RECENT ADVANCES IN THE CLINICAL ELECTROPHYSIOLOGY OF MUSCLE AND NERVE

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THE past few years have witnessed a number of important advances in clinical electromyography. Previous reviews have been made by Marinacci (1955), Lambert (1956), Buchthal (1957a) and Gilliatt (1957). Rather than attempting a general survey of the subject, it seemed more profitable in a short article to select for consideration four topics in which significant advances had been made since these reviews appeared.

1. The Functional Organization of the Motor Unit

The Parameters of Normal Motor Unit Potentials

The functional unit in a muscle, the motor unit, consists of the muscle fibres controlled by a single anterior horn cell. In examining the electrical activity of a muscle the record obtained is markedly influenced by the type of recording electrode, but with the concentric needle electrodes usually employed for clinical electromyography the action potentials seen during voluntary contraction in a normal muscle are produced by the summated activity of the component fibres of single motor units. The electrical field produced by the fibres of the motor unit depends upon their number and anatomical arrangement and the temporal dispersion of their activity. A detailed analysis of the organization of the motor unit has been made by Buchthal and his collaborators and has been summarized by Buchthal (1957b) and Buchthal, Guld and Rosenfalck (1957).

Using a multilead electrode, Buchthal *et al.* (1957) examined the *territory* of single motor units in biceps brachii. In this muscle the fibres pass without interruption from one end of the muscle to the other. Although the territories of neighbouring motor units overlap, each unit was found to be composed of a number of 'sub-units' distributed within a restricted cylindrical zone having a diameter of about 4 to 6 mm. Other limb muscles were examined by Buchthal, Erminio and Rosenfalck (1959) and a similar restricted motor unit territory was found, the diameter of the territory tending to be a little greater in lower limb than in upper limb muscles.

The *duration* of the motor unit potential reflects

the temporal dispersion of the propagated action potentials of the component fibres of the unit as they pass the recording electrode. Theoretically, this might be due to differences in propagation time in the terminal branches of the motor nerve fibre, the extent of the longitudinal scatter of end-plates in the innervation zone or differences in conduction velocity between the various muscle fibres of the unit. It has been shown (Buchthal, Guld and Rosenfalck, 1955) that the end-plates of a single motor unit are activated almost simultaneously and hence varying delay in the terminal branches of the motor nerve fibre can only be slight. Moreover, measurements of conduction velocity in a large sample of muscle fibres revealed that this varies within a relatively narrow range (Buchthal *et al.*, 1955) and the amount of temporal dispersion that could be introduced in this way is insufficient to account for the observed duration of the motor unit potential. It therefore seems likely that the longitudinal scatter of end-plates in the innervation zone is the important determining factor, and that the duration of the potential depends upon variations in the distance between the recording electrode and the end-plate for the component fibres of the unit. Measurement of the length of the innervation zone by needle electrode recordings in biceps brachii gave a value of appropriate magnitude.

The *amplitude* of the potential is related to the number of muscle fibres per unit and their density within the territory of the unit. Thus the amplitude of the potentials is generally less in muscles with a small number of fibres per unit, such as the facial or external ocular muscles, than in the limb muscles, where the units may be composed of as many as one or two thousand fibres (Feinstein, Lindegård, Nyman and Wohlfart, 1955). The amplitude of the potential is also markedly influenced by the position of the recording electrode in relation to the active muscle fibres. Buchthal *et al.* (1957) found that the amplitude of spike components derived from sub-units declined exponentially with the distance between the potential source and the recording electrode.

The temporal and spatial dispersion of the

potentials derived from the different sub-units as they pass the recording electrode will also determine the *form* of the total motor unit potential. This again is probably mainly accounted for by the spatial scatter of end-plates in the innervation zone.

Disturbances of Motor Unit Organization in Disease

The increase in the amplitude, duration and complexity of form observed in the action potentials of surviving motor units in partially denervated muscles has been studied recently by multilead electrode recordings (Erminio, Buchthal and Rosenfalck, 1959). It was found that co-existent with the increase in amplitude, indicative of an increase in the number of muscle fibres in the unit, there was a spread of the territory of the unit over the cross-section of the muscle. These changes were greater when the denervation was due to anterior horn cell disease than when it was the result of peripheral nerve injury. There is now good evidence that these changes involve collateral sprouting by surviving axons, which extend motor unit territory by re-innervating adjacent denervated muscle fibres. The anatomical studies on this topic have been reviewed by Wohlfart (1958).

The characteristic changes in myopathic disorders, where there is a diffuse loss of fibres, are initially in the appearance of the motor unit potentials without substantial alterations in their numbers (Kugelberg, 1949; Pinelli and Buchthal, 1953; and others). The potentials are of reduced amplitude and duration and are often polyphasic. Although it is clear that the reduction in the voltage of the potential can be attributed to the loss of muscle fibres, it was possible that alterations in muscle fibre conduction velocity might be involved in the other changes (Pinelli and Buchthal, 1953). A multilead electrode analysis of motor unit territory and fibre density in myopathic disorders by Buchthal, Rosenfalck and Erminio (1960) has helped to elucidate this question. The most marked abnormalities were observed in cases of long-standing pseudo-hypertrophic muscular dystrophy where there was a reduction in motor unit territory coupled with a decrease in the maximum voltage within the unit, indicating a reduction in fibre density. Measurements of conduction velocity in myopathic muscle gave values within the normal range. The diminution in the duration of the motor unit potential is therefore likely to be due to the reduction of the spatial scatter of end-plates in the innervation zone consequent upon fibre loss. Similarly, the polyphasic form of the potential is seen to be the result of the thinning of fibres from the unit, so that the potentials derived from the different sub-units are observed discretely.

2. The Mechanism of Fibrillation

After complete acute denervation of a muscle, extracellular needle electrode recording shows no electrical activity for two to three weeks, after which fibrillation potentials begin to appear. The original descriptions of these potentials in human muscles were given by Denny-Brown and Pennybacker (1938) and Weddell, Feinstein and Pattle (1944), and they are generally considered to represent propagated action potentials of single muscle fibres. They are not universally seen after denervation and even with thorough sampling approximately 20% of denervated muscles fail to show these potentials (Richardson, 1951). The occurrence of fibrillation can be enhanced by the administration of prostigmine and is reduced by cooling (Feinstein, Pattle and Weddell, 1945); fibrillary activity may also be evoked by mechanical stimulation, as by movement of the needle electrode within the muscle.

The mechanism of production of fibrillation potentials is still under debate, but there have been a number of recent experimental studies that have a bearing on this question.

In a normally innervated muscle fibre, intracellular recordings at the region of the neuromuscular junction reveal two types of electrical activity. Firstly, the arrival of a nerve impulse produces a local depolarization (end-plate potential), which leads to the production of a propagated muscle action potential; secondly, random spontaneous subthreshold potentials (miniature end-plate potentials) occur, which are probably the result of the intermittent release of multi-molecular packets of acetylcholine from the nerve terminals (Fatt and Katz, 1951, 1952). Birks, Katz and Miledi (1960) have investigated the changes occurring at the neuromuscular junction after denervation in the frog. Neuromuscular transmission fails at about five days after nerve section and, at approximately the same time, the spontaneous miniature end-plate potentials cease. These potentials usually reappear during the ensuing week, but at a lower frequency, and their reappearance precedes the development of supersensitivity to acetylcholine by the muscle fibres. They were thought to occur as a result of acetylcholine produced at the degenerated end-plates, possibly by Schwann cells. The relationships of these changes to spontaneous fibrillation is not known, as spontaneous fibrillation is rarely seen in amphibian muscle; a study of these phenomena in mammalian muscle would be of considerable interest. Jarcho, Berman, Dowben and Lilienthal (1954) reported that in denervated rat muscle, fibrillation potentials arise only in the region of the degenerated end-plates.

However, Li (1960), on the basis of observations

on cats, is of the opinion, as was Eccles (1941), that fibrillation potentials do not necessarily arise from degenerated end-plates. Li found that, whereas the membrane potential of the normal muscle fibre is highly stable, that of the denervated muscle fibre shows rhythmic fluctuations, which, if they exceed a certain amplitude, result in a spike discharge. These findings, if confirmed, will be of considerable importance in relation to the origin of spontaneous fibrillation.

It has been known since the observations of Brown (1937) that denervated muscle fibres have a greatly enhanced sensitivity to acetylcholine. This phenomenon has been re-examined by Axelson and Thesleff (1959) and Miledi (1960). It seems likely that the supersensitivity is due to the spread of acetylcholine responsiveness, which is normally confined to the end-plate region, to the whole of the fibre. The relevance of this altered sensitivity to the occurrence of spontaneous fibrillation is still uncertain, although it was suggested by Denny-Brown and Pennybacker (1938) that fibrillation occurs in response to small amounts of free acetylcholine in the tissues. Moreover, fibrillation is unaffected by doses of curare that reduce the response to acetylcholine (Reid, 1942). Katz and Miledi (1961) have shown that isolated nerve-free segments of frog muscle develop acetylcholine sensitivity. It would be of value to discover whether this also occurs in mammalian muscle and, if so, whether it is accompanied by spontaneous fibrillation.

Fibrillation is not necessarily associated with nerve degeneration. It has recently been reported that supersensitivity to acetylcholine develops after experimental poisoning with botulinum toxin in the rabbit (Thesleff, 1960) and that spontaneous fibrillation also occurs (Josefsson and Thesleff, 1961). Botulinum toxin is known to prevent the release of acetylcholine without causing degeneration of the axon or nerve terminals. Disuse atrophy produced by immobilization does not give rise to fibrillation (Solandt, Partridge and Hunter, 1943).

3. The Electromyographic Study of Neuromuscular Transmission in Myasthenia

The degree of neuromuscular block in myasthenia can be assessed by observing changes in the size of the compound action potential of a muscle evoked by maximal electrical stimuli to the motor nerve. The abnormalities in myasthenia gravis have been analysed by Johns, Grob and Harvey (1955). There is some degree of block in response to a single electrical stimulus, since the size of the muscle action potential may be increased by prostigmine, this not being seen in normal subjects. Following the passage of a single

impulse, the degree of block shows a slight temporary increase. The response to a train of impulses is complex. At first the degree of block increases, then diminishes slightly and subsequently increases again, the magnitude of the block increasing with the frequency of the stimulus. Rapid repetitive stimulation is followed by a period of reduction in the degree of the block (post-tetanic facilitation), although the passage of subsequent impulses is diminished (post-tetanic exhaustion). The improvement in the response to repetitive stimulation produced by prostigmine (Harvey and Masland, 1941) has been used as a diagnostic test for myasthenia, but has not been found to give consistently reliable results.

Observations have been made on the effects of decamethonium salts and acetylcholine on neuromuscular transmission in myasthenia gravis. In normal subjects decamethonium produces a depolarization block after an initial transient stimulation. In myasthenia Churchill-Davidson and Richardson (1953) reported that clinically weak muscles show an initial improvement in power and then a transmission block having the features of competitive inhibition. Clinically unaffected muscles show an increased tolerance to decamethonium. The effects of acetylcholine were described by Grob, Johns and Harvey (1955). In both normal subjects and in patients with myasthenia an intra-arterial injection of acetylcholine produces stimulation followed by a transient depolarization block; this is followed by a late prolonged block, that in normal muscles has the features of a depolarization block, but in myasthenia gravis is of competitive type. It is possibly produced by choline resulting from the hydrolysis of acetylcholine.

Although these findings indicate an abnormality of the end-plate responses to depolarizing substances, more recent evidence tends to suggest that the basic disturbance in myasthenia gravis is prejunctional and dependent on a failure in acetylcholine synthesis or release. Dahlbäck, Emlqvist, Johns, Radner and Thesleff (1961) made intracellular recordings in the end-plate region in biopsies of muscles from patients with myasthenia gravis and compared the results with those obtained in normal human muscles. In the myasthenic muscles the resting membrane potential was similar to that of normal muscle fibres, but miniature end-plate potentials were consistently reduced in frequency or entirely absent. Elevation of the potassium concentration in the bathing fluid to an extent that gives rise to a marked increase in the frequency of miniature end-plate potentials in normal muscle failed to have this effect in myasthenic muscle. On the other hand, the amplitude and time course of the miniature

end-plate potentials that were seen in the myasthenic muscle were normal.

Desmedt (1958) has drawn attention to the similarity between the electrical findings in myasthenia gravis and those produced by hemicholinium HC₃, a substance that strongly inhibits the synthesis of acetylcholine by nervous tissue. This also suggests that the fault in myasthenia is prejunctional. Desmedt examined the compound muscle action potential evoked by 3 per second supramaximal shocks to the motor nerve after tetanus by faradization. In myasthenia there is a brief post-tetanic facilitation followed by exhaustion. The response to hemicholinium HC₃ was examined in the cat and resembled that seen in myasthenic patients, but differed from the competitive block produced by curare. In muscles partially paralysed by d-tubocurarine tetanus is not followed by any increase in the extent of the block, although post-tetanic potentiation is seen.

In an attempt to explain the abnormalities in the reaction of the end-plate shown by myasthenic patients, Desmedt suggested that a persistent prejunctional abnormality might produce secondary changes in the response of the end-plate.

Lambert and his associates (Rooke, Eaton, Lambert and Hodgson, 1960) have studied the electromyographic characteristics of the myasthenic syndrome sometimes associated with carcinoma of the bronchus and have reported several interesting differences from typical myasthenia gravis. The differences are quantitative rather than qualitative; for example, there is a marked post-tetanic potentiation preceding the phase of post-tetanic exhaustion.

4. The Examination of Peripheral Nerve Conduction

The measurement of conduction velocity in human motor nerve fibres was first applied clinically in 1948, when Hodes, Larrabee and German described slowed conduction in regenerating nerves after suture. Since then slowing has been reported in relation to various localized nerve lesions and also in generalized disorders involving the peripheral nerves. A detailed review has been made by Gilliatt (1961).

In the determination of motor nerve conduction velocity the nerve to the muscle is stimulated with brief electrical shocks at a strength supra-maximal for motor fibres. The latency of the first deflection of the evoked muscle action potential, recorded either with surface or needle electrodes, is obtained for two or more stimulus positions along the nerve trunk. By subtraction of the latencies and division into the distance between the stimulus positions, an estimate of conduction velocity is obtained. Since the measurements are

made to the initial deflection of the muscle action potential, this value represents conduction in the fastest motor nerve fibres to the muscle. Normal values for the fibres to the small muscles of the hands and feet have been given by Norris, Shock and Wagman (1953), Henriksen (1956) and Thomas, Sears and Gilliatt (1959) and for more proximal limb muscles by Redford (1958). Critical evaluations of the technique have been made by Carpendale (1956), Henriksen (1956) and Thomas *et al.* (1959). The adult velocity is achieved by the age of five (Wagman and Lesse, 1952; Thomas and Lambert, 1960) and a decline occurs in later life (Norris *et al.*, 1953). The range of conduction velocity for the motor fibres to the extrafusal fibres of the small muscles of the hands and feet was investigated by Thomas *et al.* (1959), who found that the slowest fibres conduct at a rate 30% to 40% below the fastest.

Direct recordings of nerve action potentials were first made percutaneously in man by Dawson and Scott (1947), who showed that on stimulation of the median or ulnar nerves at the wrist with brief electrical shocks the potential due to the afferent volley could be recorded from surface electrodes placed over these nerves at the elbow. This is contributed to both by conduction in the larger sensory fibres and by antidromic conduction in motor fibres. Later (Dawson, 1956) it was shown that on stimulating the digital nerves of the finger with ring electrodes an action potential could consistently be recorded over the median or ulnar nerves at the wrist in normal subjects. This technique provides a direct method for studying sensory nerve conduction and was first applied for clinical purposes by Gilliatt and Sears (1958).

Recently recordings have been made from the lateral popliteal nerve on stimulation of the anterior tibial nerve at the ankle, both in normal subjects and in patients with neurological disorders (Gilliatt, Goodman and Willison, 1961).

Changes in Nerve Conduction with Localized Peripheral Nerve Lesions

Nerve Section

The duration of neuromuscular function after nerve section has been examined by Landau (1953) and Gilliatt and Taylor (1959), in the former instance mainly in the median and ulnar nerves and in the latter in the facial nerve. Nerve stimulation fails to evoke a muscle response after three to five days, and during this period there is little change in the latency of the muscle response. The precise cause of the failure is not known for human nerves, but animal experiments have demonstrated that failure of neuromuscular transmission slightly precedes cessation of conduction in degenerating axons during the course of

Wallerian degeneration (Lissák, Dempsey and Rosenblueth, 1939).

Conduction velocity in regenerating motor nerve fibres after nerve suture was measured by Hodes *et al.* (1948) and found to be reduced. Regenerating nerve fibres are known from animal experiments to be of small calibre and to conduct slowly (Berry, Grundfest and Hinsey, 1944; Sanders and Whitteridge, 1946).

Carpal Tunnel Syndrome

Simpson (1956) demonstrated that in a proportion of patients with the carpal tunnel syndrome, when the median nerve was stimulated at the wrist, the latency of the evoked action potential in abductor pollicis brevis was increased. This finding was made independently by Carpendale (1956). The results of a large series have recently been examined by Thomas (1960), who found that approximately two-thirds of patients with a clinical diagnosis of the carpal tunnel syndrome had a latency that exceeded the upper limit of normal. Gilliatt and Sears (1958) showed that the sensory nerve action potential obtained over the median nerve at the wrist on stimulating the digital nerves in the index finger was reduced or absent, or of abnormal latency, in approximately 75% of their series of cases. Electrical changes may be present in the absence of abnormal physical signs on clinical examination and hence the technique is helpful in the diagnosis of uncertain cases.

The explanation of the slowing of conduction is not clear. Simpson (1956) suggested that it was the result of the ischaemia of the compressed segment of nerve. An alternative explanation is that it is secondary to the narrowing of the nerve fibres at, and distal to, the site of the lesion, as was observed to occur in experimental constrictions by Weiss and Hiscoe (1948).

Fullerton (1961) has observed that in some patients with the carpal tunnel syndrome failure of motor nerve conduction below the wrist occurs rapidly if the arm is rendered ischaemic. This tended to occur not in patients with the severest lesions as judged by physical signs, but in those having the most frequent attacks of nocturnal paraesthesiae.

Ulnar Lesions in the Hand

Simpson (1956) also reported the electrical findings in a patient with a lesion of the deep palmar branch of the ulnar nerve in the hand and who showed considerable slowing of nerve conduction over the affected segment. This finding was confirmed and extended by Ebeling, Gilliatt and Thomas (1960). In this condition gross slowing of nerve conduction is confined to the hand. In patients in whom there is a lesion of the deep

palmar branch distal to the hypothenar muscles slowing of conduction is found only in the motor fibres to muscles supplied by this branch of the nerve. In patients with a more proximal lesion at the wrist, in whom there is also involvement of the hypothenar muscles with accompanying sensory disturbance, there may, in addition, be some slowing in the motor fibres to the hypothenar muscles and a disturbance of the afferent volley from the digital nerves of the fifth finger.

Cases of compression of the ulnar nerve in the hand may at times provide diagnostic difficulty and the clear abnormalities of nerve conduction found in these cases may be useful. The measurement of motor nerve conduction times also gives a quantitative estimate of the severity of nerve damage and, as pointed out by Ebeling *et al.* (1960), may be helpful in the detection of early recovery.

Ulnar Lesions at the Elbow

The changes encountered with lesions of the ulnar nerve at the elbow have been described by Simpson (1956), Henriksen (1956), Gilliatt and Sears (1958) and more recently by Gilliatt and Thomas (1960).

Motor nerve conduction has been examined for the fibres to abductor digiti minimi and the first dorsal interosseous muscle. Slowing is found in most of the severe cases, but is not constantly seen, even in patients with muscle wasting. Since conduction in the fastest motor nerve fibres is examined, survival of even small numbers of normal fibres will give a normal result. Although slowing may be present throughout the nerve below the level of the lesion, it is of interest that it may be maximal in the region of the elbow itself.

Nerve action potentials have been examined over three segments of the ulnar nerve, namely, with stimulation of the fifth finger and recording at the wrist, with stimulation at the wrist and recording just above the elbow, and stimulation above the elbow and recording in the axilla. Gilliatt and Thomas (1960) found that in a series of patients, all of whom had relatively severe lesions, no potentials could be recorded over the finger-wrist and wrist-elbow segments, whereas potentials were successfully recorded between the elbow and axilla.

The recording of nerve action potentials is likely to be of particular value in the diagnosis of mild cases in which conduction velocity in the fastest motor nerve fibres is normal. Gilliatt and Sears (1958) pointed out that the recording of a nerve action potential depends upon the passage of a synchronous volley of impulses under the recording electrode and that loss of the potential can

result from dispersion of the volley, even although some fibres may be conducting at a normal rate.

Brachial Plexus and Nerve Root Lesions

Sensory nerve conduction from the fingers has been studied in patients with brachial plexus lesions peripheral to the dorsal root ganglia (Gilliat and Sears, 1958) and central to the ganglia (Bonney and Gilliat, 1958). In the latter the nerve action potentials at the wrist on stimulation of the digital nerves were preserved despite complete sensory loss, whereas in the former they were absent. Motor nerve conduction velocity may be slightly reduced as a result of nerve root lesions from cervical spondylosis (Gilliat, 1961).

Changes in Nerve Conduction Proximal to Peripheral Nerve Lesions

It has been noticed that a mild degree of slowing of conduction may be present proximal to isolated peripheral nerve lesions, this having been shown for lesions of the ulnar nerve in the hand (Ebeling *et al.*, 1960), of the median at the wrist (Thomas, 1960) and after nerve suture (Gilliat, 1961). It is likely that this corresponds to the slowing of nerve conduction observed in the central stump after peripheral nerve injury in animals and associated with a reduction in fibre diameter (Kraly and Krnjević, 1959; Cragg and Thomas, 1961).

Nerve Conduction in Generalized Peripheral Neuropathies

Among most striking results that have emerged from the studies of nerve conduction made in different neurological disorders are the changes in chronic polyneuritis. In chronic polyneuritis from a variety of causes, extreme slowing of motor nerve conduction may be present (Lambert, 1956; Gilliat and Sears, 1958; Johnson and Olsen, 1960), and sensory nerve action potentials are frequently lost (Gilliat and Sears, 1958). Values

for motor nerve conduction velocity of as little as a tenth of the normal may be obtained.

The magnitude of the slowing makes it clear that it cannot be explained in terms of slow normal surviving fibres. Whether it depends upon gross structural changes or upon metabolic alterations in the affected nerves, or whether it represents conduction in regenerating fibres of small diameter, is as yet unknown.

The situation in acute polyneuritis requires further investigation. Although Henriksen (1956) found little change in motor nerve conduction velocity under these circumstances, early slowing has been reported by Johnson, Guyton and Olsen (1960).

Severe slowing of motor nerve conduction is also present at times in peroneal muscular atrophy (Henriksen, 1956; Gilliat and Thomas, 1957; Christie, 1960). In this condition (Gilliat and Sears, 1958) and in Friedreich's ataxia (Thomas, unpublished results) sensory nerve action potentials may be unobtainable.

Nerve Conduction with Anterior Horn Cell Disease

Hodes (1949) observed that in surviving motor nerve fibres after acute anterior poliomyelitis some degree of slowing of conduction velocity may be evident. This result was confirmed by Henriksen (1956), although he emphasized that in paralytic limbs especial care must be taken to guard against the effects of cooling. A slight reduction may also be seen in motor neurone disease (Henriksen, 1956). It seems likely that in both these instances the reduction represents the differential loss of faster conducting fibres: the slowing does not exceed the lower limit of the normal range of velocities to a single muscle found by Thomas *et al.* (1959). In both acute anterior poliomyelitis (Hodes, Peacock and Bodian, 1949) and in motor neurone disease (Wohlfart and Swank, 1941) there is anatomical evidence that the larger motor nerve fibres tend to be selectively lost.

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