - 191	10.2	4.2 ± 0.3	3.9 - 4.8	6.2

TABLE 1

Accuracy in measurement of M-wave amplitudes and in estimation of motor unit numbers in the EDB and soleus muscles of 2 female controls aged 25 and 26 years. Measurements were made on 10 occasions over a period of 5 weeks. Coeff. = coefficient of variation.

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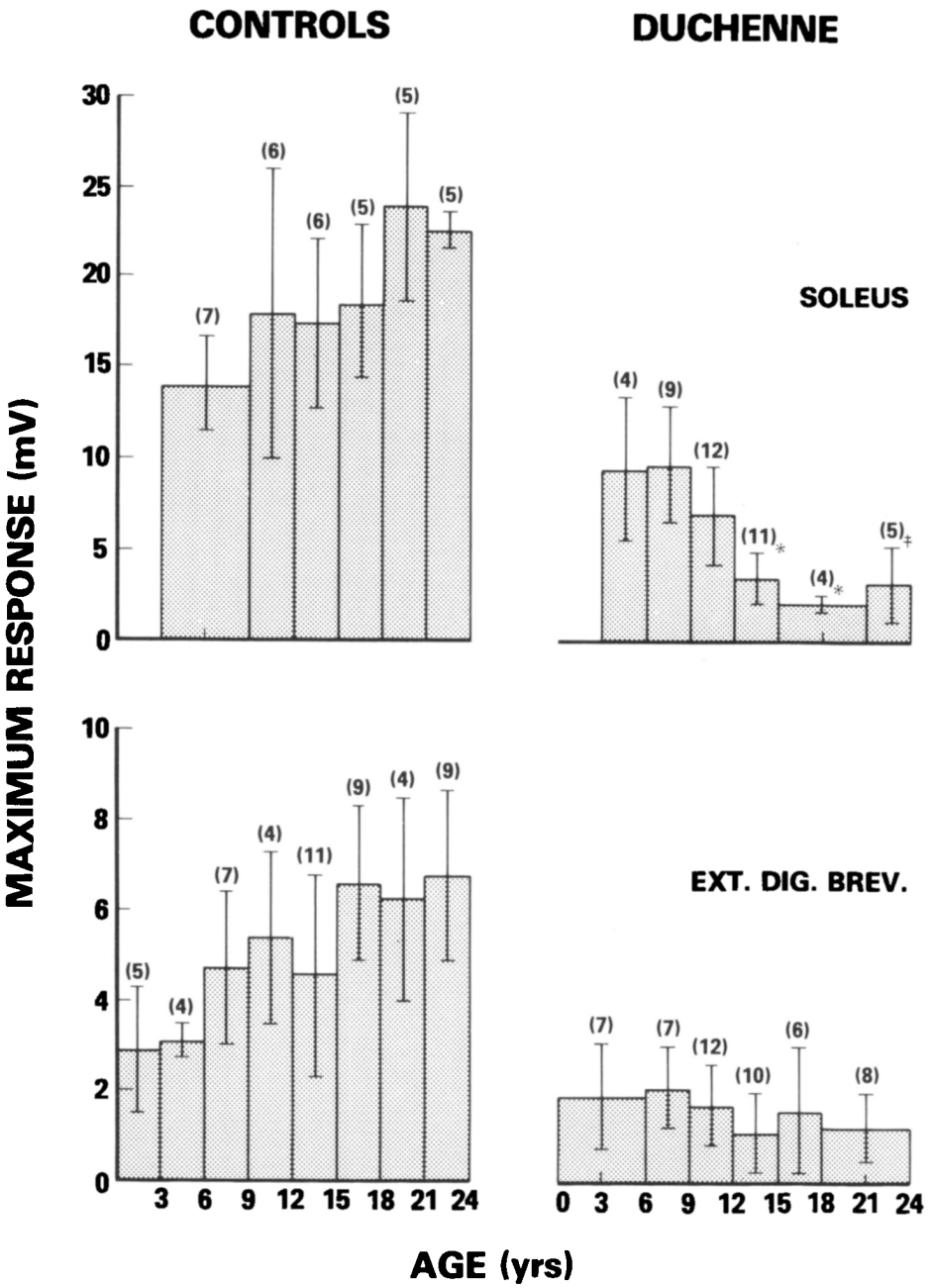

Figure 1—Maximum evoked responses (M-waves) of normal and dystrophic soleus and EDB muscles. Values given as means±S.D. for successive epochs of 3 years (or 6 years, if insufficient observations); numbers of observations given in parentheses. Mean values significantly different from those of earliest epochs are indicated (* , P = .01 or less; ‡ , P = .02).

RESULTS

Maximum evoked muscle responses (M-waves)

The responses evoked by a muscle following maximal stimulation of its motor nerve fibers may be recorded with satisfactory reproducibility, provided sufficiently large surface electrodes are employed to average the extracellular potentials generated by the underlying muscle fibers (see Methods). Table 1 shows the coefficients of variation determined in two normal subjects tested twice weekly on 10 occasions. Fig. 1 shows the maximum M-waves of EDB and soleus muscles as mean values (± 1 S.D.) for successive three-year epochs. Control observations made on healthy males over a similar range of ages are shown for comparison.

For both the EDB and the soleus it can be seen that the M-wave amplitudes of the youngest children examined were respectively 65 and 66 percent of those of their age matched controls. As would be expected, the control values increase with advancing age, the EDB maximum being reached at about 15 (cf McComas, Petito and Sica, 1973). The two types of dystrophic muscle behaved differently, both from their respective controls and from each other. Whereas the mean EDB response showed a slight but insignificant reduction in amplitude, the mean soleus response declined to 38 percent of the initial value. Fig. 1 shows that most of this reduction took place in the 9-11 year epoch, no significant change occurring thereafter.

Motor unit numbers

The estimates of functioning motor units in EDB and soleus muscles are given in Fig. 2. As anticipated, the control values show no correlation with age over the range studied (McComas et al, 1971b). In both types of dystrophic muscle, however, significant losses were already present in the muscles of the youngest patients examined, amounting to 57 and 40 percent respectively in the EDB and soleus. The loss in the solei became more obvious with advancing age, particularly before 12, but the motor unit population appeared stable during later adolescence.

Motor unit potential amplitudes

Some indication of the mean sizes of the motor unit potentials in dystrophy can be gained from a comparison of the M-wave amplitudes and numbers of motor units for subjects within a particular age group (i.e. Figs. 1 and 2 respectively). A more detailed analysis of this relationship is presented in Fig. 3, in which the mean motor unit potential sizes for single muscles have been plotted against the corresponding maximum evoked responses. Neither for EDB or for soleus are there significant correlations; nevertheless, it is relevant for a dis-

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cussion of neuropathic mechanisms in DMD (see below) that 6 of the 7 soleus muscles having the largest mean motor unit potentials were dystrophic.

DISCUSSION

The present results have shown marked differences in behavior between a small distal muscle, the EDB, and a larger and more proximal limb muscle, the soleus, in DMD. While both muscles exhibit losses of functioning motor units at birth, only in the soleus does this increase significantly during later life. The changes in the M-wave are more striking, for while there was a slight decrease in EDB, the soleus response declines to approximately one third of its initial amplitude. In this population study there is a suggestion that the rate of change in soleus is greatest at about 9-12 years. This suggestion has been strengthened by serial observations on four boys, initially aged 8-9 years, whose progress was followed over a further period of 4 years (McComas, Sica and Brandstater, 1977). In three of these subjects it was possible to demonstrate a relatively sudden decrease in soleus function; for example in one patient the M-wave amplitude dropped to 28 percent of its starting value in the space of 18 months. Clinical experience also supports the concept of a decline in DMD at about 9-12, for it is usually at this time that the child becomes unable to walk and therefore dependent on a wheelchair. The parents of a child of this age will often comment that during the preceding year there had been a marked deterioration in strength. Although no direct evidence is available, it is likely that the neurophysiological changes reported in soleus are mirrored in other large muscles, such as those of the trunk and of the hip and shoulder girdles.

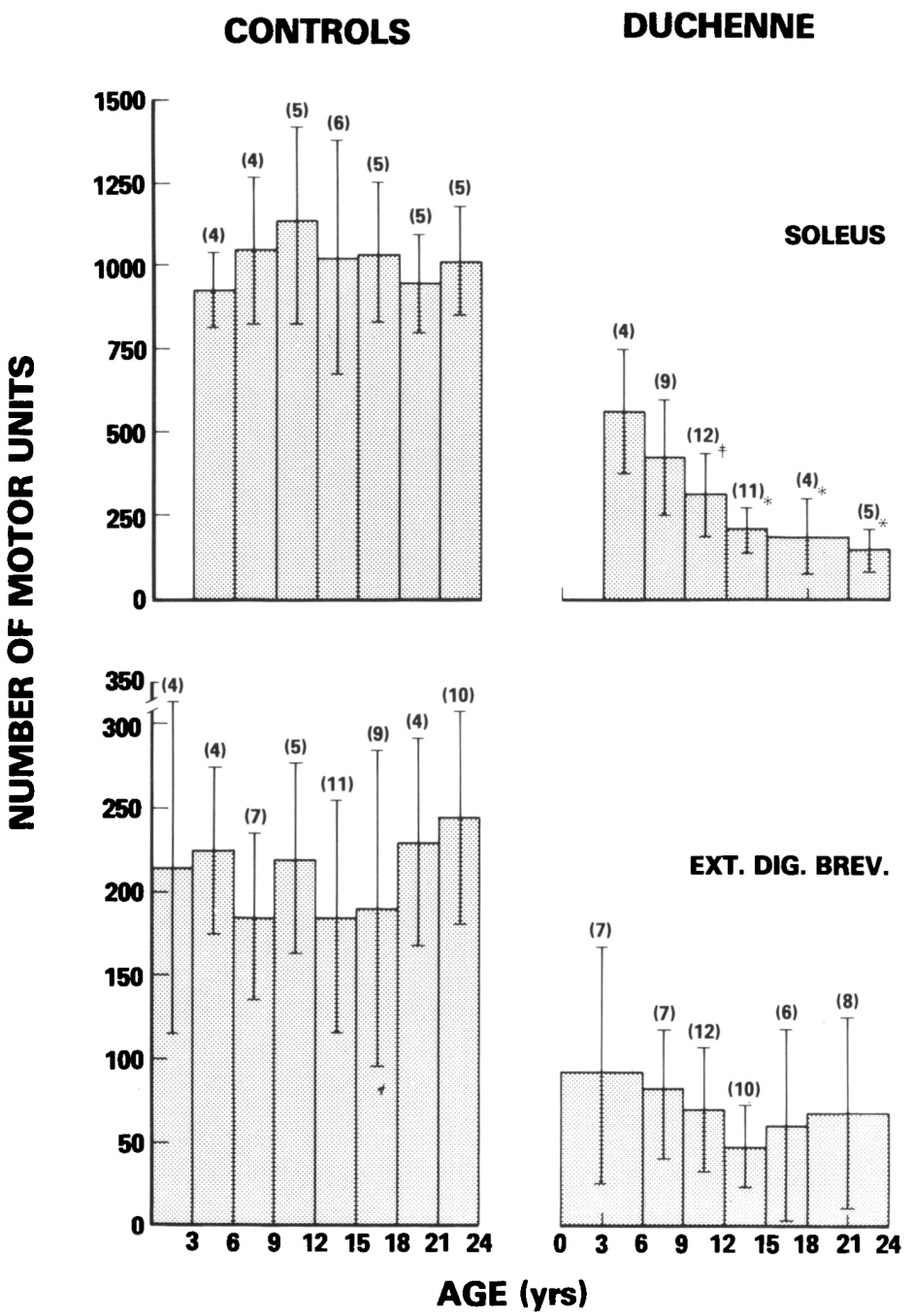

Figure 2—Numbers of functioning motor units of normal and dystrophic soleus and EDB muscles. Presentation and notation as for Fig. 1.

At present it is only possible to speculate on the mechanism responsible for this deterioration. It seems unlikely that the type of metabolism utilized by the fiber is responsible since there is no clear cut difference in fiber type composition between the large and small human muscles, excluding those of the face (Johnson et al, 1973). While it is possible that the greater lengths of the fibers in the larger muscles may be a factor, an alternative explanation is that the greater sizes of the motor units are in some way responsible. Thus it could be argued that the motoneurones innervating the largest colonies of muscle fibers would be those most rapidly 'exhausted' through the continued synthesis and delivery of neurotrophic material. Such an explanation would also account for the further losses of functioning motor units found to take place in the soleus, particularly during the critical age period of 9-12.

What is the explanation for the losses of motor units found in the

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EDB and soleus muscles of the youngest patients? Since the EDB values do not show any further decline over the range of ages studied (15 months to 23 years), it was probable that the motor unit loss was already present at birth. In myotonic dystrophy we now have definite evidence that this can occur. In a floppy infant, born prematurely to a female patient with this disorder, moderately severe losses of functioning motor units were already present in the thenar and EDB muscles at the equivalent of 34 weeks gestation (McComas, unpublished observations).

It is relevant that in two strains of dystrophic mice, Montgomery and Swenarchuk (1977), by examining low-power electron micrographs of ventral roots, has been able to demonstrate reductions in the numbers of motor axons at birth. Montgomery also found that the loss of axons preceded a decline in the numbers of muscle fibers. A corollary to this observation is that the surviving motor units must have been rather larger than normal at birth. A similar situation may pertain in DMD since in the EDB muscles the losses of functioning motor units were larger than the reductions in excitable muscle fibers, as reflected in the maximum responses (57 and 35 percent mean losses respectively). In the soleus muscles also, the potentials of the surviving motor units in some of the younger boys were rather larger than normal (cf Fig. 3).

There are certain other observations which, although open to more than one interpretation, are at least compatible with the concept of motoneurone dysfunction in DMD. With the technique of single fiber electromyography, Stalberg (1977) and Schwartz, Moosa and Dubowitz (1977) have demonstrated increased muscle fiber densities within individual motor unit territories; this type of abnormality is presumably responsible for the enlarged motor unit potentials noted in some of the DMD solei in the present study. Prolonged terminal motor latencies (McComas et al, 1971d; Ballantyne and Hansen, 1975), fibrillation po-

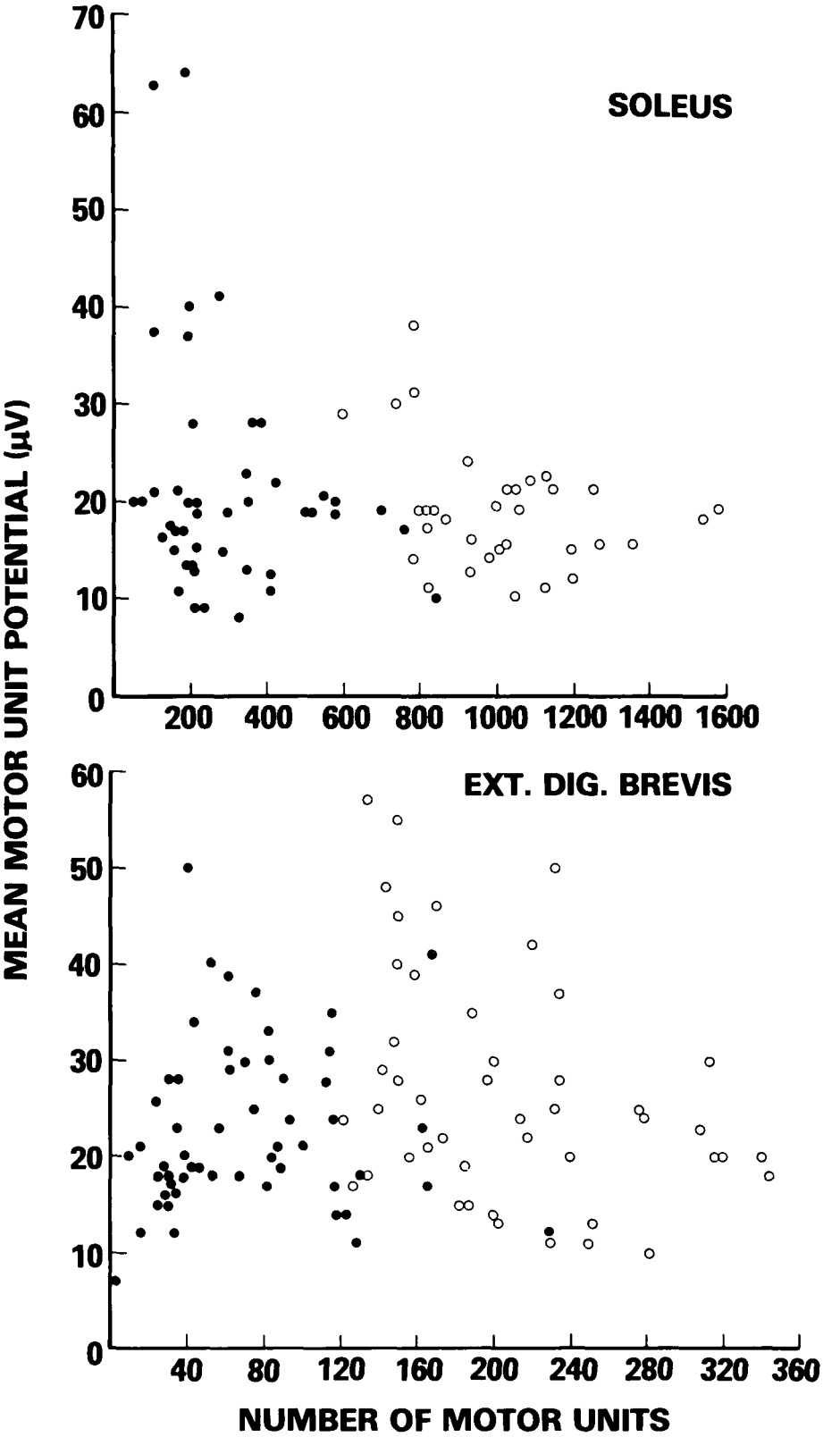

Figure 3—Mean motor unit potential amplitudes as functions of numbers of motor units in normal (o) and dystrophic (•) EDB and soleus muscles. Mean amplitudes were 26.9 ± 11.9 μV and 22.6 ± 8.4 μV for normal and dystrophic EDB muscles respectively and were 18.7 ± 5.4 μV and 21.4 ± 12.0 μV for normal and dystrophic solei. The differences between corresponding normal and dystrophic populations of units were not significant.

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tentials (Buchthal and Rosenfalck, 1966) and increased durations of motor unit potentials (Desmedt and Borenstein, 1973) have also been found. Morphologically, clusters of muscle fibers belonging to the same histochemical fiber type have been demonstrated by Engel (1977) and grouped atrophy has been noted by Dastur and Razzak (1973). All six types of observation would normally be explained in terms of collateral reinnervation associated with a neuropathic process. It is also of interest that the pattern of involvement of the distal musculature in DMD is the same as that in the axonal neuropathies associated with ageing, diabetes, renal failure and vincristine toxicity; thus the EDB and thenar muscles have significantly greater losses of functioning units than the hypothenar group (McComas, Sica and Brandstater, 1977).

The inability of Ballantyne and Hansen (1974) and of Panayiotopoulos, Papapetropoulos and Scarpalezos (1974) to detect losses of functioning motor units in DMD has been analysed elsewhere (McComas, 1975, 1977) and will form the subject of a further communication. It should be noted that Brown, Milner-Brown and Drake (1975) were able to demonstrate apparent losses in 2 of 5 patients with DMD.

What is the condition of those motoneurones, without excitable connections in the periphery, which are responsible for the finding of reduced numbers of motor units in dystrophy? Three observations suggest that many of these cells are still present in the spinal cord. First, no loss of anterior horn cells can be demonstrated post-mortem in cases of DMD (Tomlinson, Walton and Irving, 1974). Second, normal numbers of axons are to be found in the peroneal nerves of patients with myotonic dystrophy (Pollock and Dyck, 1976) even though 80 percent of patients with this disorder have electrophysiological evidence of losses of functioning units (Polgar et al, 1972). Finally, in two of sixteen DMD muscles studied serially over four years, the numbers of functioning motor units showed significant temporary fluctuations. Similar variations have been observed in patients with renal failure (McComas, Upton and Jorgensen, 1975) and suggest that motoneurones may acquire or relinquish excitable synaptic connections with muscle fibers, presumably in the absence of significant axonal pathology. It is also relevant that in rats with irradiation neuropathy it has recently been shown that neuromuscular junctions may enter a phase of inexcitability, probably lasting some weeks, before loss of the axon terminals takes place (Fewings, Harris, Johnson and Bradley, 1977).

The concept of synapses which, although inexcitable, might still transmit some chemically-mediated trophic influence to muscle fibers could be crucial to an understanding of dystrophy. Not only could the concept be compatible with normal ultrastructure of the axons terminals (Jerusalem et al, 1974), but it might explain the paucity of signs of denervation in muscle fibers. For example, Drachman and Fambrough (1976) found no spread of acetylcholine receptors in myotonic dystrophy while Ringel, Bender and Engel (1976) noted a small incidence of affected fibers in DMD; as the latter authors point out, the variable duration of the postulated denervation introduces a further difficulty in interpreting this type of finding.

The losses in functioning motor units in distal muscles resemble two other central nervous system changes described in DMD, mental retardation and EEG abnormalities, in their variability from patient to patient. There is a further resemblance to mental retardation in the lack of progression with age (Zellweger and Hanson, 1967). If the pathogenesis of dystrophy in the chicken is similar to that in DMD, the embryonic events responsible for the development of dystrophy occur early, at the time when inductive phenomena are taking place (see below). The term induction, as employed by embryologists, denotes the ability of one tissue to initiate the further differentiation of another during development. One of the earliest descriptions of this phenomenon was that of Spemann (1903); he showed that the formation of the lens of the eye by ectoderm depended on the influence of the optic vesicle growing out from the forebrain.

In relation to nerve and muscle, it is known that the differentiation of ectoderm into neural tissue is dependent on receipt of an inductive signal from underlying mesoderm (Spemann and Mangold, 1924). Continued development of the nervous system then involves inductive activity between its component tissues. Theoretically, it would be possible for the CNS changes in DMD, including those involving motoneurones, to have arisen because of a faulty inductive signal from abnormal mesoderm. The mesoderm itself, because of its inherent abnormality, would then develop into dystrophic muscle. The experiments of Rathbone's group in the dystrophic chicken, however, suggest that the true situation is the reverse. These workers have been able to produce two of the biochemical features of dystrophy in breast musculature of control chickens by substituting neural tube segments from dystrophic embryos (Rathbone, Dimond and Vetrano, 1975; Rathbone, Stewart and Vickers, 1976). The experiments must be performed at 48-52 hours; manipulation of nerve- or muscle-forming tissue any later is ineffective, as judged by the negative results of limb-bud transplantation (Linkhart, Yee and Wilson, 1975).

As embryonic development proceeds in the normal fetus, the power of inductive processes declines, but even in the adult animal or man it is still possible for one type of tissue to exert an important controlling action on the metabolism of another. This influence may be hormonal or, in the case of nerve and muscle, may depend on the transfer of messenger molecules at synaptic sites or on the presence of impulse-mediated activity in the target tissue. These latter effects are termed neurotrophic; like induction, they are achieved by the regulation of gene activity in the nuclei of the recipient tissue (Grampp, Harris and Thesleff,

1972). It is perhaps valid to picture induction and neurotrophic activity as representing two levels of intensity along a continuum of cell interdependence.

As stated above, experimental manipulation of nerve or muscle tissue after the critical inductive period has little effect on the course of dystrophy. Nevertheless, some changes do take place; for example, Law et al, (1976) found in their parabiotic cross-innervation experiments that the muscle fibers surviving in dystrophic muscles, although much fewer than in normal muscles, exhibited improvements in histochemical staining reactions and in their resting membrane potentials. Similarly, against the negative muscle transplant studies of Cosmos (1973) in the mouse must be set the contrasting results by Hironaka and Miyata (1975) in the same species. These conflicting results may well depend on the plasticity of the myonuclei. If the myonuclei can be made to 'dedifferentiate', perhaps by crushing or otherwise injuring the muscle, the nuclei formed by mitosis may, for a certain period of time, become more susceptible to external manipulation of their genetic information. The most extreme example of this type of phenomenon has been provided by the remarkable experiments of Gurdon (1968). By transplanting into an unfertilized frog ovum the nucleus of a fully differentiated cell from the intestinal mucosa of a mature frog, he demonstrated that the latter could be made to switch on all the genetic machinery necessary for the development of a complete animal.

The muscle fibers are not the only mesodermal tissue to develop abnormally in DMD for the fatty connective tissue undergoes immense hyperplasia in some of the limb muscles, particularly those of the calves. A chance observation suggests that this hyperplasia may also be neurally dependent, for it has been observed by ourselves in the calf muscles of a patient who had inadvertently received an analgaesic injection into the ipsilateral sciatic nerve (McComas, 1977; see also Lapresle, Fardeau and Said, 1973).

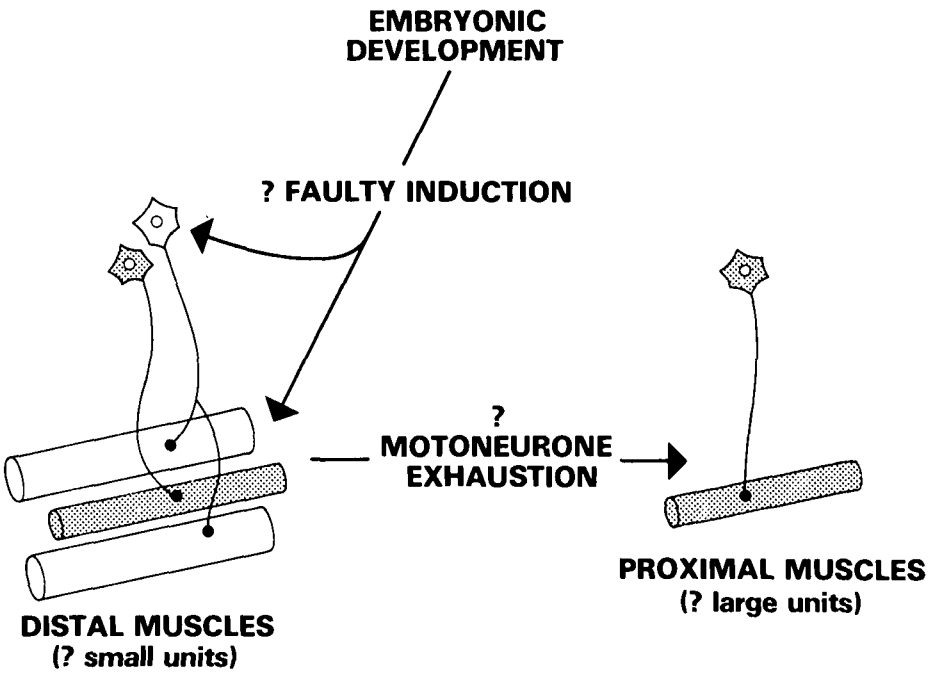

Figure 4—Pathogenesis of neuromuscular abnormalities in DMD. Due to the faulty inductive action of ectoderm on mesodern there is a loss of functioning motor units in most muscles at birth. In large muscles, such as the soleus, additional deterioration occurs at 9-12 years. The thenar and hypothenar muscles behave similarly to EDB (McComas et al, 1967). See text.

In an inductive hypothesis of DMD, how can the abnormalities reported in red cell membranes, such as altered protein kinase activity (Roses, Herbstreith and Appel, 1975), be accounted for? One possibility is that these changes, together with the dystrophic cardiomyopathy, are also consequences of faulty inductive processes in embryonic mesoderm. An alternative explanation is that an abnormality in the membranes of all fetal cells interferes with the formation of the cell contacts necessary for the inductive process to take place (cf Lehtonen, 1976).

The membrane deficiencies reported in dystrophic muscle fibers (Mokri and Engel, 1975) might also be part of a generalized cell abnormality. If however, they are a necessary initiating step for the destruction of a muscle fiber in dystrophy, it is more likely that they are expressions of faulty embryonic induction. In passing, it should be noted that there is no fundamental conflict between the neural inductive hypothesis, as presently conceived, and the membrane, vascular or other hypotheses of the dystrophies. Should the neural inductive hypothesis prove correct it will still be necessary to determine the sequence of molecular events in a dystrophic muscle fiber which eventually results in its breakdown. Fig. 4 summarizes the present concept of the pathogenesis of the neuromuscular abnormalities observed in DMD (See also Fig. 28.5 in McComas, 1977).

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