Functional changes in motoneurones of hemiparetic patients

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SUMMARY Forty-six patients have been studied after upper motor neurone lesions of cerebro-vascular origin. The numbers of functioning motor units in extensor digitorum brevis muscles were reduced to approximately half between the second and sixth months after a hemiplegic episode. The surviving motor units tended to have slow twitches and appeared to increase their sizes after the lesions had been present for about 20 months. The findings are explained on the basis of trans-synaptic changes in alpha-motoneurones after degeneration of corticospinal fibres.

The observation that muscle wasting occurs in the affected limbs of hemiplegic patients is an old one (Hall, 1836) and the nature of the underlying process has since aroused much speculation. The various mechanisms possible, and their relationships to each other, are shown diagrammatically in Fig. 1 and have recently been reviewed by Fenichel, Daroff, and Glaser (1964) and by Namba, Schuman, and Grob (1971). One hypothesis is that wasting results from disuse alone, while another holds that the wasting is a consequence of an alteration in blood supply to hemiplegic limbs. A third suggestion is that the muscle atrophy is secondary to arthropathy in the affected limb. Damage to the parietal lobe has also been incriminated, since there is some evidence for the presence, within the postcentral gyrus, of a 'trophic' centre for muscle. In a patient who has been immobilized in bed or in a chair, the development of pressure neuropathies
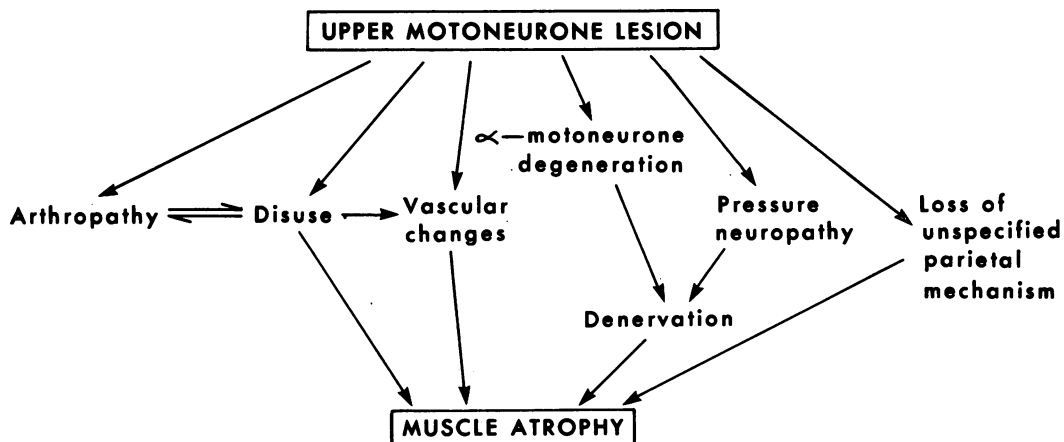

FIG. 1. *Mechanisms which have been proposed to account for muscle wasting after upper motor neurone lesions (see text).*

must be considered as an additional cause of wasting.

The final hypothesis is that trans-synaptic changes take place in motoneurones after degeneration of corticospinal fibres. In the present paper we have set out to explore this last possibility using a recently described electrophysiological technique which enables numbers of functioning motor units to be estimated (McComas, Fawcett, Campbell, and Sica, 1971c). The results of this study have shown in a convincing manner that after a hemiplegic episode. a substantial proportion of motoneurones innervating the paralysed limbs cease to function. The onset and time course of this process, its magnitude. and the consequences for surviving motoneurones are considered. A preliminary account of this work has already appeared (McComas. Sica. Upton, Aguilera, and Currie. 1971d).

METHODS

SUBJECTS The study involved 46 patients who had been rendered hemiplegic or hemiparetic after a cerebrovascular lesion. In the younger patients the commonest lesion was rupture of a cerebral aneurysm. In older patients thrombotic or haemorrhagic complications of atherosclerosis had been diagnosed on the basis of the clinical and laboratory findings. In all of the patients the weakness had been sufficient to prevent walking for one or more days. With the exception of a man who had been hemiplegic for three days only, the patients had recovered sufficiently to be able to walk and many were back to work. In view of the recovery of movement in the affected limbs, the term hemiparesis has been preferred to hemiplegia in the text as a description of the patient's disability at the time of investigation.

In those patients in whom the cerebrovascular episode had occurred more than a month previously there were, in addition to extensor plantar responses, increased muscle tone and exaggerated tendon reflexes; muscle wasting was usually evident. In 38 of these patients, it was possible to compare the results on the affected and normal sides. In a further eight patients, also with cerebrovascular disease, it was not possible to study an unaffected limb. In two there had been a fracture in the opposite limb, while in the remaining six there was evidence of bilateral upper motor neurone lesions. Coincidental causes of muscle wasting were eliminated from the study by rejecting patients who were over the age of 60 years

(Campbell and McComas, 1970) or who had worn calipers or taken anticonvulsant drugs.

ELECTROPHYSIOLOGICAL TECHNIQUES The numbers of functioning motor units in extensor digitorum brevis (EDB) muscles were estimated by the method of McComas *et al.* (1971c). In some patients isometric twitches of the extensor hallucis brevis muscle (most medial subdivision of EDB) were recorded using the technique of Sica and McComas (1971). Measurements of conduction velocity and terminal latency were made in the manner described by McComas, Campbell, and Sica (1971).

STATISTICAL TREATMENT Mean values are shown with their standard errors. The significance of the difference between two means was estimated by Student's t test, while recognizing that in some instances the data did not fall into normal distributions.
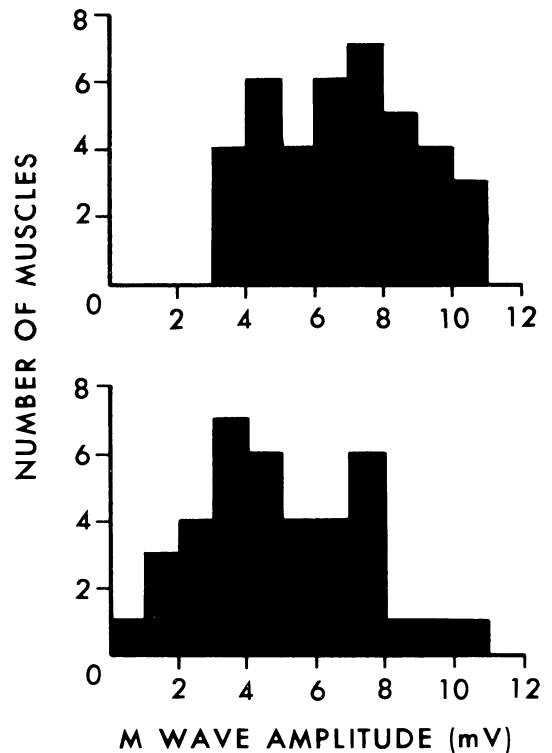

FIG. 2. *Maximum M wave amplitudes of EDB muscles in 38 hemiparetic patients. Upper histogram, normal limbs (mean = 6·5 ± 0·3 mV); lower histogram, affected limbs (mean = 4·9 ± 0·4 mV, P < 0·005).*

RESULTS

MUSCLE ATROPHY Muscle atrophy may be assessed by a simple electrophysiological method which compares the maximum responses evoked in corresponding muscles in affected and normal limbs. The amplitudes of these responses will be proportional to the total cross-sectional areas of the active muscle fibres in each muscle, provided that the stigmatic recording electrode averages all the muscle fibre action potentials. In the present study this requirement was met by the use of a silver strap fixed to the skin across the full width of the EDB muscle belly (see McComas

et al., 1971c). The sizes of the responses ('M waves') evoked in EDB muscles after maximal stimulation of deep peroneal nerves in 38 patients are shown in Fig. 2. In this Figure the amplitudes of the M waves developed by the muscles on the normal and hemiparetic sides have been compared (upper and lower histograms respectively). It can be seen that the pooled results for the affected sides showed a shift towards low values of M wave amplitude and that eight observations fell beyond the lower limit of the normal range. In addition the mean amplitude for the normal sides ($6 \cdot 5 \pm 0 \cdot 3$ mV) differed significantly
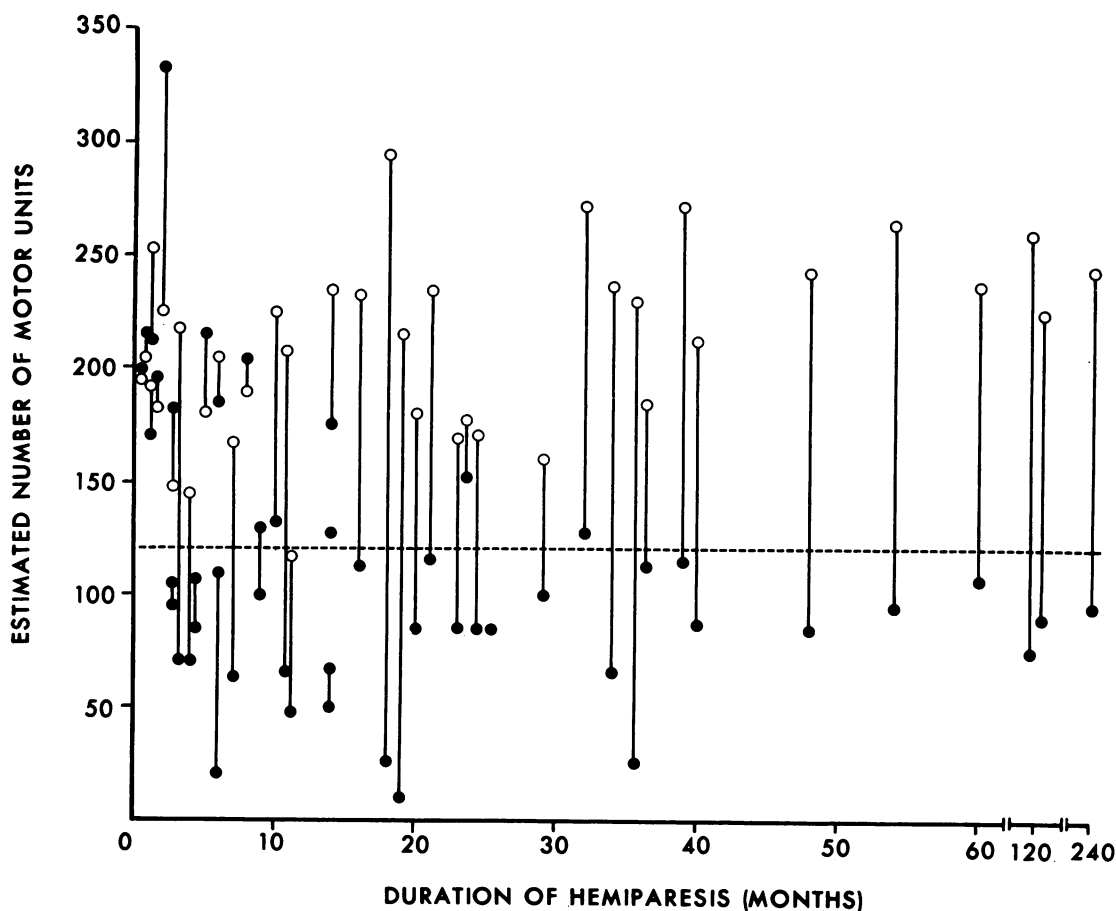

FIG. 3. *Numbers of functioning motor units in EDB muscles of 46 patients with upper motor neurone lesions, of whom 38 were hemiparetic (see text). Open and filled circles denote values in normal and affected limbs respectively. Duration of illness shown on abscissa. Lower limit of normal range (121 units) indicated by interrupted line.*

from that for the affected sides (4·9 ± 0·4 mV, P = <0·005).

NUMBERS OF FUNCTIONING MOTOR UNITS In Fig. 3 the numbers of functioning motor units have been compared in the normal and affected limbs of the 38 patients who were hemiparetic. In a further six patients there was evidence of an upper motor neurone lesion affecting the supposedly normal leg, even though there had been no history of weakness on that side. These last results have been shown separately in Fig. 3; also included are values from two patients in whom control observations could not be made because of past injury to the contralateral leg.

In Fig. 3 it can be seen that no change had occurred in any of the six patients with hemiparesis of less than two months' standing. In contrast to this finding, 31 of the 40 patients who had been hemi- (or quadri-) paretic for longer than two months were estimated to have numbers of units below the lower limit of the control range (120). This loss of functioning units was already evident in two of the patients at three months. Of the nine patients with normal values, it is possible that those with the most

recent illnesses would also have developed a loss of units had sufficient time elapsed. On the other hand, inspection of Fig. 3 suggests that further loss of units was unlikely to occur after six months. This suggestion was tested by analysing the results for the 31 patients with weakness of seven to 24 months' duration. In these patients no correlation was found between the length of illness and the number of surviving units ($r = -0·02$).

Within this population the mean estimated number of units in affected legs of the 27 patients with unilateral weakness was 93·7 ± 8·4 and roughly half that obtained for the normal legs of the same subjects (216·7 ± 7·9; P <0·001). This last mean was in reasonable agreement with the value of 197·0 ± 7·2 obtained from a population of 66 healthy subjects aged between 3 and 58 years.

SIZES OF REMAINING MOTOR UNITS There was no evidence in the present study that a loss of functioning motor units was more likely to occur with a lesion of one hemisphere than the other (see Discussion). For example, of the 11 patients with right-sided weakness the number of func-
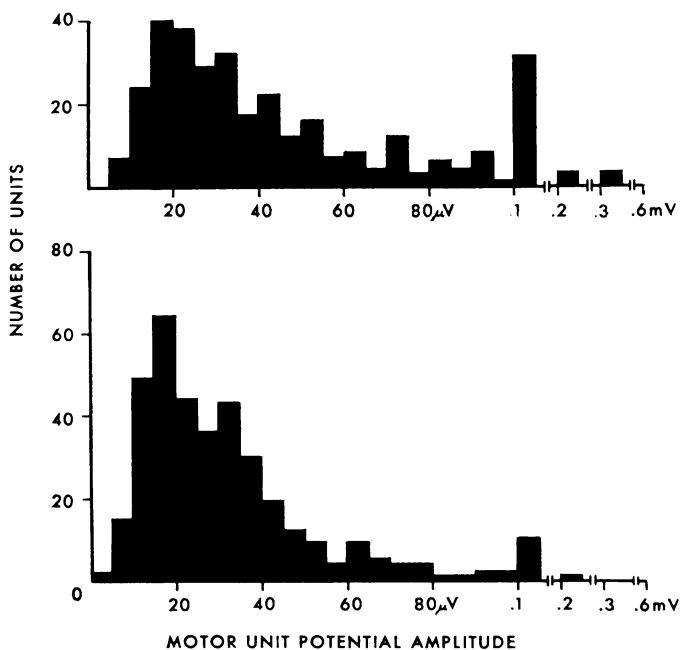

FIG. 4. *Pooled amplitudes of EDB motor unit potentials in affected legs (upper) and normal legs (lower) of patients with upper motor neurone lesions. Mean values for normal and affected legs were 31·2 ± 1·4 μV and 49·7 ± 3·2 μV respectively (P < 0·001).*
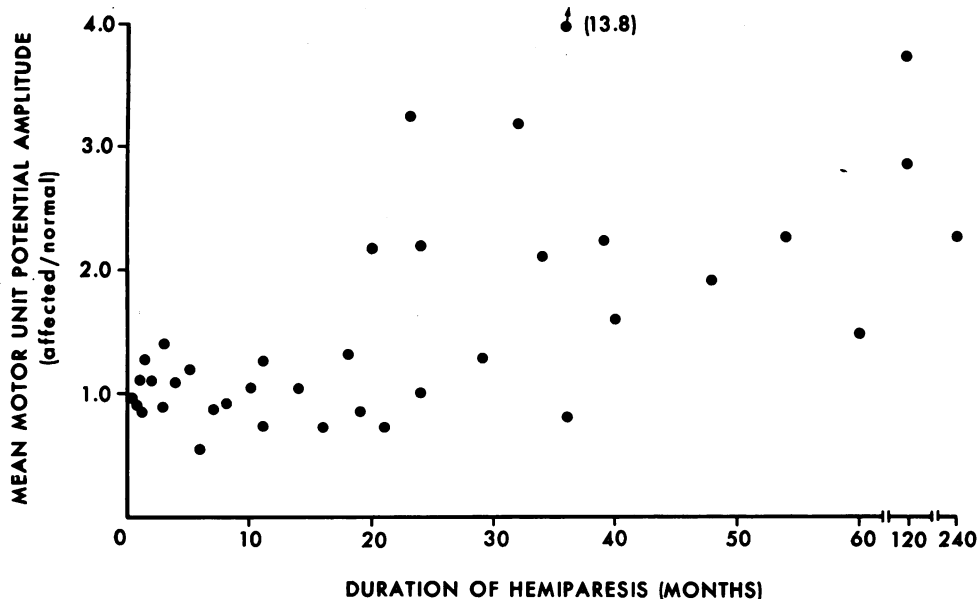
FIG. 5.   *Mean amplitudes of motor unit potentials of EDB muscles in normal and affected legs of 38 patients with hemiparesis. For each patient the mean value for the affected limb has been given as a fraction of that for the normal limb. Duration of hemiparesis shown on abscissa.*

tioning motor units was reduced in eight; for the 16 patients with left-sided weakness the corresponding number was 14. Other evidence that laterality was not important was that four of the six patients with quadriparesis had reduced numbers of units on both sides.

The sizes of the motor unit potentials in the affected muscles were of considerable interest, in that they gave an indication of the functional status of those motoneurones which still innervated muscle fibres (see Discussion).

In Fig. 4 the measurements of motor unit potential amplitude have been pooled for all the hemiplegic patients, irrespective of the duration of illness or the number of surviving units. Although the range of values derived from muscles in the normal and affected limbs were similar, it can be seen that there was a tendency for the results in hemiplegia to be larger. When the means for the two populations were compared, it was found that the one from affected limbs (49.7 ± 3.2 μV) was significantly greater than that for normal legs (31.2 ± 1.4 μV; $P < 0.001$).

Finally, in Fig. 5, the possible significance of the duration of the hemiparesis has been considered. For each patient the mean size of motor unit potentials on the affected side has been expressed as a proportion of that on the normal side. It can be seen that little change in mean size occurred before 20 months but that substantial enlargement took place in most subjects afterwards. Thus, the mean value of results between the 7th and 19th months was 38.6 ± 3.1 μV and was significantly less than that for longer illnesses (67.1 ± 6.2 μV; $P < 0.001$). This difference was not related to the numbers of surviving motor units, since it has already been shown that there was no further loss of functioning units beyond the sixth month (see above).

ISOMETRIC TWITCHES   In nine patients the isometric twitches were compared in the normal and affected legs. As would be expected, the maximal twitch tensions of the muscles on the hemiparetic side were reduced, though, within this small sample, the means did not differ significantly (normal legs, 260 ± 26.2 g; affected

legs, $205 \pm 28 \cdot 8$ g; $0 \cdot 1 > P > 0 \cdot 05$). When the results for a further 11 affected legs were included, for which no control observations were possible, the corresponding mean was $209 \pm 8 \cdot 2$ g. This new mean differed significantly from the value of $310 \pm 9 \cdot 4$ g obtained from muscles of healthy subjects aged between 17 and 60 years ($P < 0 \cdot 001$).

The most obvious difference between the twitches on the normal and hemiparetic sides was in relation to the contraction times. In the nine subjects investigated the mean contraction time for the affected sides was $81 \cdot 7 \pm 2 \cdot 9$ msec and was significantly slower than that for the normal sides ($72 \cdot 0 \pm 2 \cdot 2$ msec; $P < 0 \cdot 01$). In contrast, the mean half-relaxation times for the two sides were much closer (normal side, $68 \cdot 4 \pm 3 \cdot 4$ msec; affected side, $70 \cdot 8 \pm 4 \cdot 0$ msec; $P > 0 \cdot 3$).

CONDUCTION STUDIES Maximal impulse conduction velocities were measured in motor axons of deep peroneal nerves in 53 affected limbs (Table). In three of the legs the values (41, 39,

latency showed a difference between the normal and affected limbs. This latency was measured as the time elapsing between stimulation of the deep peroneal nerve at the ankle and the onset of postsynaptic activity in the EDB muscle. In normal subjects this latency has not been found to exceed $5 \cdot 0$ msec. In 15 of the 53 affected limbs studied slightly larger values were recorded, the maximum being $6 \cdot 0$ msec and the mean for the population being $4 \cdot 62 \pm 0 \cdot 11$ msec. This mean differed significantly from that of the control population and also from that of unaffected limbs in hemiparetic patients ($3 \cdot 95 \pm 0 \cdot 09$ msec and $3 \cdot 63 \pm 0 \cdot 14$ msec respectively; $P < 0 \cdot 001$ in each case; see Table).

MUSCLE RESPONSES TO REPETITIVE NERVE STIMULATION In many of the hemiparetic patients the

TABLE

MAXIMAL CONDUCTION VELOCITY AND TERMINAL LATENCY MEASUREMENTS IN AFFECTED AND UNAFFECTED LEGS OF PATIENTS AND IN CONTROL SUBJECTS AGED 17–58 YEARS

	Conduction velocity (m/sec)			Terminal latency (msec)		
	Unaffected legs	Affected legs	Control subjects	Unaffected legs	Affected legs	Control subjects
n	10	53	32	10	53	32
Mean	48·1	47·4	48·4	3·63	4·62	3·95
± SE	± 1·5	± 0·6	± 0·7	± 0·14	± 0·11	± 0·09
P	> 0·3		> 0·2	< 0·001		< 0·001

and 37 m/sec) lay just beyond the lower limit of the normal range (42 m/sec) determined for 32 healthy control subjects aged between 17 and 58 years. When the observations on the affected legs were pooled the mean value, $47 \cdot 4 \pm 0 \cdot 6$ m/sec, was very close to that of the control population ($48 \cdot 4 \pm 0 \cdot 7$ m/sec) and also to that of the unaffected limbs in 10 hemiparetic patients ($48 \cdot 1 \pm 1 \cdot 5$ m/sec). In contrast with the conduction velocity results, the observations of terminal
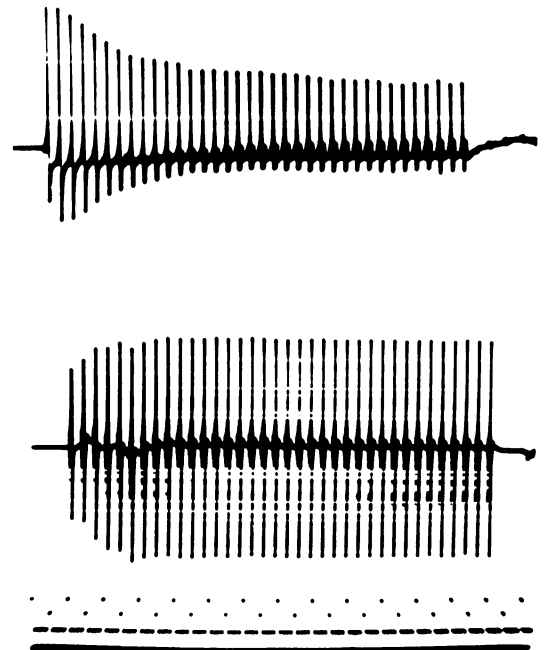

FIG. 6. *Responses of EDB muscles to indirect stimulation at 30 shocks/sec. Recordings made in affected limb of a hemiplegic patient (upper) and in a control subject (lower). The respective amplitudes of the initial responses were 5.2 mV and 4.1 mV in the control and hemiplegic subjects. The intervals between the largest markings on the time scale represent 100 msec.*

responses of the EDB muscle to repetitive stimulation of the deep peroneal nerve were studied. The stimuli were approximately 1·5 times the maximal intensity and were delivered at a rate of 30/sec for 1 sec. In normal subjects there is usually a slight increment in the EDB response which is probably due to shortening of the muscle fibres under the cutaneous electrode (Fig. 6, *lower*); reductions of more than 10% have not been encountered. In the present study repetitive stimulation was performed on 47 affected limbs of patients with upper motor neurone lesions. In 15 of these, response decrements of 20% or more were observed (Fig. 6, *upper*).

DISCUSSION

The present study has clearly shown that, after an upper motor neurone lesion, there is a reduction in the number of functioning motor units. Before proceeding further, it is important to consider whether this finding might have resulted from increased pressure on peripheral nerves in immobilized limbs or from accidental blows to superficially situated nerves during movement. Examination of the pooled observations suggests that this explanation is unlikely. Thus, the trauma should have been greatest in the earliest part of the illness when the patients were either confined to bed or else experiencing most difficulty in attempted movements. Instead, it was found that the loss of functioning motor units did not commence until after the second month of illness and was relatively abrupt, being complete by the sixth month.

Since traumatic neuropathy did not appear to be a major factor in the present study, it follows that the loss of functioning motor units must have resulted from trans-synaptic degeneration of motoneurones. This type of degeneration has been studied most fully in the lateral geniculate nucleus after section of the optic nerve (Glees and Le Gros Clark, 1941; Cook, Walker, and Barr, 1951; Goldby, 1957; Hess, 1957; Matthews, Cowan, and Powell, 1960). The occurrence of trans-synaptic degeneration in the mammalian spinal cord is less widely accepted, however, for although authors such as Barron (1933) and Young (1966) have reported motoneurone degeneration following spinal transection, others

have attributed this to interference with the blood supply of the cord. Indeed, transection of the cord has long been a favoured method for examining the effects of disuse on muscle, as opposed to those of denervation (Tower, 1937).

In man, degeneration of motoneurones was described in the last century by several workers, including Charcot (1893) but was denied by Déjérine (1889). It is of interest that the last author also examined peripheral nerves postmortem and observed marked fibre degeneration. The finding of axonal degeneration in the presence of an apparently intact soma is now recognized as a feature of a 'dying back' process (Cavanagh, 1964). In this type of reaction, lesions which are thought to affect the soma so as to render it dysfunctional or 'sick' (McComas, Sica, and Campbell, 1971a) produce their most marked effects in distal parts of the axon, presumably by interfering with the centrifugal flow of trophic factors. In keeping with the concept of sick motoneurones in hemiplegia was the observation that some axons mediated responses with prolonged distal latencies, although the impulse conduction velocities were normal proximally. In other axons it has recently been shown that slowing of impulse conduction may ultimately extend towards the soma (Namba *et al.*, 1971). Also compatible with a dying-back process was the frequent occurrence of decremental responses to repetitive stimulation of motor nerves observed in the present investigation. Mention should also be made of the electromyographic studies by Goldkamp (1967) and Notermans (1968), both of whom described the presence of fibrillation potentials and positive sharp waves in muscles of hemiplegic patients. Less direct evidence of denervation has come from muscle biopsy studies such as that of Edstrom (1970) in which 'target-like' fibres were reported.

In the past there has been much speculation concerning the region of the brain which must be involved by the lesion for hemiplegic atrophy to occur. One opinion is that the postcentral gyrus is the critical area of cortex. For example, Silverstein (1955) reported that sensory loss of the parietal type was present in all of the patients studied with hemiplegic atrophy. Penfield and Robertson (1943) also regarded the parietal lobe as specific, having found that damage apparently

restricted to this region during the first three years of life produced marked failure of growth of bones and muscles on the contralateral side. More recently, Botez (1971) has developed the argument in favour of the postcentral gyrus and has raised the possibility of hemispheric dominance for a somatic trophic influence. In an extensive study of patients with cerebral tumour, he noted that wasting was clinically evident in most of those with lesions of the minor hemisphere but occurred infrequently when the dominant hemisphere was involved. The neuroanatomical and physiological basis for a trophic influence of the postcentral gyrus on alpha-motoneurones undoubtedly exists, since Penfield and Boldrey (1937) have found that stimulation of this region in man can produce movement and it is now recognized that there is a heavy projection of fibres from the parietal lobe into the pyramidal tracts (Levin and Bradford, 1938).

Against parietal lobe specificity for muscle atrophy are the observations of Fenichel et al. (1964) who found wasting in two patients without sensory loss and who cite similar observations by earlier authors. Fenichel et al. (1964) emphasize the importance of the precentral gyrus and it is relevant that Fulton (1936, 1949) was able to produce marked wasting in chimpanzees after ablation of the motor strip, though lesions of the postcentral gyrus were ineffective. In the present study only patients with hemiparesis were investigated and all those with muscle atrophy demonstrated the signs usually associated with a lesion of the motor cortex or pyramidal tract fibres on the opposite side— hyperactive tendon reflexes, spasticity, and a Babinski response. Nevertheless, there were five patients with signs of an upper motor neurone lesion in whom atrophy was absent and the estimated numbers of motor units were within the normal range. It was unlikely that these patients were exempted from atrophy by the presence of lesions which did not involve the critical area of cortex, since some had evidence of more severe loss of cortical function than others in whom the reductions in functioning motor units were marked. While accepting that involvement of the corticospinal fibres issuing from the motor cortex will induce trans-synaptic degeneration of motoneurones in man, we are left with the possibility that this degeneration

may sometimes be prevented by compensatory spinal mechanisms (see below). So far as the significance of laterality was concerned, it was not possible to find any correlation between the presence or absence of motor unit loss and the side of the lesion (see Results).

Of particular interest to a detailed consideration of trans-synaptic degeneration is the time-course of the reduction in the functioning EDB motoneurone pool. It was found that, on the basis of axonal stimulation and motor unit recording, motoneurones maintained their functional properties for the first two months after a cortical lesion. At some time within the next four months the number of functioning motoneurones was reduced to approximately half. The marked loss of motoneurones in the two patients with histories of three months' duration indicated that the trans-synaptic degeneration could take place relatively abruptly. In the initial two month period after the lesion, Wallerian degeneration will have taken place in the corticospinal fibres followed by functional changes in the alpha-motoneurone soma and finally in the motor axon. From the studies of Miledi and Slater (1970) it is known that, if a motor axon is divided, neuromuscular transmission fails at a time when the axon still remains capable of conducting impulses. In the rat phrenic nerve the trophic factors necessary for neuromuscular function travel with a velocity of 4 cm/45 minutes and are not stored in appreciable amounts within the nerve terminal. Assuming a total conduction distance of 180 cm between cortex, lumbosacral motoneurones, and EDB, and similar axoplasmic flow rates for corticospinal and motor axons, only two days would be required for the exhaustion of residual trophic material in axons. Hence, the greater part of the initial two month period must represent the time taken for the motoneurone soma to cease functioning after a loss of corticospinal input.

In the literature there are several reports of muscle changes occurring relatively soon after a lesion of the cerebral hemisphere. For example, Goldkamp (1967) was able to detect fibrillation potentials and positive sharp waves two weeks after a stroke. Similarly, Silverstein (1955) has described the appearance of wasting in paralysed extremities as early as 48 hours after injury to

FIG. 7. *Postulated sequence of events after an upper motor neurone lesion. (a) shows situation in health with alpha-motoneurone (mn) receiving corticospinal and segmental (seg) inputs. In (b) a cerebrovascular lesion destroys cells in motor cortex or emergent axons. Motoneurone now becomes dys-functional and may lose part of motor unit. Atrophy of muscle (mu) ensues. Two developments are now possible. In one (c) the motoneurone ceases to function and may actually degener-ate. In the other (d) the segmental input to the motoneurone is increased by axonal sprouting. The improved supply of trophic material restores the motoneurone to full function and collateral reinnervation of muscle fibres can now proceed (e).*
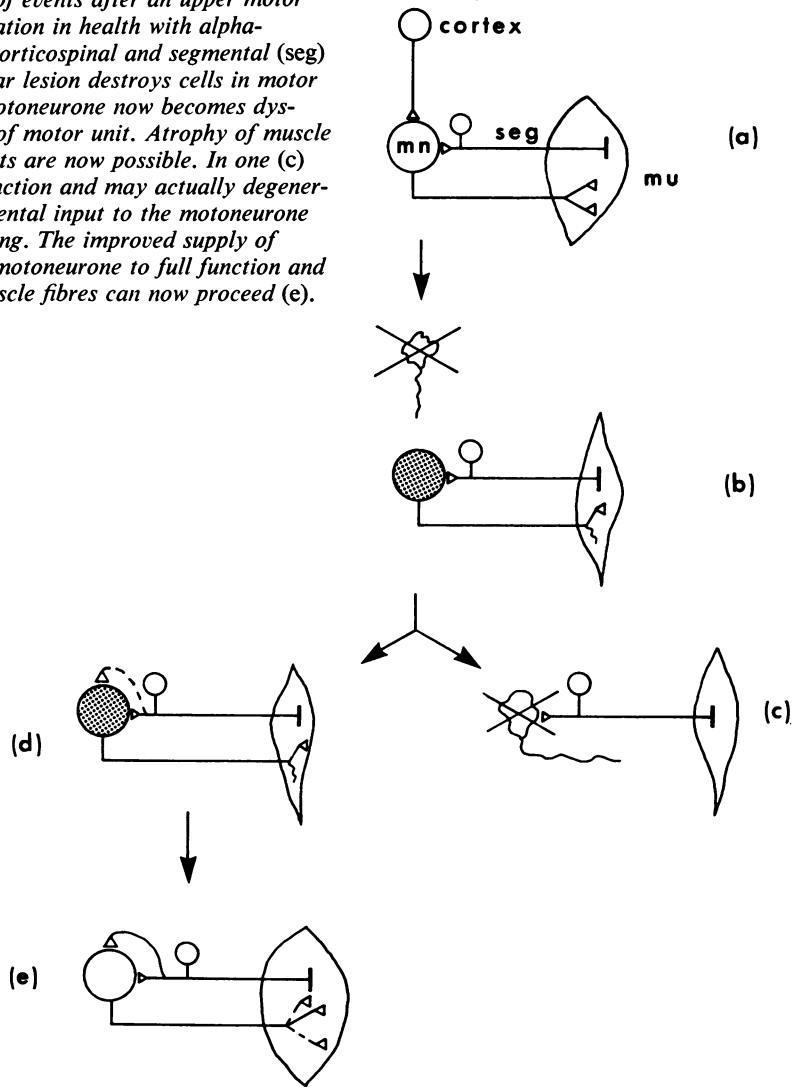
the parietal lobe. Nevertheless, in the present study it has been shown that at least two months are required before motoneurone dysfunction reaches the stage at which the axon becomes electrically inexcitable. It is also evident from the work of Goldkamp (1967), among others, that muscle degeneration is likely to be more severe in some muscles than others. Distal muscles, especially those of the hand, usually show more wasting and, in Goldkamp's study, a higher incidence of fibrillation potentials, than proximal muscles. These differences indicate a greater susceptibility of some motoneurone pools to trans-synaptic changes than others and pre-sumably reflect inequalities in the density of the fibre projection normally received from the cortex. So far as the EDB muscle is concerned, cortical mapping studies have shown that the area of motor cortex devoted to movements of the toes is considerably less than the area for the fingers (Penfield and Boldrey, 1937). In keeping with this difference is the recent observation that

voluntary potentiation of segmental reflexes is more marked for those reflexes involving hand muscles than for those of the foot (Upton, Sica, and McComas, 1971). In the EDB muscle about half the motor units retained function after a cerebral lesion. It is possible that the corresponding motoneurones may have been the ones which had received smallest corticospinal inputs and the largest segmental ones. The measurements of twitch contraction time suggested that these surviving motoneurones tended to innervate muscle fibres having relatively slow isometric twitches. It is consequently of interest that in a histochemical study of muscle biopsies from hemiplegic patients, Edstrom (1970) has found evidence of hypertrophy in type I muscle fibres and atrophy in fibres of type II. It is unlikely that the surviving motor units are a homogeneous slow-twitch population, however, since comparison of the mean EDB contraction time with values for single units in normal subjects (Sica and McComas, 1971) indicates that some units with relatively fast twitches must also have been spared.

In the present study the amplitudes of the motor unit potentials were of considerable interest, insofar as they gave an indication of the functional status of the motoneurones. It was found that in the 6 to 19 month period after an upper motor neurone lesion the potential amplitudes generated by the surviving motor units remained unchanged. This finding suggested that the corresponding motoneurones cannot have been 'healthy', since otherwise they would have responded to the presence of denervated muscle fibres by axonal sprouting and collateral fibre reinnervation. This observation, together with the frequent occurrence of decremental responses to repetitive motor nerve stimulation and the sometimes prolonged terminal latencies, indicated that many of the surviving motoneurones were dysfunctional. After 19 months, however, the measurements of M wave amplitude suggested that there was some regression of the muscle atrophy. This was not due to recovery of function in motor units, since the numbers of viable units remained unchanged. Instead, the mean motor unit potential size increased, due either to axonal sprouting and the adoption of denervated fibres or to muscle fibre hypertrophy, or to both. Irrespective of the mechanism involved, it

appeared that most surviving motoneurones had changed back from a dysfunctional to a healthy state. The reason for this improvement was not clear but one possibility was that the motoneurones had received increased trophic inputs from other spinal neurones. These last neurones, by axonal sprouting, would have been able to take over the synaptic territory relinquished by the degenerating corticospinal fibres on the alpha-motoneurones (see McCouch, Austin, Liu, and Liu, 1958). Not only should the excitatory or inhibitory effects of the spinal neurones have been larger, but the trophic influences of these cells on the alpha-motoneurones should also have been greater. It is therefore conceivable that the return of the motoneurones to complete function may have resulted from compensatory enhancement of trophic inputs from spinal sources. Although the findings of the present study are only strictly applicable to man, it is of interest that, in the rat, Solandt and Magladery (1942) observed that there was some restoration of muscle bulk six weeks after spinal section rostrally. The postulated sequence of events after an upper motor neurone lesion is shown diagrammatically in Fig. 7.

In conclusion, the present investigation has confirmed those early studies in which transsynaptic degeneration of motoneurones was reported. Because the approach applied here has been a physiological rather than a morphological one, it has had the advantage of increased sensitivity and of enabling the reduction in motoneurone function to be measured and its time course established. The patient with an upper motor neurone lesion has provided a satisfactory model for the study of trophic mechanisms within the central nervous system. It is hoped that, in turn, the information acquired may ultimately lead to improved methods for the rehabilitation of such patients.

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