IMPAIRED REFLEX SENSITIVITY

CAUSE AND EFFECT

A Thesis submitted by

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IMPAIRED REFLEX SENSITIVITY - CAUSE AND EFFECT

When a voluntarily contracting human muscle is stretched its surface reflex electromyographic response has both short-latency (M1) and long-latency (M2) components. The M1 component occurs at a latency compatible with monosynaptic reflex activation. The long-latency component results from stimulation of skin and other subcutaneous receptors.

In the initial experiment, using the first dorsal interosseous muscle (FDI) of the hand, the reflex sensitivity in normal human subjects was studied by comparing the various components of the electromyographic response generated by briefly stretching the voluntarily contracting muscle in subjects of various ages. It was found that age-related changes occur in the reflex response of human subjects. Although it is already known that the reflex response in human muscle slows with age, the result of the experiment showed that the size of that reflex response becomes smaller. The evidence suggests an impaired reflex sensitivity in older people which could be reflected in other motor control systems within the body. A detailed investigation was then undertaken to discover the causes of this change.

Although the reflex response (M1) was found to alter with age the M2 component did not. This would seem to rule out neuromuscular block (NMB). NMB as a cause of the change was investigated and was found not to occur in the paradigm employed in this investigation.

Possible changes in the mechanical properties of muscles and joints were looked for in a series of experiments using an accelerometer. No changes large enough to account for the reflex impairment could be found.

In a further series of experiments the effects of fatigue and the effects of training on the electrical response of the FDI were studied.

In a final series of experiments the changes with age, in the effects of coffee upon blood pressure were investigated.

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SUMMARY AND GENERAL INTRODUCTION

The nervous system, together with the endocrine system, provides the majority of the control functions for the human body. The nervous system comprises the brain and spinal cord (the central nervous system), and the sensory and motor nerve fibres that enter and leave the central nervous system or are completely outside it (the peripheral nervous system). Organisation of this system in human beings is enormously complex involving integration of both its central and peripheral components. There is therefore, the possibility of the existence of a general condition in which the sensitivity of reflex responses is changed. The work described in this thesis is largely concerned with the effects of the ageing process on reflexes and their function in the human. The experimental work in this thesis is primarily about a simple reflex, the stretch or myotatic reflex.

A reflex is an involuntary response to a specific stimulus. When a muscle is stretched, the elongation causes excitation of muscle spindle primary endings. This excitation is conducted to the spinal cord *via* afferent fibres and results in an increased motor discharge which produces reflex contraction of the muscle.

The electrical response of a muscle to stretch has several components representing several distinct groups of action potentials. The initial component, M1, is now generally accepted as being the spinal stretch reflex since its latency is compatible with the monosynaptic activation of alpha motor efferents by group Ia afferents. The second component, M2, has a longer latency and it is likely to be due to activation of skin afferents.

In human subjects, examination of the amplified, rectified and summed electrical records from the first dorsal interosseous muscle of the hand reveals age differences. The stretch reflex, M1, is smaller, and has a higher mechanical threshold in older people, whilst the skin response, M2, is not impaired with age.

Experiments were conducted to investigate the cause of these changes in the reflex response with age. To discover whether the changes lay in the reflex centre or in the muscle receptors, electrical stimulation of the muscle nerve was employed. The ulnar nerve was electrically stimulated at the wrist and the electromyographic response recorded in the biceps muscle. In this way the primary afferents were stimulated just as they would be if the muscle spindles of the FDI were stretched by a prod to the index finger. Stimulating the Ia afferents, as well as producing a reflex response in the FDI electrically, produces a reflex response in the biceps. The theory behind this experiment is that if electrical stimulation produces changes in the M1 component with increasing age, in the same way that the mechanical stimulation of the muscle spindles had done, it would indicate that the change does not lie in the muscle receptors. Alternatively, if the M1 component in the biceps muscle showed no alteration with increasing age the result would lend support to the idea that the changes with age were occurring peripherally.

Possible changes in the mechanical properties of muscles and joints were looked for in a series of experiments using an accelerometer. No changes in the mechanical response associated with age that were large enough to account for the reflex impairment could be found.

Nerve conduction was also studied and appears to play no part in the change observed with age.

In experiments where the muscle was fatigued by a strong voluntary contraction, the stretch reflex was abolished for up to one minute; this impairment did not appear to depend upon the age of the subject. Neuromuscular block as a cause of the change was investigated and was found not to occur in the paradigm employed in this investigation. However, neuromuscular block was found to occur in single muscle fibres in the one

minute immediately following a strong fatiguing contraction. The block lasted for up to one minute.

It is possible that the effects of age on reflexes (described above) could be due to a negative "training-effect" (disuse atrophy). In other words old people use their muscles less and in consequence the reflex size is diminished.

Accordingly in another series of experiments, the effect of training on the electrical response of the FDI was looked at. Statistically significant changes occurred in the M1 and M2 components of the stretch reflex; both increased in amplitude during the training period.

The evidence suggests an impaired reflex sensitivity in older people which is progressive. If other control systems in the body show a similar impairment with age, various disease processes such as essential hypertension, hypothermia and respiratory failure could stem from the abnormality.

Several reflex adjustments are known to make physiological compensations in the circulatory system when caffeine is administered. If the foregoing assumptions about reflex impairment have any validity, it might be predicted that the response to ingestion of caffeine (in the form of coffee or tea) would be abnormal in older subjects. Therefore, the effects of coffee on blood pressure were compared in young and old subjects. In a significant number of the older subjects, coffee caused a highly significant rise in blood pressure which lasted for several hours after the intake of caffeine.

HISTORICAL INTRODUCTION

The functional activity of muscle was one of the earliest branches of physiology to be investigated. Aristotle, who lived in 384-322 B.C., incorporated in his writings the beliefs of the Greeks concerning the functions of the body. It is clear that the ancients, especially Aristotle, took shortening for granted and considered the geometrical relations of muscles and joints. But it was Galen (131-201 A.D.), a young Asiatic Greek who settled in Rome, who is considered to be the founder of experimental physiology. In the history of biology he was the first to look to experiment for an answer to questions confronting him. He put forward the theory, which gave expression to ideas then current, that the nervous system controlled muscle through the passage of fluid ("animal spirits") down the nerve trunks.

The work and writings of the philosopher Rene Descartes (1596-1650), show that he dimly grasped the concept of reflex action - but did not recognise the significance of his ideas - as the following extract from his writings shows:

> "The animal spirits resemble a very subtle fluid, or rather a very pure and lively flame, and are continually generated by the heart, and ascend to the brain as a sort of reservoir. Hence they pass into the nerves and are distributed to the muscles, causing contraction, or relaxation, according to their quantity.
>
> In proportion as the animal spirits enter the cavities of the brain, they pass thence into the pores of its substance, and from these pores into the nerves; where according as they enter, or even only tend to enter, more or less, into this or that nerve, they have the power of changing the shape of the muscles into which the nerves are inserted and by this means making all the limbs move."

However, Descartes concept of reflex action was an assumption unaccompanied by any experimental justification. Throughout the middle ages and in the seventeenth and eighteenth centuries the theory of animal spirits formed the basis of all experimentation. There were, of course, those who opposed this theory, Francis Glisson (1597-1677) being the first. As a result of his experiments he reasoned that animal spirits could not be the immediate cause of movement since the volume occupied by muscle during contraction did not increase but actually seemed to diminish. No one heeded his experiments (Fulton, 1930).

The concept of reflex action formed the beginning of the modern interpretation. Some of the first experiments were made in about 1730 by Hales & Stuart who found that decapitated frogs lost the flexion reflex if the spinal cord was destroyed, a result which strongly suggested that the nervous pathway ran via the spinal cord. But it was Robert Whytt (1714-1766), a neurologist from Edinburgh, in his remarkable book, "An essay on the vital and other involuntary motions of animals", who, with adequate experimental justification for his conclusions, established that the spinal cord is essential for reflex action and described the pupillary response to light - still known as Whytt's reflex. The book indicates that he also grasped fully the mechanism and significance of reflex action.

In 1791 Aloysio L. Galvani (1737-1798) presented his theory of animal electricity and the idea of animal spirits gradually lost favour in scientific circles. The classical "nerve fluid" was, in fact, none other than electricity.

The work of Georgius Prochaska (1749-1820), an anatomist of Vienna, attempted a more precise allocation of the elements of a reflex to known structures in the nervous system. In the 1780's he introduced the concept of a "sensorium commune" - that region of the central nervous system which

"reflects" to the motor nerves the sensory impressions received by the brain. He made no suggestion in his writings of sensory or motor roots, but sensory and motor fibres are implicit. He had generated the concept but had no significant experimental data.

Back in Edinburgh in the School of Anatomy, Alexander Walker (1779-1852) deserves the credit for having insisted, prior to Bell and Magendie, on the separate functions of the posterior and anterior roots of spinal nerves. But, having based his conclusions purely on anatomy, he thought that posterior roots were concerned with motor functions and anterior roots sensory. He published a paper in 1809.

The chief credit for elucidating the function of the posterior as well as anterior roots belongs to François Magendie (1783-1855), a pioneer experimental physiologist in France. He began a new era in physiology. He established the fact that the functions of the anterior spinal roots subserved motion, and the posterior belong to sensation.

Sir Charles Bell (1774-1842) was yet another anatomist from Edinburgh. His claim to the discovery of the functions of the anterior and posterior roots of the spinal cord have been the subject of prolonged controversy. Privately he printed a paper in 1811. From studying this it is clear that Bell's claim rests on his having demonstrated the motor functions of the posterior roots; he did prove incontestably that the function of nerves differ. In 1821 the concept was published. The paper was reprinted several times - Bell changed the original text several times after Magendie's discovery but kept the 1821 date.

It was Herbert Mayo (1796-1852), a physiologist at the Middlesex Hospital in London, who took the next step after Bell and Magendie towards clarifying the problem of reflex action. In 1822, in the first part of his Anatomical and Physiological commentaries, he described the function of the nerves of the face, ascribing motor power to what is termed the VIIth and

common sensibility to the Vth. This started an unfortunate controversy with Bell who claimed, as in the controversy with Magendie, that he had made the discovery and had presented it in the 1821 paper. But he had not.

Marshall-Hall (1790-1857), a neurologist, read a paper to the Royal Society in 1833. In it he introduced the concept that the spinal cord is a chain of segments whose functional units are separate **reflex arcs**, and although he had had several other papers printed shortly before this, he was denounced in this country as a propagator of absurd and idle theories, despite the enthusiastic reception of this work abroad.

In any study of the history of reflexes there are other major advances in the understanding of nervous tissue which should be mentioned. So far nothing has been said about transmision of excitation. Modern understanding of the nerve impulse began with Hermann von Helmholtz (1821-1894). In 1850 he demonstrated that the influence, whatever it was, that passed down the nerve from the point of stimulation to the muscle and made it contract, travelled at a definite velocity which he measured. About the same time Emil Du Bois-Reymond (1818-1896) and others were investigating the electrical phenomena of nerve and muscle which led eventually to the electrical theory of nerve conduction - the **resting potential** and the **action potential**. A little later in 1871 Henry Pickering Bowditch (1840-1911) published his paper in which the **"all or none"** principle of contraction of cardiac muscle was for the first time enunciated.

Sir Charles Scott Sherrington - Waynflete Professor of Physiology at Oxford - began the modern analysis of reflex physiology in the late nineteenth century (Sherrington, 1906). He developed an experimental preparation using cats whose brain stems had been transected surgically at the level of the midbrain between the superior and inferior colliculi. Later, in examining the reflexes in the hind limb of a decerebrate cat Sherrington, in collaboration with

Edward Liddell, found that when they attempted to force the rigidly extended limb passively into a flexed position, the limb resisted the force by active muscular contraction. They called this the **stretch reflex** or **myotatic reflex**. This was in 1924 (Liddell & Sherrington, 1924). By 1925 Sherrington and Liddell had carefully characterized the stretch reflex in the knee extensor (quadriceps) and had concluded that the stretch reflex enhances the springlike properties of muscle and offers a graded resistance to change in length (Sherrington, 1931). Stretch reflexes are seen in both flexor and extensor muscles, but they are most highly developed in the latter. It is the change in length of the muscle that excites the stretch reflex and not the change in tension.

About this time the vacuum tube entered physiology and with it the possibility of amplifying small electrical events without distortion and delay. The principle of valve amplification and the use of an inertialess recording system (cathode ray oscillograph) was introduced by Herbert S. Gasser & Joseph Erlanger in 1922. Erlanger and Gasser together with their co-workers in St. Louis solved the problem of conduction velocity; conduction velocity was found to be proportional to fibre diameter. In investigating the properties of nerve fibres in the 1920's, Erlanger and Gasser were the first to look at the different sizes of fibre. They categorized the myelinated fibres of peripheral nerve, calling them the A group. The A group of fibres was subdivided into alpha, beta, gamma and delta fibres according to diameter. They also allocated function to the various waves in their action current records.

The discovery of the stretch reflex, when correctly conceptualised by Sherrington, has served as a firm stepping stone in experimental neurophysiology for the rest of the twentieth century. Nonetheless there is some evidence that Sherrington himself thought that his measurement, charting and analysis of **spinal inhibition**, and the innate pattern of **reciprocal**

innervation were the most important results that he ever obtained. The principle of reciprocal innervation means in the first instance merely that such a mechanism exists; it had, in fact, been observed before Sherrington made something out of it by systematic analysis. Sherrington investigated the conditions under which the mechanism is operative, to what extent it can be overridden by central control, and whether it is symmetrical with respect to flexors and extensors. Sherrington's results on inhibition were briefly summarized by him in 1932:

> "Inhibition like excitation can be induced in a 'resting' centre. The only test we have for inhibition is excitation. Existence of an excited state is not a prerequisite for the production of inhibition; inhibition can exist apart from excitation no less than, when called forth against an excitation already in progress, it can suppress or moderate it. The centripetal volley which excites a 'centre' finds, if preceded by an inhibitory volley, the centre so treated is already irresponsive or partly so."

It was Sherrington who, round the turn of the century, found out where the afferents came from that gave typical reflex patterns. A reflex, after all had to begin somewhere peripherally in a sense organ. Back in 1865, Kuhne had discovered **muscle spindles** and had speculated that they were some form of contractile element in skeletal muscle,but it was Sherrington who proved that the mammalian muscle spindle was a sense organ, and in the same experiments he also showed that the Golgi tendon organs were sensory endings.

For Sherrington it was essential to know how cells were interconnected and intuitively he headed straight for the contact or neurone theory since there was one good argument in favour of this notion: Waller's fine discovery (Wallerian degeneration) which had shown that degenerations generally stopped short of the next neurone. It was the work of Ramon y Cajal (1852-1934) that

ultimately provided him with the facts that he needed. In 1949 Sherrington wrote of Cajal:

> "He solved at a stroke the great question of the direction of the nerve-currents in their travel through brain and spinal cord. He showed, for instance, that each nerve-path is always a line of one-way traffic only, and that the direction of that traffic is at all times irreversibly the same.....The nerve-circuits are valved, he said, and was able to point out where the valves lie, namely, where one nerve cell meets the next one."

With the discovery of the actual contact points by Hans Held & Leopold Auerbach (the second) - Held published his work in 1897 - Sherrington incorporated the end-feet, or **bouton terminaux**, in his ideas. In fact, in that very year (1897) and still unaware of Held's work, Sherrington, contributing to the new edition of Foster's textbook, had written:

> "So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell-body on which it impinges. Such a special connexion of one nerve cell with another might be called a synapsis."

Today Sherrington's "synapsis" is, of course, the synaptic knob or synapse from the Greek word meaning contact.

By the early twentieth century it was definitely understood that the nervous message was likely to be an action-current travelling along the nerve at a finite velocity and setting up some intermediate process when it arrived via afferent fibres through dorsal roots into the spinal cord. On the ventral or efferent side it would again resume the character of an action-current and travel out to effector organs or muscles.

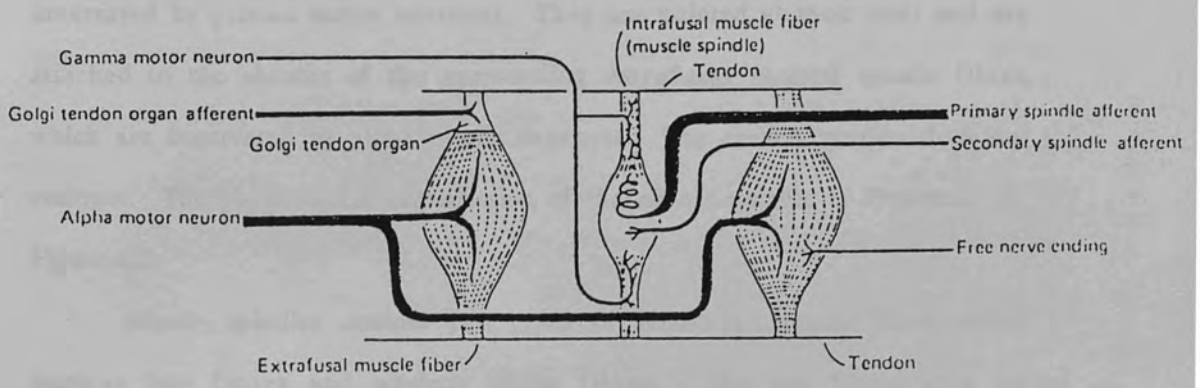
THE MOTOR UNIT AND MOTOR CONTROL

At this stage it is necessary to introduce some terms commonly used in this field. Muscles and joints contain a variety of receptors. Among these different receptors, two have been most thoroughly studied and have important and specific actions on motor neurones. These are the **muscle spindles** and the **Golgi tendon organs**. Although both of these receptors discharge when the muscle is stretched, differences in their anatomical arrangement within the muscle are reflected in differences in the information they convey to the central nervous system. Muscle spindles, because they are arranged in parallel with the muscle fibres, provide information about the length of the muscle. Golgi tendon organs because they are arranged in series with the muscle fibres, inform the nervous system of the tension exerted by the muscle on its tendinous insertion to the bone (Figure 1.1).

Muscle spindles

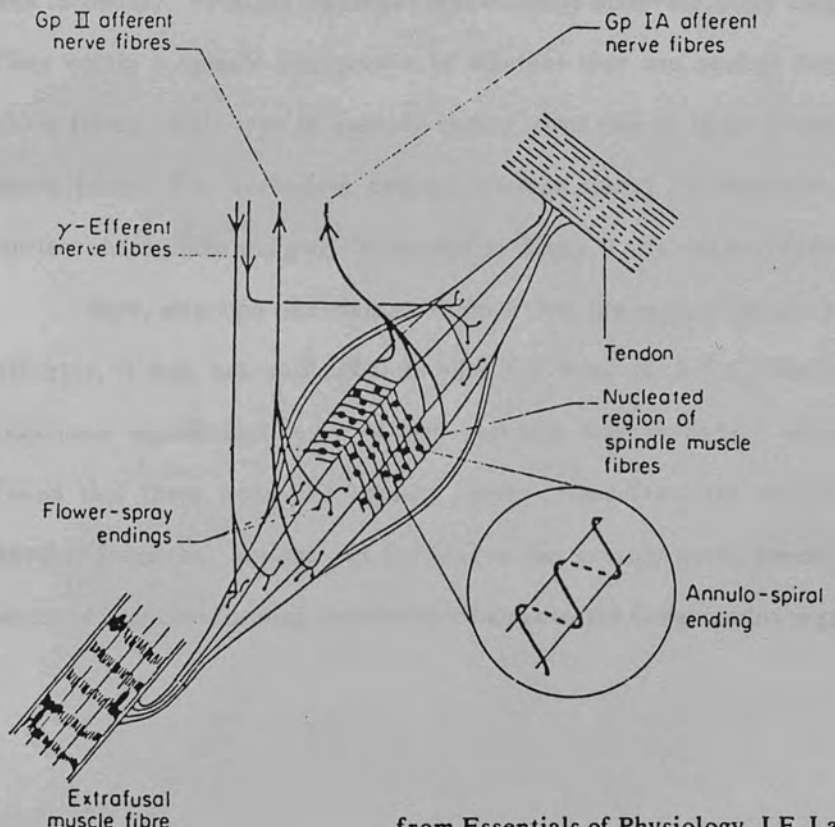
Mammalian muscle spindles are receptors that are distributed throughout the fleshy parts of skeletal muscle. Each spindle, which consists of an encapsulated group of specialized muscle fibres, is tapered at each end and expanded at its centre in a fluid-filled capsule (Matthews, 1972).

FIGURE 1.1 PHYSIOLOGICAL SET-UP OF MUSCLE SPINDLES



from Principles of Neural Science, E.R. Kandel & J.H. Schwartz.

FIGURE 1.2 DETAIL OF MUSCLE SPINDLE



from Essentials of Physiology, J.F. Lamb *et al.*

Within this capsule the muscular elements are entwined by the terminal branches of afferent fibres. The small muscle fibres within the spindle - typically around three to ten in number - are called **intrafusal fibres**; they are innervated by gamma motor neurones. They are pointed at their ends and are attached to the sheaths of the surrounding **extrafusal** skeletal muscle fibres, which are innervated by alpha motor neurones. The central portion does not contract. The physiological organization of the muscle spindle is illustrated in Figure 1.2.

Muscle spindles contain two types of intrafusal muscle fibres called **nuclear bag fibres** and **nuclear chain fibres**. The bag fibres have nuclei clustered in twos or threes; the chain fibres have nuclei in single file and are shorter and more slender than the bag fibres. The bag and chain fibres also differ in the kind of contraction they exhibit: bag fibres produce slow contractions, whereas chain fibres produce fast (or twitch) contractions.

There are two types of afferent terminals in muscle spindles: primary and secondary. **Primary endings** (annulospiral) innervate every single intrafusal fibre within a spindle irrespective of whether they are nuclear bag or nuclear chain fibres. This type of sensory ending gives rise to large Group Ia afferent nerve fibres. The secondary endings (flower spray) lie almost exclusively on nuclear chain fibres and give rise to smaller Group II afferent nerve fibres.

Now, although Sherrington showed that the muscle spindle was a sensory receptor, it was not until 1930-33 with the work of B.H.C. Matthews, that its functional significance as a stretch receptor was realised. Matthews (1933) found that there were two sensory routes. One from the muscle spindle and another from the tendon. In the tendon the sensory nerve breaks down into a series of branches forming the structure known as the Golgi tendon organ.

Golgi tendon organ

The Golgi tendon organ is a slender capsule approximately 1mm long and O.1mm in diameter. Each organ is in series with about 15-20 extrafusal skeletal muscle fibres that enter the capsule through a tight-fitting, funnel-like collar. The muscle fibres terminate in musculo-tendinous junctions after entering the capsule and give rise to collagen fibre bundles that become braided and run the length of the capsule. An afferent fibre enters the capsule in the middle and branches many times becoming twisted within the collagen fibre bundles. They respond to a rise of tension whether this is due to contraction of the muscle fibres or to externally applied stretch.

B.H.C. Matthews, in the classic series of experiments at Cambridge University in 1933, first analyzed the relationship between muscle spindles and Golgi tendon organs. His results showed that passive stretching of the muscle distorts and thereby activates both the tendon organ and the muscle spindle receptors. Contraction further stretches the tendon organ. However, active contraction of the extrafusal muscle fibres makes the intrafusal fibres go slack, unloading the spindle so that it is no longer stretched. The discharge of tendon organs is increased and the discharge of spindle organs is decreased during muscle contraction (Matthews, P.B.C., 1972).

Reciprocal innervation

The work on reflexes led Liddell & Sherrington (1924) to the discovery of a key principle of reflex organization: reciprocal innervation. It revealed to Sherrington the large part played by inhibitory processes in the nervous system and that it was a common feature of movement. The principle, stated very simply, was that when a limb moves, the muscles in it that would oppose the movement are caused to relax. This can be seen clearly in the flexion reflex elicited in the leg of a decerebrate cat. The rigid extensor muscles of the knee

immediately relax; this occurs even if the flexors of the knee are detached from their insertion so that the knee is not moved, or even if the motor nerves to the flexors are cut so that they do not contract at all (Lippold & Winton, 1979).

The inhibition is produced by the activation of interneurones which inhibit the antagonist motoneurones. This inhibition of antagonist motor neurones facilitates shortening of synergistic muscles during the stretch reflex.

In addition to being present at the muscles of a joint this inhibition also arises between the two halves of the spinal cord. With reciprocal inhibition, an incoming nociceptive stimulus can excite flexor motor neurones and, while inhibiting the ipsilateral neurones of the antagonistic muscles, also can excite the contralateral motor neurones of extensor muscles (crossed extensor reflex).

The mechanism of reciprocal innervation appears to be in the spinal grey matter. Movements elicited by electrical stimulation of the motor cortex also exhibit reciprocal innervation (Gottlieb, Myklebust, Penn & Agarwal, 1982). They gave their support to the expansion of the traditional concept of spinal reciprocal innervation to include both inhibitory and excitatory connections. Other workers have, in recent years, continued to expand our knowledge of this mechanism not only in animals but also in humans.

Tanaka (1980) and Kagamihara & Tanaka (1985) showed that the excitability of the Ia inhibitory pathway from the ankle flexors to the extensors was directly proportional to the voluntary dorsiflexion of the foot. In 1981 and 1984 Day, Marsden, Obeso & Rothwell illustrated the peripheral and central components of the reciprocal inhibition between the extensor and flexor muscles in the human forearm.

In 1984 Day *et al.*, presented work which indicated that there was a decline in transmission in the inhibitory pathway from the extensor muscle Group I afferents as voluntary flexor activity increased. Also in 1984, Shindo *et al.*, showed that there is a close parallelism between the excitability of

agonist motor neurones and the exicitability of the Ia inhibitory pathway to the antagonist.

Although the majority of the inhibition arises from excitation of Ia inhibitory interneurones in the spinal cord, there is modulation of interneuronal activity from supraspinal centres and peripheral input from agonist muscle spindle Ia afferents. Supraspinal command can excite agonist muscles whilst inhibiting their antagonists centrally *via* the Ia inhibitory interneurone. In 1985, Wetts, Kalaska & Smith and a separate paper by Smith in the same year proposed that the supraspinal control of reciprocal inhibition comprises a contribution from the cerebellum, which could exert an important function in switching excitation and inhibition between antagonist muscles.

It is important to note, however, that not all types of muscular action employ reciprocal innervation. It is very clear that flexors and extensors can readily be made to contract together by voluntary effort, and the same thing occurs automatically to fix the joints in standing. In this instance the limbs are stationary; there is reciprocal innervation only when movement occurs.

Renshaw inhibition

Another important inhibitory spinal interneurone is the Renshaw cell, named after its discoverer, Birdsey Renshaw. In 1941 he found that an antidromic volley excites a burst of action potentials of extremely high frequency, up to 1500 per second, in interneurones - now known as Renshaw cells - lying in the ventral horn of grey matter.

This neurone receives direct excitation from collateral branches of spinal motor neurones, and in turn inhibits many motor neurones, including the one that gave rise to its input. This process is called **recurrent inhibition**. It is believed that normal, orthdromic, discharge of motor neurones activates the Renshaw cells via the axon collaterals in just the same way as do antidromic

impulses. Renshaw inhibition can be thought of as a local negative feedback loop onto synergistic motor neurones. It tends to curtail the motor output from a particular collection of motor neurones called the motor pool. It may also highlight the output of motor neurones that are strongly activated, because those motor neurones exert strong feedback inhibition to other neighbouring motor neurones, suppressing their output. Although the strongly activated motor neurones themselves also receive recurrent inhibition, their output, though diminished, can still be expressed because they are highly activated. This shows that the motor system utilizes the principle of lateral inhibition to focus, or sharpen, its signals. The Renshaw cell can limit the duration and magnitude of a Ia afferent-mediated reflex response, since Ia afferent activation of a homonymous motor neurone will in turn produce Renshaw inhibition of that motor neurone and, at the same time, disinhibition of the antagonist motor neurone by inhibiting the Ia inhibitory interneurone. It is widely accepted that Renshaw inhibition is part of the mechanism ensuring that motor neurone firing is asynchronous (Hammond, Merton & Sutton, 1956).

Although recurrent inhibition via Renshaw cells is widespread, it is not universal. In cats, the discharge from the recurrent collaterals of the larger phasic motor neurones (those recruited last) to the gastrocnemius-soleus muscle has been proposed as the major source of excitation of Renshaw cells (Wand & Pompeiano 1979). And Datta & Stephens in 1980 found that human FDI motor neurones innervating fast twitch muscle units (those ordinarily recruited only in the largest reflex responses) directed more recurrent axon collaterals towards the Renshaw cell area than motor neurones innervating slow twitch units (recruited first).

In 1980 Ellaway & Murphy wrote that Renshaw cells, in addition to mediating recurrent inhibition from motor neurone axon collaterals to alpha

motor neurones and Ia inhibitory interneurones, mediated recurrent inhibition to other Renshaw cells and gamma motor neurones to muscle spindles.

Presynaptic inhibition

In 1981 Iles & Roberts found vibration of the Achilles tendon or belly of the soleus in normal subjects depressed soleus monosynaptic reflexes. Back in 1973 Delwaide said that this effect is usually attributed to presynaptic inhibition of Ia afferents by those afferents activated by vibration. He also found that presynaptic inhibition of soleus reflexes is reduced in some subjects with spasticity. This was also found by Iles & Roberts, 1983.

In 1984 Morin, Pierrot-Deseilligny & Hultborn attributed inhibition of soleus Ia fibres to vibration of the tendon of tibialis anterior. Iles & Roberts (1983) suggested that there may be separate pathways in the spinal cord controlling the level of inhibition and its modulation during movement. They proposed a type of inhibition which acts upstream of the motor neurone by reducing the amount of transmitter released from the excitory synaptic ending by each impulse.

In this type of inhibition, terminals of the inhibitory neurone form synaptic connections on to presynaptic terminals of other neurones. This type of inhibition is more selective than postsynaptic inhibition which is produced by a membrane hyperpolarization. The result is to reduce the effectiveness of all excitory synaptic input to that neurone.

In presynaptic inhibition, the effectiveness of a given presynaptic neurone can be reduced while leaving other inputs unaffected. Similarly, presynaptic inhibition could act selectively at certain terminals of a particular presynaptic neurone.

The time sequence needed for this type of inhibition differs from that of postsynaptic inhibition. Although it requires many milliseconds to develop,

once it does occur, it can last for as long as half a second or perhaps even longer. Postsynaptic inhibition, at least of the anterior motor neurones, lasts for anything up to 60ms.

Presynaptic inhibition occurs especially at the more peripheral synapses of the sensory pathways. Shortly after a strong sensory signal enters the sensory pathways, negative feedback automatically causes increasing presynaptic inhibition. This, in turn, reduces the degree of transmission of the sensory signals. Therefore, the greater the intensity of the input signal, the greater also becomes the negative feedback inhibition. In this way presynaptic inhibition acts as a sensitivity control on the sensory input. It also sharpens the boundaries between stimulated and non stimulated areas of the sensory pathway because it prevents excessive spread of the sensory signals to the unexcited neurones - a process called "contrast enhancement".

A REVIEW OF EMG COMPONENTS M1 AND M2

From studies of reflex organization a great deal of knowledge has been gained about human motor control. The stretch reflex in particular has been the subject of continuing study, probably because of the ease with which muscles can be stretched and their activity recorded.

A rapid stretch of a voluntarily contracting human muscle results in a reflex contraction which evokes an increase in electromyographic (EMG) activity. Hammond (1955) was the first to study the stretch reflex in intact human muscles. While his subject maintained a voluntary flexion effort, he recorded the involuntary activity in biceps following a sudden stretch of the muscle; he found the EMG records had a diphasic wave which occurred about 18ms after the stretch, a delay which accorded well with the time required for transmission round the reflex arc. Following this wave there was a 'silent period' (Merton, 1951) which was interrupted abruptly if the subject was instructed to 'let go' when the muscle was stretched. During the next few years further work (Hammond, 1956; Hammond, Merton & Sutton, 1956 and Hammond, 1960) expanded upon the first paper and their findings confirmed that the sudden stretch of upper limb muscles in humans resulted in two distinct periods of increased EMG activity that occurred at a short- and long-latency relative to the onset of muscle stretch.

It is now well established that the electromyographic response to the sudden stretch of a voluntarily contracting muscle in a human subject usually has two reflex components: one which has a latency consistent with it being the segmental, monosynaptic tendon jerk (M1) and a later, commonly larger, one (M2) occurring at a longer latency. (Hammond, 1956, 1960; Melvill Jones & Watt, 1971; Tatton, Forner, Gerstein, Chambers & Liu, 1975; Allum, 1975; Evarts & Granit, 1976; Marsden, Merton & Morton, 1976b, 1977b; Iles, 1977 and Evarts & Vaughn, 1978).

It is generally thought that the short-latency component (M1) of the stretch reflex response is mediated by a spinal pathway since its latency is compatible with monosynaptic activation of fast afferents (Magladery *et al.*, 1951).

But what is the physiological basis of the long-latency (M2) component? This is proving difficult to establish, and has given rise to several hypotheses:

1. TRANSCORTICAL
2. RESONANCE
3 SPINDLE SECONDARY AFFERENT
4. LARGE CUTANEOUS AFFERENT

More detailed evidence for each hypothesis will now be given in individually headed sections, followed by a general discussion of the current position, based on these findings.

1. TRANSCORTICAL LOOP HYPOTHESIS

Hammond (1956, 1960) was the first to draw attention to the ability of normal subjects to enhance or suppress the longer latency response (M2) according to their preformed intention to 'resist' or 'let go' upon presentation of an unexpected stretch. This ability has now been demonstrated in several different human muscles, and in different experimental situations (Newsom Davies & Sears, 1970; Evarts & Granit, 1976; Iles, 1977 and Evarts & Vaughn 1978).

Now, as Hammond *et al.*, (1956) had shown that the long latency response could be largely negated by a voluntary intention not to oppose the impending stretch, it was thought possible that if impulses could be relayed to the cerebellum and/or Deiter's nucleus (Eccles, 1966) it might account for this capability of modifying the stretch reflex response according to circumstances. In 1971 Melvill Jones & Watt using the human gastrocnemius, like Hammond *et al.*, in 1956, also concluded that the late response, like the early one, was a reflex response since its latency was shorter - by about 25% - than the fastest voluntary response.

It was Eccles, in 1966, who interpreted the findings of other earlier workers as demonstrating the presence of a 'long-loop' reflex. He suggested that this loop originated in group Ia muscle afferents; that it travelled up to the cerebellum and back down the spinal cord, exciting or inhibiting motor neurones bilaterally at all levels. His proposal was supported by Yap (1967), Taborikova & Sax (1969) and Starr *et al.*, (1981).

Phillips (1969) was the first to point out the possibility of a transcortical stretch reflex loop via pyramidal tract neurones (PTN) by way of group Ia fibres, in his experiments with baboons as this extract from his 1968 Ferrier Lecture indicates:

> "It remains to consider the possibility that in the case of the primate's hand this segmental circuit...has been overlaid in the course of evolution by a transcortical circuit....".

Indeed, he found that both group Ia and II muscle afferents were capable of activating PTN's after some 20ms (Phillips *et al.*, 1971; Wiesendanger, 1973 and Lucier *et al.*, 1975). This is in agreement with the observation that, by applying sudden displacements to a handle which a monkey had learned to hold in a given position (Evarts, 1973), or to move from target to target (Conrad *et al.*, 1975), precentral cortical neurones (some identified as PT cells) could be found discharging at a minimum latency of 20-40ms. In 1973 Evarts suggested that these PT cells may play a role in mediating the EMG activity which began at 30-40ms in the stretched muscles.

Supporting Evarts' work, Marsden *et al.*, (1973 and 1976a) on their own calculations - based on the conduction of afferent information from the hand to the cortex, as indicated by somatosensory evoked potentials, and from the cortex back to the forearm muscles, as taken from the results of direct cortical stimulation in man - thought that there did appear to be time for a supraspinal response (Marsden *et al.*, 1982 and 1983). It should be noted that Marsden *et al.*, in 1972 thought that a transcortical stretch reflex was "very much on the cards" although "jumping ahead of the evidence".

Evidence which suggested the possibility of a transcortical stretch reflex loop with input from both group Ia and group II muscle afferents - and which reinforced Evarts work - came from Rosen & Asanuma, (1972) and from Fetz *et al.*, (1976).

Newsom Davis & Sears (1970) presented another view of the long-latency response. They envisaged, as a result of their experimental work with expiratory intercostal muscles, a process of neural 'evaluation' going on in the

time between presentation of a load and the reflex response to it. Their conclusions were like those described by Hammond and others in which the response recorded could be enhanced or reduced according to the instruction given to the subject prior to the loading. The long latency of the reflex was seen as a delay permitting central evaluation of the load and resulting in a reflex response which was appropriate to intent (that is matched to the succeeding voluntary response).

This hypothesis could be taken to suggest that the long latency of the reflex could be modified, in a period shorter than a voluntary reaction time, according to a process of evaluation which commences on presentation of the load; a mechanism which 'conjoined load perception with servo action' (Sears, 1974). If correct, this possibility would significantly blur the distinctions presently recognized between 'voluntary' and 'reflex' actions.

However, Colebatch *et al.*, (1979) did not give their support to this idea. They said that Newsom Davis & Sears (1970) instructed subjects prior to a perturbation that they should 'resist' or 'let go', 'when they perceived the load'. But, they state, that in neither Newsom Davis & Sears' experiments, nor in theirs, was it necessary for the perturbations to be perceived before the long-latency responses could be modified. Colebatch *et al.*, concluded that by pre-setting excitability levels within the long-latency pathway according to instruction and intent, responses to a perturbation could be pre-set, whether or not perception of those perturbations occurs.

Support for this idea came from Tanji & Evarts (1976) and Evarts & Tanji (1974) in their work with monkeys; they revealed instruction-induced changes of neuronal activity during the period intervening between the instruction and the perturbation-triggered movement. Again they had the two dissociable components M1 and M2; changes in the latter being dependent upon prior instruction.

Newsom Davis & Sears (1970) pointed out that the latent period between perturbation and long-latency response allows 'the subsequent phase of reflex action to be matched in sign and intensity to the voluntary movement occurring consequent on perception of the unexpected load' (Sears, 1974).

Colebatch *et al.*, (1979) found no evidence of such matching. They found that in a series of stretches in which simultaneous instructions were given, long-latency reflex responses frequently occurred without subsequent voluntary activity, and marked voluntary activity frequently occurred without prior long-latency reflex responses.

In 1973, Chan & Catchlove put forward evidence for a supra-spinal contribution to the M2 response to sustained stretch. Chan *et al.*, (1979a and 1979b) found, in their experiments with primates, strong evidence that their cortically mediated long-loop pathways probably did originate from muscle afferents (Phillips, 1969 and Wiesendanger, 1973).

Indirect evidence for a transcortical route for M2 is available from studies involving monkeys or human subjects with lesions of structures along the transcortical route. In 1975 Tatton *et al.*, in their work with monkeys, found that unilateral postcentral cortical lesions abolished M2 in the contralateral limb for up to ten months after the lesion while M1 was unaffected. Since, they argued, the mechanisms for control of distal upper limb musculature appear to be very similar in man and higher primates, it should be possible to use the results of primate studies as a basis for investigating the manner in which motor control mechanisms are altered in patients with neurological disorder. And this they did, and found homology in man and monkeys (Tatton *et al.*, 1975). In another paper of the same year (Lee & Tatton, 1975), they put forward the results of an investigation into the responses of a young woman with multiple sclerosis and this provided further evidence for the supraspinal hypothesis (see also Lee, Murphy & Tatton, 1983).

It was in 1972 that Marsden *et al.*, first wondered whether M2 employed a pathway via the sensorimotor cortex and their later work (1976a, 1977a, 1977b) provided a variety of indirect evidence to support this suggestion.

Marsden *et al.*, (1976b) reported that M2 had longer latencies in muscles of the lower limb than in those of the upper limb, and pointed out that this was consistent with the idea that the afferent signal elicited by stretch of the muscle traversed a supraspinal loop before reactivating the muscle. This observation that the latency of M2 increased in muscles located at increasing distances from the brain was backed up by the later work of Chan *et al.*,(1979a and 1979b).

On the other hand, it has been shown that M2 responses similar to those seen in healthy subjects can also be obtained in spinal cats and monkeys (Ghez & Shinoda, 1978 and Tracey, Walmsley & Brinkman, 1980).

In 1978 Hendrie & Lee found that vibration, a potent activator of muscle spindle primary endings, suppressed the M1 response to angular displacements of the wrist in normal subjects, but not the M2 response to the stretch stimulus. They considered this supported the supraspinal theory. A short time later, in 1980, Agarwal & Gottlieb showed that vibration produces similar selective supression of the early component of reflexes in the lower extremity elicited by torque perturbations at the ankle.

The observation that the latency of M2 increased in muscles located at increasing distances from the brain (Chan *et al.*, 1979a, 1979b and Marsden *et al.*, 1976a) is consistent with the idea of a supraspinal loop.

Gottlieb & Agarwal (1979) found that the gain of M2 could be influenced by the nature of the instructions given to the subject, and agreed with earlier workers that supraspinal centers can alter the general level of segmental excitability. Their findings also showed that postural gain was not a factor; only when there was a deliberate contraction was there any significant change.

In their work with Cebus monkeys, Miller & Brooks (1981) concluded that the reflex EMG response to a perturbation could be produced in the primate spinal cord and brainstem with facilitation by the sensorimotor cortex being possible.

More recently, during a variety of different manoeuvres using the human wrist flexors, parallel changes in cortical potentials and in the long-latency stretch reflexes were found (Abbruzzese, Berardelli, Rothwell, Day & Marsden, 1985).

Another group, working with subjects with spinal and central lesions, also provided supporting evidence using the leg muscles, triceps surae and tibialis anterior (Diener *et al.*, 1985).

Also in 1985, Noth, Podoll & Friedemann provided more supporting evidence in their experiments using the first dorsal interosseous and thenar muscles of the human hand.

Providing support for the spinal mediation of the stretch reflex, Angel & Weinrich (1986) found that the subject's preparatory set produced no significant modulation of the reflex response in the FDI which improved the performance of an intended voluntary movement.

2. RESONANCE HYPOTHESIS

According to their studies in man, Hagbarth *et al.*, (1980a; 1980b; 1981 and Eklund *et al.*, 1982a and 1982b), a sudden joint displacement, and other types of brisk muscle perturbations, may give rise to successive peaks of afferent spindle discharges. They suggested that these resulted from mechanical oscillations initiated by the impact (Dominant oscillations were within the 30-50Hz range).

With initial background contraction in the stretched muscles, synchronous volleys of spindle discharges produce, via segmental reflex arcs, modulation of the EMG with the appearance of two or three EMG peaks separated by intervals of 20-30ms. They suggested that the segmented response could be due, at least in part, to rhythmical excitability changes in the motor neurone pool.

They also suggested that the relationship between mechanical oscillations and segmentation of the EMG response was backed up by the fact that variations in the interval between the first and second accelerometer deflexions (in ramp stretch as compared to tendon tap experiments) were accompanied by similar variations in the interval between the M1 and M2 peaks.

To test this hypothesis Darton *et al.*, (1985) , using a brief mechanical stimulus to stretch the FDI, performed two experiments; one in which the finger was free to oscillate after the stimulus and a second where it was not. Their findings showed that no consistent differences in the nature and timing of the M1 and M2 responses resulted from the change in mode of stimulation. If M1 and M2 were due to a damped train of mechanical oscillations within the muscle, fixation as opposed to free oscillation might have been expected to abolish or diminish M2. It did not.

They found that the waveform recorded by the accelerometer could not usually be satisfactorily aligned with the EMG responses - their frequencies were different. Furthermore, they reported that the time intervals between the successive EMG peaks were dissimilar and thought it unlikely that the components M1, M2 and M3 that resulted from muscle stretch were due to oscillation in the muscle.

Nonetheless, since the hypothesis was first put forward by Hagbarth *et al.*, (1980a and 1980b) it has received support from various quarters. The latency measurements in the experiments of Eklund *et al.*, (1982) indicated that the oscillation-induced modulation of the stretch reflex response was mediated by a spinal, probably mono-synaptic pathway.

The observations of Prochazka and Wand (1981) were also in accordance with the hypothesis. In their work with cat calf muscle they reported a grouping of the afferent discharges during the stretch phase, and a tendency for EMG responses to occur at latencies of about 10ms after the onset of each afferent burst. With a lower speed of stretching, the second afferent burst was delayed and a shift in latency was then noted for the second EMG burst; it was also delayed.

3. GROUP II HYPOTHESIS

Matthews & Stein (1969) suggested that the Ia fibres did not provide the sole source of the autogenetic excitation elicited by muscle stretch. By 1973 McGrath & Matthews were testing the hypothesis that the Group II fibres from the secondary endings of the muscle spindle provided an excitatory contribution to the tonic stretch reflex of the decerebrate cat. The findings then, and later, (Matthews, 1983a, 1983b, and 1984) supported such a hypothesis. The essential finding was that in contrast to the effect of stretch, vibration largely failed to elicit the long-latency response. Matthews reasoned that if vibration produced its action by Ia excitation, then the long-latency response to stretch must depend on something else. In addition the latency of M2 was about right if the conduction velocity of the group II afferents was about half that of the Ia afferents. Of course, if the group II hypothesis is correct, there is not sufficient time available for it to have been mediated transcortically. Additional evidence to support this concept was provided by Stanley (1978), who investigated the early and late EMG responses from the intrinsic hand muscles following electrical stimulation of peripheral nerves. He concluded that M2 was mediated by slower conducting afferent pathways than M1, and suggested that Group II afferents might contribute to the M2 response.

However, it should be noted, two communications from Matthews in 1987 (Matthews, 1987a and 1987b) in which he looked at the effects of cooling on long-latency reflex responses in the FDI, concluded that "it may contain components elicited by fast afferent fibres from both muscle and skin".

However, the original Matthews hypothesis has received support from Cody, Goodwin & Richardson (1986 and 1987a) in their stetch and vibration experiments with the human wrist flexor and flexor carpi radialis. They found that during ischaemic conduction block, M1 stretch responses declined more rapidly and to a greater extent than did M2 reponses (see also Jaeger *et al.*,

1982a and 1982b) and upon recovery from the block, M2 returned before M1. The results suggested that the M1 and M2 responses used reflex afferents of different diameters, the large diameter fibres being affected by the block more and sooner than those of smaller diameter. They thought it possible that these smaller diameter afferents were Group II muscle spindle afferents, the slower conduction velocity would, of course, result in the extended latency.

In spastic and normal subjects (Cody *et al.*, 1987b) vibration of flexor carpi radialis failed to elicit M2 despite being maintained for a similar period to stretch (i.e., it would be expected to produce strong Ia afferent discharge). They concluded that the long-latency stretch reflexes of the normal flexor carpi radialis depended upon Group II afferent activity rather than that of Ia afferent activity.

Dietz *et al.*, (1987) recording EMG responses of the leg musculature in man following perturbation of the limb during walking on a treadmill also gave their support for muscle proprioceptive input from Group II afferents.

There has also been support from Berardelli, Sabra & Hallett (1983) in triceps surae and tibialis anterior again in man. They found abnormal long-latency reflexes in Parkinson's disease patients which were not abolished by vibration. Since Brown *et al.*, (1967) had shown that Group II afferent terminals are not sensitive to vibration in the cat, Berardelli *et al.*, considered their finding provided evidence in favour of the Group II hypothesis. Kirkwood & Sears (1975) in cat intercostal and triceps surae muscles, measured the conduction velocity of individual intercostal afferents and showed that the conduction velocity was consistent with Group II afferents monosynaptically exciting alpha motor neurones

The hypothesis that Group II muscle afferents are responsible for M2 is supported by the observation by Lee & Tatton (1982) that a shortening of

stimulus duration from 200ms to an abrupt cessation at 30-40ms causes a decrease in the amplitude of M2 with a preserved M1.

4. LARGE CUTANEOUS AFFERENT HYPOTHESIS

Evidence for the contribution of cutaneous afferents to the long-latency response have come from a variety of experimental paradigms, and include experiments making use of nerve blocks - using local anaesthetics or ischaemia - and the use of electrical stimulation. Cooling experiments have also contributed to the understanding of these cutaneous inputs to reflex responses.

Perhaps the most notable conclusion which can be drawn from the numerous experiments involving nerve blocks is the variability of responses obtained depending upon which muscle had been studied, and in some cases upon the subject.

In 1971 Marsden *et al.*, found that anaesthesia of the thumb could abolish M2 in the human flexor pollicis longus, and that, in addition, M1 was also abolished or greatly reduced. These results were surprising since the anaesthesia should not have affected the muscle spindles in the long flexor. In 1975 Marsden *et al.*, reported that a dissociation of the M2 and M1 components had been made in the hand, and this suggested that signals from the skin of the thumb or possibly joint contributed to stretch reflexes. Anaesthesia of the hand produced by a cuff distal to the muscle had greatly depressed M2 in the long flexor of the thumb, without affecting M1.

However, they found the stretch reflexes for the infraspinatus, pectoralis major and the long flexor of the big toe were unaffected by anaesthesia, and presumed their servo action to be based predominantly on muscle receptors. They did acknowledge that skin or joint receptors were playing an important part, perhaps the key part in the M2 responses in the thumb (Marsden *et al.*, 1975 and 1977a).

In later years, several groups (Marsden, Rothwell & Traub, 1979; Matthews, 1984; Loo & McCloskey, 1985 and Marsden, Merton & Morton, 1985) found no regularly reproducible reduction in M2 in flexor pollicis longus as a

result of anaesthesia. What other evidence is there for a cutaneous afferent input to the stretch response? There have been a number of experiments involving electrical stimulation which provide support for the theory. In 1980 Garnett & Stephens looked at the reflex responses of single motor units in human FDI following cutaneous afferent stimulation, and were impressed by:

> "the powerful reflex effects of quite modest and restricted cutaneous stimuli. For the most responsive first dorsal interosseous motor units,light mechanical taps applied to the nail of the index finger can produce large changes in their pattern of firing, the size of the late excitatory response reaching 2-3 x the control level."

They felt that their results emphasized the important role cutaneous input played in modifying motor outflow during movement, not only by the size of the responses but also that - for a given muscle - they could only be elicited from skin areas, the natural stimulation of which would normally be expected to be associated with movements involving activites in that muscle.

Similar large changes in surface recorded EMG activity were found in human abductor pollicis brevis following mechanical stimulation of the same finger (Caccia *et al.*, 1973). The mechanical stimulus consisted of a series of taps delivered to different regions of the index finger by an observer using a blunt probe.

Garnett & Stephens (1980) felt tempted to suppose that the long-latency EMG effects of both muscle (Buller *et al.*, 1980) and skin were mediated along some common final pathway, since pre-central neurones (including pyramidal tract neurones) receive input from both cutaneous and muscle afferent inputs (Lemon & Porter, 1976a, 1976b and Goldring & Ratcheson, 1972).

Chan *et al.*, (1979a and 1979b) noted that skin and joint afferents must have been activated, and refer to Meier-Ewert *et al.*, (1973) who showed that

cutaneous stimulation had elicited long-loop spino-bulbo-spinal reflexes in man. But the results of their ankle block experiments in man showed that no significant change in response characteristics occurred with blockage of impulses arising from cutaneous and joint receptors in the ankle and foot. Chan (1983) reported that her findings, like those of Marsden *et al.*, 1977a, suggested that any contribution from cutaneous receptors was probably negligible in the initiation of response. The findings could not be generalized to all muscles.

In 1981, Bawa & McKenzie elicited reflexes before and after anaesthetic blocks of palm cutaneous and wrist joint afferents in human subjects. They concluded that the contribution of joint and cutaneous afferents to the longer-latency reflexes in the wrist flexor muscles in humans was not significant. Their reasoning was as follows: cutaneous reaction times to electrical stimulation of the hand via ring electrodes was more than 160ms, and although this decreased to 90ms as the voltage was increased - possibly resulting from excitation of deeper receptors in the hand - they thought that cutaneous afferents could not be responsible for M2. Cody *et al.*, (1986 and 1989) when looking at EMG reflexes in human wrist flexors, concluded that both M1 and M2 components in flexor carpi radialis arise mainly from intramuscular receptors and so supported the view of Bawa & McKenzie.

Working in human thenar muscles, Deuschl, Schenck & Lucking (1985) concluded that long-latency reflexes to electrical stimulation of the motor nerve were most likely to be mixed reflexes of motor and cutaneous afferents. Stimulation of pure cutaneous afferents mechanically or electrically, evoked a long-latency reflex similar to that of M2. The velocity of the cutaneous afferents mediating the long-latency reflex was in the range of group Ia afferents, whose long central delay would also be compatible with a transcortical reflex route.

The same year Darton, Lippold, Shahani & Shahani showed that M2 is generated by the skin and subcutaneous tissue stimulation occurring inevitably in any experiment where muscle receptor activation is produced by limb displacement. Their conclusions are supported primarily by the following evidence:

1. Either one or both of the components M1 and M2 can be elicited according to the siting of the stimulus. This depends on whether or not the mechanical stimulus is effective in stretching the muscle and whether or not the appropriate area of skin is stimulated.

2. If the skin and subcutaneous tissue that is transmitting the mechanical stimulus to the muscle (i.e. the skin beneath the prodder) is rendered anaesthetic, the second component M2 is abolished.

They contended that M2 was abolished in FDI only when the finger was completely anaesthetized, and this was achieved by a combination of arterial block and cooling - either one alone being insufficient.

Recently, further support for the cutaneous hypothesis has come from Matthews (1987b). He looked at the effect of arm cooling on long-latency responses from the human FDI, and it should be made clear that his findings supported the view that both muscular and cutaneous afferents can elicit M2 responses from FDI by way of fast afferent fibres acting with a long central delay. His conclusion is right but his reasoning is wrong. He said that the skin of the finger is supplied by the median nerve. It is not. It is served by the radial nerve (Chapters 6, 7 and 8; Grays Anatomy, Figure 975). In recording F waves from muscles in the thenar eminence, which is indeed supplied by the median nerve, he thought that cooling slowed these fibres by only one third to one quarter as much as ulnar fibres, and presumed that this was because the former lie deeper. He reasoned, therefore, that for comparable-sized afferents, a cutaneous reflex should be slowed less than a muscular reflex and the ulnar-

elicited F wave. In all three subjects such lesser slowing was found for the M2 response elicited by a tap, suggesting that it was was due to a cutaneous reflex.

GENERAL DISCUSSION

So what is the current position?

The idea of a transcortical loop has stimulated many studies and there is much compelling circumstantial evidence to support it. The evidence for the operation of this loop can be summarized as follows:

1. that the neuronal circuitry for this loop exsits,

2. that neurones in the various stages of the transcortical loop respond in the manner and with the timing predicted for this circuit when unexpected perturbations are introduced,

3. that the magnitude of the motor response thought to be the output of this circuit is related to the magnitude of sensory input, and

4. that lesions of various points along the transcortical loop diminish or abolish the motor response presumed to be the output of the loop (Wiesendanger & Miles, 1982).

Taken by themselves, however, the results of lesion experiments do not preclude the possibility that the effect of the lesions is caused by removal of cortical facilitation of a subcortical pathway for M2.

Gottlieb & Agarwal (1979 and 1980) found that the magnitude of each component of the EMG was linearly related to the velocity of stretch, but found that M2 was more labile, showing less consistency of shape than M1.

The dependence on the rate of stretch of M1 is in keeping with the accepted behaviour of the reflex arc, but the longer latency of M2 would permit a more complex array of afferent inputs to participate in its generation. It is possible, therefore, that M2 represents the summed activity of several reflex arcs involving other peripheral receptors (Evarts & Tanji, 1976). Group Ib afferents from Golgi tendon organs and muscle spindle secondaries are two classes of inputs that could be expected to have significant segmental input and also to be influenced by voluntary contractions of their muscles. Tendon organs are well

known to be extremely sensitive to tension changes of actively contracting motor units (Houk & Hennemen, 1967).

M2 responses are evoked by larger torque steps (Vilis & Cooke, 1976) and by higher velocity displacements (Dufresne *et al.*, 1979). Vilis & Cooke also noted that with torque steps of increasing amplitude, the M1 response became saturated before M2, leaving the latter as the only source of motor output related to the magnitude of the sensory input. It is important to emphasize that the segmental reflex response in man undoubtedly continues beyond the time of the monsynaptic peak, which only signals its onset (Houk, 1978). In addition, the size of the stretch reflex electrical response reflects inhibitory as well as excitatory components. Lee & Tatton (1982) reported that the gain of the M2 response also appeared to be very dependent on the duration of the perturbation and on the type of ongoing motor task.

Hagbarth *et al.*, (1980a, 1980b and 1981) have demonstrated with microneurographic techniques that abrupt wrist extensions produce grouped spindle discharges that could account for the grouped EMG responses. Eklund *et al.*, (1982b) showed that as soon as muscle stretch exceeded a critical velocity, damped muscle oscillations and segmentation of the EMG appeared at the same time. From this the authors concluded that late EMG responses to sudden joint displacements "depend to a large extent on the inherent resonance characteristics of musculo-tendinous structures." The mechanical oscillations could be responsible for the previously demonstrated bursts of discharges of primary muscle spindle endings.

The demonstration that cutaneous afferents are involved in generating long-latency responses (Delwaide, 1973 and Darton *et al.*, 1985) provides yet more evidence for the extremely complex nature of these physiological responses.

Chan *et al.*, (1979a and 1979b) and Marsden *et al.*, (1976a) reported that the intervals between the early and late responses were shorter for arm muscles than for leg muscles, and shorter for head muscles than for arm muscles. Eklund *et al.*, (1982a), also found similar variation in the interval between initial and second EMG peaks follwoing tendon taps to calf muscles, wrist flexors and jaw elevators However, they also demonstrated that "similar differences were observed with respect to the intervals between the damped intramuscular oscillations initiated by the impacts." Darton *et al.*, (1985) found there was no such change in the interval between M1 and M2. From this it can be concluded that the impulses cannot have been delayed by traversing long-loop spinal pathways. Crago, Houk & Hasan (1976) and Nicols & Houk (1976) suggested that segmental stretch reflexes subserve a muscle stiffness-regulating system.

But what if Phillips was right when he said:

> "It may well be that the most important function of fusimotor co-activation in the case of the hand is to maintain the inflow of information of muscle length to the cortex and cerebellum".

Time will tell.

From the foregoing discussion, it becomes apparent that the nature of control of the long-latency stretch responses remains a matter of dispute.

THE EFFECTS OF AGE ON THE NERVOUS AND MUSCULAR SYSTEMS

The central nervous system (CNS) plays an essential role in the regulation of adaptive responses to the environment, and changes in its function can have vital repercussions on the ageing of the whole organism, manifested most dramatically in the general "slowing" of motor and sensory function. This involves alterations at several levels of the nervous system. Changes in motor function with advancing age are familiar phenomena; older people experience and exhibit varying degrees of loss of those abilities that require fine coordination and rapid initiation of movement.

It is evident that the efficacy of signals transmitted within the CNS may be disturbed not only by irregularities in the action of the cells carrying the signals but also by the amount of random background activity ("neural noise"); i.e. the signal-to-noise ratio may be impaired either by a reduction in signal strength or by an increase in noise level. Of the several electrophysiological characteristics of the aged CNS, those most likely to affect signal strength and noise level would seem to be, the reduction in number of functional cells, the increase in random activity, the longer after effects of neural activity and the decrease in arousal (Timiras, 1972).

Clinical observations in aged individuals show that many simple reflex phenomena that depend upon intact afferent pathways are decreased or absent. Although historically there seems to have been a considerable difference of opinion in the interpretation of changes in nerve fibres with age, many reports indicate a positive correlation between increasing age and decreasing number of fibres in a pathway or nerve trunk. These include: Cottrell (1940) in human median, femoral sciatic and peroneal nerves; Bruesh & Arey (1942) in human optic nerve; Corbin & Gardner (1937) and Gardner (1940) in human spinal roots and Bergstrom (1973) in human vestibular nerve. Bergstrom found around 35

per cent decreases in fibre number in these structures, and also reported a decrease in the proportion of heavily myelinated nerves in the vestibular nerve.

Several studies have been made of the changes in conduction velocity of human motor nerves throughout the life-span. All have been in agreement that maximal velocity drops by 5 to 10 per cent in aged people (Magladery, 1959). This reduction may be explained in part by one or more of the following factors:

1. localized ischaemia due to vascular changes;

2. metabolic depression associated with changes in permeability and/or other transmembrane transport mechanisms of nerve fibres;

3. selective degeneration and subsequent loss of the fastest-conducting fibres;

4. temperature changes in the nerve fibres and surrounding tissues.

Slowing of motor nerve conduction in association with increased age was first described by Wagman & Leese (1952). However, when measured directly in the sciatic nerve, conduction time was not shown to change with age (Birren & Wall, 1956). Nerve conduction velocities of afferent fibres have not shown any differences among subjects of different ages.

Depression or loss of the ankle reflex is a common finding in the elderly (Critchley, 1931 and Howell, 1949), as is impaired appreciation of vibration sense in the feet (Pearson, 1928). The anatomical location of the lesions responsible for these changes has been suggested (Lascelles & Thomas, 1966) to be in the peripheral nerve, manifested as segmental demyelination and remyelination resulting in irregularities of the internodal length. It is explained that this results in a loss of tendon reflexes and vibration sensitivity since both depend upon the ability of the nerve to conduct a synchronous volley of impulses.

At the segmental level there is convincing evidence of increased synaptic delay with age (Wayner & Emmers, 1958). The increase with age is regular and unbroken, indicating decreased excitability at single synapses rather than conversion to a polysynaptic response. Whether these changes in central delay with age are related to changes inherent in the motor neurones themselves or other neuronal pathways converging on the motor neurone pool is not clear.

Since neuromuscular activity appears capable of strongly influencing neuronal function, it is conceivable that part, at least, of the decline with age in reactivity of the nervous system is secondary to the general physiological decline associated with ageing and lack of use.

The muscular atrophy characteristic of the aged has been related to:

1. disuse;

2. reduction or loss of the trophic function of the nerve cells, mediated by spontaneous quantal release of acetylcholine (ACh) and/or other neurotrophic agents;

3. decrease of hormonal control - as illustrated by the effect of gonadal hypofunction on motor activity and metabolism of muscle.

This marked deterioration of muscle mass which occurs with ageing is characterized by decreases in the size and number of muscle fibres, decreases in the muscles' respiratory capacity, and increases in connective tissue and fat. In addition, it has been suggested that the average number of fibres per motor unit gets larger with advancing age. Ageing results in decreases in isometric and dynamic strength, and speed of movement. There is a loss of fibres from individual motor units - generally held to be due to a loss of the nerve cells that supplied them. This results in less available contractile force when a motor unit is recruited.

The decreased speed of contraction in old age, which is observed before senile muscle wasting becomes manifest (Larsson & Edstrom, 1986), has been

proposed to be secondary either to a loss of fast-twitch motor units or to changes in the properties of the contractile material during ageing, or to both (Campbell *et al.*, 1973). However, in further experiments in 1987, Edstrom & Larsson concluded that the reduced speed of contraction in old age is primarily due to alterations in contractile properties in remaining motor units in both fast- and slow-twitch muscles and that the age-related decrease in the number of type II fibres (rat soleus muscle) is of considerably less importance. Preliminary results also indicated that fibre type proportions were altered prior to the muscle fibre loss and this they thought suggested a transformation of type II muscle fibres to type I followed by an unselected loss of motor units in middle age. This age-related loss of functioning motor units has been supported in man (Campbell *et al.*, 1973) and in the mouse and rat (Caccia *et al.*, 1979).

Additionally, the nature of the motor units changes: there is a selective loss of fast twitch muscle fibres which diminishes available strength and power.

The loss of the muscle's biochemical capacity is characterized by decreases in succinate dehydrogenase, pyruvate and malate dehydrogenase, and cytochrome oxidase. In very old age, there is evidence of the formation of incomplete or inactive enzymes. Decreases in mitochondrial mass may also occur. All of these changes will affect ATP production and thus impair physical working capacity.

The mechanisms involved in muscle contraction are also impaired, which contributes to the loss of strength and power. Ageing muscle is less excitable and has a greater refractory period. Thus a greater stimulus is needed for contraction (i.e., a higher threshold potential is required for the all or nothing response), and a longer period of time is required before the muscle can respond to another stimulus. Myosin-ATPase activity, ATP and CP are also reduced, particularly in fast-twitch muscle, which further impairs muscle function.

The decrease with age in the response to various environmental stimuli may be due partially to impaired excitation of receptor organs, in particular muscle spindles. Swash & Fox (1972) studied the effect of age on the morphology and innervation of the muscle spindles in 22 subjects from birth to 81 years and reported that the mean capsular thickness increased linearly with age with a slight decrease in the mean number of intrafusal fibres in the oldest subject. They also found some changes in the spindles consistent with denervation and changes in the fine structure of the muscle spindle innervation consisting of spherical axonal swellings and expanded abnormal motor end plates (Gutmann & Hanzlikova 1972a, 1972b and 1975).

Age changes in human motor nerve endings in distal muscles were studied by Harriman, Taverner & Wolf (1970). They reported spherical axonic swelling of the longest axons of the motor nerves and elaborate and multiple motor end plates with elevation of terminal innervation ratio to be expressions of ageing in motor end plates.

There is some random degeneration of end plates and changes in muscle similar to those after denervation (e.g., the increase in proteolytic activity and a shift to synthesis of sarcoplasmic proteins) which suggest a neurotrophic disturbance in addition to a decline in nerve impulse activity. Specifically, the muscle end plates show a decrease of synaptic surface and cholinesterase activity, an unfolding and retraction of the postsynaptic membrane and an increase of lysosomal structures, suggesting that the stability of membrane components at the end plate and in other regions of the muscle is disturbed. These changes are associated with a marked reduction of frequency of miniature end-plate potentials to 25 per cent of values observed in young animals, indicating a marked decrease in transmitter release. This might suggest that the atrophy of the senile muscle may combine features both of disuse and of trophic malfunction of the nerve cell. However,

electrophysiological studies have shown that the profound ultrastructural alterations in the neuromuscular junction in old age (Gutmann *et al.*, 1971) do not impair neuromuscular transmission and that they are either not rate-limiting or are well compensated for (Banker, Kelly & Robbins, 1983).

Age changes in motor unit threshold firing rate in the FDI in man have been reported by McDonagh *et al.*, (1987). They found a significant decrease in the threshold firing rate with age, apparently independent of the voluntary force threshold; this is consistent with the longer contraction time found in the FDI in older subjects.

Joint stiffness and loss of flexibility are common in old people; joints become less stable and less mobile with age. Ageing can be associated with degradation of collagen fibres, fibrous synovial membranes, joint surface deterioration and decreased viscosity of synovial fluid.

Collagen - together with elastin and ground substance - is a component of connective tissue. Connective tissue functions in a number of important ways in the body, serving as mechanical support, means of exchange of metabolites between blood and tissues, storage of fuel in its adipose cells, protection against infection and repair of injury. In particular, it is found around the structural elements that constitute organs and tissues.

Collagen

Collagen is a protein, is ubiquitous in the body and undergoes identifiable changes with age. It is a macromolecule deposited in the form of fibres (Figure 1.3). It occurs as almost chemically pure collagen in the tendons, and as interstitial fibrous tissue between muscle fibres. The fibres have great tensile strength and are designed for resistance to elongation at the amino acid level. The two principal amino acids are 5-hydroxylysine, a very short molecule, and 4- hydroxyproline, a five-membered ring with four carbon atoms

and one of nitrogen (Figure 1.3). Together these two amino acids form polypeptides with little or no possibility of rearrangement to permit elongation.

The amino acids are assembled into a polypeptide chain, four of which link together to form a coiled helix with a molecular weight of about 110,000, called an alpha- chain. Three such helices then combine to form a single molecule of tropocollagen, with a molecular weight of about 336,000 consisting of some 3000 amino acids. Tropocollagen molecules are thin structures 260 nm in length and about 1.5 nm wide.

The molecules of tropocollagen polymerize, head to tail, and the resulting threads cross-link with other threads in a characteristic pattern. The heads of the molecules in one thread are displaced by one quarter of the length of the molecule, relative to the neighbouring thread. Collagen fibrils contain variable numbers of such threads but, because of the characteristic linking between threads, all have transverse bands clearly demonstrable by electron microscopy. The bands occur every 64 nm.

Synthesis takes place within a fibroblast up to the formation of alpha-chains; these are secreted in modified form by the cell as procollagen, and are converted to alpha-chains by an enzyme at the cell surface. The formation of soluble tropocollagen from these chains and the polymerization of tropocollagen into collagen fibres occur outside the cell.

Collagen solubility decreases with age and this decrease has been related to increased cross-linking. Cross-linking represents the formation of new bonds between molecules, and is brought about by the presence of reactive groups, either found normally on the macro-molecules or produced by various agents, such as free radicals (formed by ionizing radiation), aldehydes (produced during energy metabolism or lipid peroxidation), peroxides (produced by lipid peroxidation), quinones (present in the electron transport system) and sulphydryl groups (derived from demethylation of methionine) and oxidation

of sulphydryl amino acids. As a result of these changes with age, collagen becomes tougher, more crystalline, its tensile strength is reduced and its plasticizing function is lost.

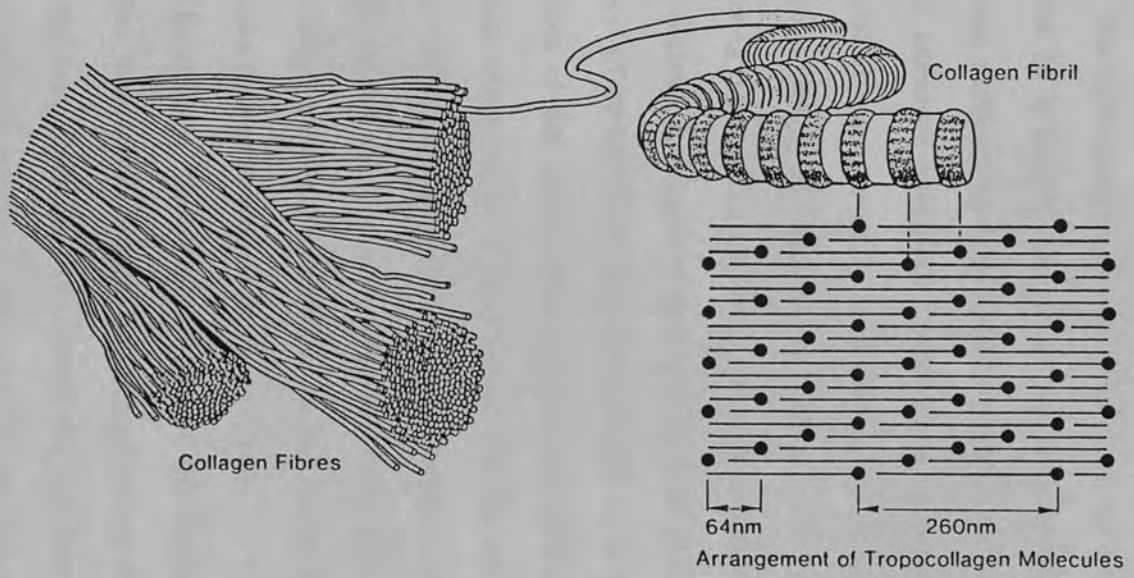
Elastin

Elastic fibres are thin, single and branching. These fibres can be stretched, each fibre extending by up to 50 per cent of its original length. When the stretching force is removed these fibres spring back to their former length. In connective tissue, the collagen and elastic fibres are finely balanced so that the collagen resists forces that would be strong enough to rupture the elastic fibres. One of the changes that occur in the body in old age is a loss of elastic fibres.

Examination of elastin in tissues also reveals changes with age, in that old elastin appears frayed, fragmented, more brittle and more yellow in colour. These changes could be interpreted as signs of wear and tear.

In general there is a significant decrease in the sensitivity of the nervous system and its motor control with advancing age. In this thesis, changes in reflex sensitivity of older people have been investigated using standard electrophysiological techniques. An effort has been made to discover where in the reflex arc such changes are taking place, their cause and their effect.

COLLAGEN



The structure of collagen fibres.

Figure 1.3 Collagen in varying densities can be seen throughout the connective tissues. The fibres have great tensile strength. In sheets of interwoven fibres, collagen forms the tough, white fascia which surrounds muscles. With the fibres all aligned and parallel, collagen makes up ligaments and tendons which have a quite remarkable ability to resist stretching.

from Cells and Tissues, An Introduction to Histology and Cell Biology. A.W. Rogers.

MUSCLE FATIGUE

Muscular fatigue is defined as a failure to maintain the required or expected force. In this brief introduction to the subject, the emphasis will be on the electrophysiological and excitatory aspects of muscular fatigue rather than those concerned with energy metabolism.

The fundamental question would seem to be: Is the force that can be generated by a muscle limited by the capacity of the nervous centres and conducting pathways to deliver motor impulses to the muscle fibres or by the intrinsic contactile properties of the fibres themselves? Does fatigue have a peripheral or central origin? Does tension fall because the degree of voluntary innervation drops or because the fibres are biochemically incapable of maintaining their contraction, or is it the result of both?

Bigland & Lippold (1954) and Merton (1954) showed that a maximal voluntary effort developed the same tension as a maximal tetantic electrical stimulation of the muscle (this maximum occurred at frequencies between 35 and 40/s), and went on to demonstrate that the same equality persisted during fatigue. These results implied that the limitation of strength was peripheral, since the tension dropped while voluntary effort was continuing to activate the muscle fully (electrical stimulation to the motor nerve during a voluntary contraction resulted in no superimposed twitch).

In addition, Merton (1954) showed that fatiguing a muscle to which the blood flow was occluded resulted in the continuation of force loss in the muscle which had been fatigued. The muscle did not recover until the blood supply was restored. This provided further proof that the fatigue was peripheral.

Merton (1954) also concluded that neuromuscular block (NMB) was not important in the fatigue resulting from a maximum voluntary contraction (MVC), since he found, even in extreme fatigue, action potentials evoked by nerve stimulation were not significantly diminished. In these experiments

Merton was recording from several small muscles (because of the electrode positions he used), but was only fatiguing adductor pollicis. His results and conclusions were correct, however, but fortuitously.

Before Merton's paper in 1954 it was generally accepted that the transmission at the motor end plate was the first function to fail during artificial stimulation. Furthermore, this type of fatigue was not thought to be of any importance for the modification of the naturally induced contraction since application of electrical stimuli to the nerve through the skin was said to elicit powerful contractions when the voluntary produced contraction was fatigued. Naess & Storm-Mathisen (1955) agreed with Merton as to the peripheral origin of fatigue during voluntary tetanic contractions, and that it was of the same nature as that during artificial indirect stimulation. Like Merton they thought that the facts seemed to exclude the possibility that changes in the transmission at the motor end plate played any significant role in the fall of tension. Direct stimulation of the muscle did not produce a stronger or more prolonged effect than indirect stimulation (Brown & Burns, 1949) even when the strength of stimulation in the experiments was decidedly supramaximal (Naess & Storm-Mathisen, 1955). In addition they found that it was impossible to produce a stronger or more prolonged tetanic contraction by indirect supramaximal stimulation than by maximal voluntary effort, and that the contraction in man was abolished subsequent to superposition of artificial stimulation during MVC's.

This conclusion does not agree with results reported by Brown & Burns (1949), who demonstrated that a contraction may be restored to normal amplitude during the fall in tension under indirect stimulation by exchanging indirect sitmulation with direct for short periods; i.e. neuromuscular block must exist and the muscle cells cannot be exhausted. However, they also considered that the development of block contributed little or nothing to the decline in

tetanic tension; that complete block was certainly not the dominant phenomenon, and probably never occurred.

Stephens & Taylor (1972), using the FDI, showed that impaired neuromuscular transmission did occur in fatigue in sustained MVC's, (the contractions lasted up to three minutes) particularly in high threshold units since the early part of the contraction force and surface electrical activity fell in proportion. This, they added, was followed later by contractile element fatigue particularly affecting the low threshold units.

The increase in electrical activity of the fatigued muscle, required to maintain the same voluntary tension, is due to a decrease in the contraction strength of the muscle fibres (Edwards & Lippold, 1956). As a contraction continues, more fibres become active. They measured the integrated EMG at various steady contraction strengths and found a linear relation between force and the EMG values. The same test in fatigued muscle yielded a similar result, but with a greater slope of EMG-force relation.

Bigland-Ritchie, Jones & Woods (1979) studied the relation between force in response to electrical stimulation and EMG activity by intermittent nerve stimulation in brief pauses in between periods of direct electrical muscle stimulation. Again a good correspondence between EMG amplitude and force was found.

Using a technique for recording the surface EMG simultaneously with electrical stimulation of human skeletal muscle, Hultman & Sjöholm (1983) showed that there was a good relation between EMG amplitude and force during fatiguing contractions in knee extensors, but reported that during recovery the relation was completely lost. For this reason they considered that EMG measurements alone as an index of fatigue could be very misleading, since a given EMG amplitude could be recorded in a muscle producing quite different force levels. From this they concluded that excitation failure

contributed only partly to the decline in tension, and that the excitation-contraction mechanism or contractile machinery were more likely as fatigue sensitive sites.

In 1983 Bigland-Ritchie *et al.*, used tungsten micro-electrodes to record the electrical acitivty of single muscle fibres in the human adductor pollicis during MVC's. Spike trains of 10-20s duration were obtained, which originated continuously from a single muscle fibre. Now, although the frequency of firing declined smoothly, there was no sudden discontinuity as would have been expected if NMB had occurred. In addition, periodic monitoring of the evoked M-wave showed no sign of neuromuscular block. These authors also noted that not all units appeared to behave in a similar manner; some evidence suggested that those with the highest initial frequencies changed rates most rapidly.

During fatigue produced by a sustained MVC of the biceps brachii muscle, discharge frequency of motor neurones falls, as does the maximum force that can be exerted (Bigland-Ritchie *et al.*, 1986b). They thought this reduction in motor neurone firing rates during fatigue an unlikely cause of the observed loss of force since the force could not be increased by supramaximal electrical stimulation of the ulnar nerve. During a 60s sustained MVC there is a two- to threefold slowing of relaxation rate such that high degrees of tetanic fusion would be maintained despite the observed reduction in mean discharge rate (Bigland-Ritchie *et al.*, 1982a).

In a further experiment using FDI, Bigland-Ritchie *et al.*, (1986b) looked at the effects of 3 minutes' ischaemic rest between a first and second MVC. Recovery with the blood supply intact was 95% complete after 3 minutes rest, but with the blood supply occluded the force and motor neurone firing rates in the second contraction remained depressed (both values were close to those seen at the termination of the initial MVC). Ischaemia did not appear to influence the force generated when brief additional contractions were injected at 1min

intervals during the period of rest when the blood supply was occluded. From this they concluded that if increasing degrees of transmission failure occurred during this time the capacity to generate force should decline continuously, and it had not (see also Bigland-Ritchie *et al.*, 1986a).

NEUROMUSCULAR BLOCK

Block of conduction has been found in both invertebrate (Castel *et al.*, 1976; Grossman *et al.*, 1973 and Van Essen, 1973) and vertebrate preparations (Farel & Thompson, 1976 and Krnjević & Miledi, 1959). Very often, it was found that block occurred at sites of **axonal bifurcation**, and sometimes occurred differentially; i.e. only one branch of the bifurcation would block.

Sodium channel density, which is lower in the parent branch than in the daughters, will result in a low safety factor, but will not give rise to differential conduction. But a difference in the membrane channel density between daughters could give rise to differential conduction, since the membrane with the higher channel density will be "leakier" even at rest. As a result, a greater current will be necessary to bring this membrane to threshold, and when the safety factor is low it will be the first branch to fail. The term **low safety factor** is used in conditions under which there is an increased probability of failure of an action potential to propagate.

Some unbranched axons have regions of low safety factor which affect the firing rate. These regions are constrictions in axon diameter (Castel *et al.*, 1976 and Smith, 1980a and 1980b), or regions of dense connective tissue (Smith & Hatt, 1976), which restrict the extracellular space.

Grossman & Gutnick (1981) working on the giant axon of the cockroach found the accumulation of extracellular potassium was linked to block of conduction. Whether this mechanism is at work in branched axons in which differential conduction occurs is uncertain. However, in this connection, Krnjević & Miledi (1959) found presynaptic block *in vitro* was not at all sensitive to substantial variations of potassium, calcium or hydrogen ion concentrations in their experiments with rats; the nerve fibres were protected from changes in their environment by the low permeability of their perineural sheaths (Krnjevic, 1954).

Interestingly, recent work by Stockbridge & Stockbridge (1988) and Stockbridge (1988), working with the squid giant axon, showed (under artificial conditions which favoured conduction block at a bifurcation) differential conduction resulting from differences in electrotonic length (with membrane properties uniform). The effect of a short electrotonic length on a daughter branch is to increase membrane current density , resulting in a lower threshold.

Krnjević & Miledi (1958 and 1959), in their work with rats, concluded that presynaptic block, commonly associated with intermittent firing, is probably caused by **anoxic changes** in the intramuscular portion of the motor nerve. They presented evidence which showed that when the muscle contraction is abolished or kept to a minimum by curare or excess magnesium (15mM), anoxia does not develop readily and then conduction block is only seen after prolonged high-frequency stimulation (100/s or more for several minutes). Their work suggested, that at frequencies of stimulation of less than 19 per second, random fluctuations of fibre threshold and/or spike height in the region of block are responsible for the observed intermittent conduction of impulses; at higher frequencies the part played by post-spike subnormality or supernormality would become increasingly predominant. In addition they found presynaptic block was sensitive to variations in temperature; higher temperatures allowed greater frequency of stimulation but earlier block.

Acetylcholine (ACh) undergoes two reactions at the motor end-plate: it combines with a receptor molecule (which leads to an increase of ion permeability in the end-plate membrane), and it combines with a hydrolytic enzyme (Dunant, 1986). In terms of ACh there are three possible ways by which NMB may occur: the end plate becomes less sensitive to the depolarizing action of ACh, or too much ACh is released so that depolarization spreads

beyond the end-plate region, or insufficient amounts of ACh are released by the nerve impulse (Feldburg, 1951).

An intermittent pre-junctional failure of transmitter release has been demonstrated during tetanic stimulation (Krnjević & Miledi, 1958), but the occurrence is not regular and it cannot alone explain transmission block. It does not account for the progressive diminution of the end plate potential during prolonged repetitive activity (Liley & North, 1953; Krnjević & Miledi, 1958). Several changes may be involved, but perhaps the most important is the decrease in the sensitivity of the end-plate to ACh (Thesleff, 1955; Katz & Thesleff, 1957 and Thesleff, 1959). With the discovery that brief application of ACh to the end-plate reversibly reduced the chemical sensitivity of that region it became possible to assume that during high-frequency stimulation, transmission failure could be due to desensitization of post-junctional receptors by the released transmitter. The end-plate becomes refractory to ACh. In addition it has been suggested (Axelsson & Thesleff, 1958) that the concentrations of ACh which produce desensitization are, at least in certain mammalian muscles, within the range of concentrations normally produced at the end-plate by motor nerve impulses, and that consequently desensitization may develop during repetitive motor nerve stimulation.

If the nerve fibre is artificially stimulated at rates in excess of 100 times per second for several minutes, the quantal release of acetylcholine (ACh) is diminished to such an extent that propagation failure results (Rosenblueth, 1950). However, Hatt & Smith (1976), working on the opener muscle of the crayfish walking leg, found that the rate of spontaneous quantal release did not decrease, arguing against transmitter depletion. They found axon conduction blocks occurred at points of bifurcation along the entire length of the presynaptic nerve. They concluded that repetitive stimulation eventually leads

to depolarization of the axon membrane, and this causes impulse propagation failure which reduces the number of synaptic release sites that are activated.

In putting forward the hypothesis that there are changes in reflex sensitivity with increasing age, the possible development of neuromuscular block has to be investigated as an explanation for it. Can block occur under normal physiological conditions in healthy subjects? Does the likelihood of it occurring under such conditions increase in older people?

Since the literature on muscle fatigue and NMB are inextricably linked further reference to the latter will be found in the Introduction to Fatigue.

TREMOR

Physiological tremor may be defined as the ripple which is superimposed upon a normal voluntary muscular contraction, and which arises solely from it. It is involuntary and occurs spontaneously. Physiological tremor is distinguished from the tremor of Parkinson's disease by the details of its frequency analysis. Normal tremor has a major peak at 8-12Hz, whilst Parkinsonian patients have tremor which has most of its energy concentrated in a frequency band around 5Hz (Lippold, 1973). Normal tremor generally occurs at lower frequencies (around 6Hz) in young children and elderly persons (Marshall, 1968).

By the end of the nineteenth century it had become clear that, normally, all voluntary muscular contraction was accompanied by fine regular, superimposed oscillations and it was at about this time that the phenomenon came to be termed "Physiological tremor". Schafer (1886), working at University College London, had clearly defined a 10Hz rhythm in the mechanical record of the contraction of muscles and limb movements in normal human subjects. Most subsequent invetigators have found this to be the predominant frequency of physiological tremor in man.

Physiological tremor, with suitable recording techniques, can be demonstrated in nearly all normal subjects. Although it is most apparent in the outstretched fingers, physiological tremor occurs in other parts of the body, including the lower extremities, the head and even the tongue.

Physiological tremor is not present in the totally relaxed extremity but increases in parallel with the tonic activation of muscles to maintain a fixed posture opposing gravity or other external forces (postural tremor).

Possible mechanisms contributing to physiological tremor can be considered under three broad categories: 1. mechanical factors, 2. reflex oscillations and 3. central oscillations.

Ballistic effect of heartbeat

Yap & Boshes (1967) concluded that cardiac action was the origin of normal finger tremor. They obtained "average patterns" of normal finger tremor, the ballistocardiogram and the electrocardiogram (using a computer of average transients) and found them to be related.

Marsden *et al.*, (1969) investigated the ballistic effect of the heartbeat using cross-spectral analysis and coherence of tremor between the two hands, and concluded that less than 10% of the tremor recorded from the outstretched fingers could be accounted for by the heartbeat. Oscillations occurring in time with the heartbeat can be recorded in completely denervated limbs or after paralysis with succinylcholine (Marsden, 1978).

Lippold (1973) commented that a muscle swelled slightly with each heartbeat and that this was enough, on occasion, to synchronize the spindle discharge with the pulse; he considered that the phenomenon was an example of introducing a mechanical stimulus into the reflex arc.

"Servo-loop" hypothesis of tremor

Several lines of evidence suggest that physiological tremor is due to oscillations occurring as a result of instability of the servomechanism associated with the spinal stretch reflex. Oscillations can develop if there are inherent delays in a mechanical system with negative feedback. Halliday & Redfearn (1956 and 1958) were the first to advance the servo-loop theory of tremor. They found that physiological tremor was absent in the disorder tabes dorsalis, in which the afferent part of the reflex loop is interrupted.

Lippold, Redfearn & Vučo (1959) obtained the same result in experiments on the anaesthetized cat. They showed that cutting of the dorsal roots coming from the limb in question abolished the rhythmical tremor peak.

Further evidence suggesting involvement of segmental reflex mechanisms was provided by Lippold (1970) who showed that physiological tremor could be modified or reset by perturbations applied to the outstretched fingers.

The effect of ischaemia

The effects of ischaemia on finger tremor were first reported by Halliday & Redfearn (1954). All frequencies of tremor were affected by ischaemia. A sphygmomanometer cuff inflated, just above the elbow to 200mmHg, led to the depression of the amplitude of tremor at all frequencies within 1 to 2 minutes. In many subjects tremor was abolished after 3 or 4 minutes, but the stretch reflex was not affected during the first 5 minutes. Following removal of the cuff, tremor returned within about 1 minute and usually regained the control amplitude in less than 5 minutes.

The reduction in tremor did not occur if a venous cuff (70mmHg) was applied; if anything this tended to increase tremor amplitude; in addition, nerve block was ineffective in altering tremor (Lippold, 1973).

Imposing ischaemia on a muscle is equivalent to altering the loop gain at its peripheral component. Reduction or abolition of tremor results because the gain in the loop - in the reflex arc - is reduced below that needed to sustain oscillation by impairment of the sensitivity of muscle spindles. Matthews (1933) found that any impairment to the blood supply to a muscle of an anaethetized cat, resulted in its spindles giving a sustained high-frequency discharge and there was an accompanying loss of sensitivity to stretch. The spindles become completely insensitive to stretching; this would be the equivalent of opening the loop, and tremor would disappear.

Firing of motor neurones

Synchronization of motor unit discharges as a possible factor contributing to physiological tremor has been suggested. Normally motor neurones fire in an asynchronous manner, so during voluntary activation the

normal firing of motor units would not be expected to produce substantial tremor, even though the firing rates at recruitment are close to the frequency of physiological tremor. However, during fatigue and isometric training there is a tendency for motor unit discharges to become synchronized (Milner-Brown *et al.*, 1975). Muscle fatigue increases the amplitude and slightly raises the frequency (Lippold *et al.*, 1960) of physiological tremor.

Central oscillations

The possibility that physiological tremor is driven by central oscillations arising from supraspinal structures has also been considered. It may be possible that synchronization of motor unit firing could occur in response to synchronous discharges originating at higher levels in the nervous system. However, Rietz & Stiles (1974), using an animal model, found that the tremor frequency was largely independent of the rate of stimulation of motor neurones. Allum *et al.*, (1978) have proposed that the firng rate of motor neurones (about 10 impulses/s), together with the filtering properties of muscle, directly determine the frequency of physiological tremor.

Alpha Rhythm

The similarity in frequency between the alpha rhythm of the electroencephalogram (EEG) and physiological tremor has led to speculation that some common form of central nervous system mechanism modulates electrical activity and may be giving rise to both types of oscillation. They vary with age in much the same way (Marshall & Walsh, 1956), and Jasper & Andrews (1938) found that both were altered similarly by a number of factors. The response of both is the same to sudden stimuli (such as a loud sound), to anaesthesia, sleep, or to general alerting. But, Jasper & Andrews (1938) demonstrated that the tremor of limb muscles did not remain in phase with the EEG; the frequency is never quite the same.

Other theories

The existence of a "pacemaker" within the spinal cord has been suggested. However, Marsden *et al.*, (1969) observed that the phase and frequency of physiological tremor in a subject's two hands were not necessarily the same and this argued against the idea of a single CNS pacemaker.

AGE CHANGES IN THE NEUROMUSCULAR SYSTEM AND THE EFFECT OF TRAINING

The effects of training can be considered as the long-lasting physiological responses of the body to intensive and repeated motor activity. Peak physiological function, for the most part, occurs at about 20 to 30 years of age. After that, most factors decline at a rate of about 0.75% to 1% a year. The decline in physical capacity is characterized by a decrease in maximal O_2 consumption (Vo_2 max), maximal cardiac output, muscle strength and power, neural function, flexibility and increased body fat. All of these factors can be positively affected by training. Exercise training does not retard the ageing process; it just allows the individual to perform at a higher level .

Marked deterioration in muscle mass usually occurs with ageing. It is characterized by decreases in the diameter (Rowe, 1969) and number (Rowe, 1969 and Gutmann & Hanzlikova, 1966) of muscle fibres, decreases in the muscles' respiratory capacity and increases in connective tissue and fat. Ageing results in decreases in isometric and dynamic strength, and speed of movement.

There is a loss of fibres from individual motor units. This results in less available contractile force when a motor unit is recruited. Additionally, the nature of motor units changes: there is a selective loss of type II fibres (fast-twitch muscle), which diminishes available strength and power.

The loss of the muscle's biochemical capacity is characterized by decreases in succinate dehydrogenase, pyruvate and malate dehydrogenase, and cytochrome oxidase. In very old age, there is evidence of the formation of incomplete or inactive enzymes. Some researchers have found decreases in the mitochrondrial mass. All of these changes will affect ATP (adenosine triphosphate) production and thus impair physical working capacity.

The mechanisms involved in muscle contraction are also impaired, which contributes to the loss of strength and power. Ageing muscle is less excitable

and has a longer refractory period. Myosin-ATPase activity, ATP and CP (creatine phosphate) are also reduced, particularly in fast-twitch muscle, which further impairs muscle function (Brooks & Fahey, 1984).

Relative strength changes resulting from training are similar in the young and old, at least in short-term programmes. There is a fundamental difference in the way the elderly increase strength. The young improve the contractile capacity of the fibres, whereas the elderly rely on improved motor unit recruitment (i.e., improve the force/unit cross-section of the muscle). Physical training seems to have little effect on the deterioration of neural function. Suominen *et al.*, (1980) could find no difference in neurobiological factors between extremely fit elderly endurance athletes and elderly sedentary men. They concluded that the effects of endurance training in the elderly are largely limited to functions that are apparently relevant to physical performance. Exercise training will improve performance in the elderly, but it will not affect the ageing process itself.

Regularly performed endurance exercise results in a twofold increase in the capacity of skeletal muscle for aerobic metabolism (Holloszy, 1967). However, oxygen supply by the circulatory system does not appear to be the main limiting factor for performance (Kaijser, 1973). The functional capacity of old people with endurance training is certainly higher than in "untrained" people The former endurance athlete has a cardiopulmonary system in many respects "younger" than his age group (Karvonen, 1969; Skinner, 1973). General effects of training include the increase of enzyme activities (Keul *et al.*,1969) and smaller fluctuations in cellular (e.g. in decrease and resynthesis of glycogen in muscle; Gutmann *et al.*, 1953) and systemic functions related to a process of more economic functional integration.

On the other hand, disuse resulting in lack of mobilization of adaptive capacities of the organism (Frolkis, 1970) can be expected to lead to marked

senescent changes in the neuromuscular system. This is also indicated by the less marked senescent changes in muscles continuously activated, e.g., the diaphragm and heart muscle.

Senescent muscle atrophy shows specific features, primarily with respect to neuronal regulation. Neuronal impulse and nonimpulse ("neurotrophic") activities may be distinguished, and a decline of the trophic function of the neurone is assumed. This disturbance is caused by a decrease in the synthesis of neurotrophic agents and probably by a slowing of axoplasmic transport. The result of this is a slowly progressing disturbance of neuromuscular contact, resulting in a loss of muscle fibres. The random character and the slowness of the process make it difficult to identify the final stage of the event, i.e., disconnection of the neuromuscular contact. Generally there is an absence of ultra-structural evidence of endplate degeneration and of electrophysiological evidence of denervation. Maintenance of the number of motor neurones - at a time at which muscle fibre number decreases - and the marked reduction of spontaneous transmitter release, reveal the specific features of senescent muscle atrophy (see Gutmann & Hanzlikova, 1972a and 1972b).

Intensive motor activity induces considerable changes in muscle and glucose metabolism. The "training" process, developing as a reaction to repeated motor activity and varying with the type of motor activity, will accordingly affect all functions of the body. This adaptation process leads to "fitness", i.e., capacity to react to exertion efficiently with a high level of functional performance. The "training" process is essentially a process of conditioning implied in the adaptation to repeated motor activity.

The overshoot reaction, i.e., the increase in glycogen or protein levels in muscle above initial levels after its stimulation, which is missing after denervation, suggests the great importance of nervous mechansims in this training effect (Gutmann, 1964). It is also missing in the muscles of old age

(Drahota & Gutmann, 1961) and suggests a disturbance of recovery processes in nerve and muscle cells. In the training process, the "overshoot" reaction is modified. The "repeated overshoot reactions" result in a higher level of metabolites in the muscle cell, a more "economical" smaller decrease after stimulation, a faster return to initial levels and a smaller increase of metabolites above initial levels in the following recovery phase (Gutmann *et al.*, 1953). Metabolic recovery processes are very much disturbed in senile muscles (Drahota & Gutmann, 1962) and this defect may be very important in the decline of functional capacity of old people.

Hormone-dependent changes in muscle may be due to:

1. reduced secretion;
2. decreased hormone secretion in response to motor activity;
3. decreased utilization of the hormone, and
4. altered responsiveness of the muscle cell.

A number of hormones, especially the somatotrophic and thyrotrophic, are of great importance in the regulation of protein metabolism during developmental growth, and changes in synthesis of these hormones might be significant in the development of senescent muscle atrophy. Reduced secretion of growth hormone (somatotrophin) (Laron, *et al.*, 1970) in old age and decreased mobilization of glucose (Jakovlev *et al.*, 1963) in response to exercise imply a diminished output of hormones and might potentiate the decrease of adaptive functions despite increased sensitivity of some organs to hormonal influences with old age (Frolkis, 1970).

Decreased secretion is probably the result of a decreased utilisation which results from accompanying general atrophy (Gussek, 1972). The changes in senescent muscle are probably not directly related to changes in activity of pituitary hormones (Finch & Hayflick, 1977).

Androgens are potent stimulators of muscle hypertrophy, protein synthesis and red blood cell production. These factors have effects on oxygen transport and the aerobic production of ATP. There is a decrease of gonadal function with age, and the diminished capacity for hypertrophy in older males may be related to decreases in testosterone and/or other anabolic steroids.

THE EFFECTS OF COFFEE ON THE CARDIOVASCULAR SYSTEM

A complete chemical analysis of the coffee bean is difficult because of the complex nature of the molecular structure of its many components. Caffeine is an alkaloid structually identified as 1,3,7-trimethylxanthine. It is one of several xanthine derivatives which occur naturally in coffee beans, tea leaves, kola nuts and cocoa beans; theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine) are two others. All three are structurally related to metabolically important compounds such as the purines, xanthine and uric acid. All three affect similar parts of the body. The differences in their pharmacological effects lie principally in their relative potencies.

Caffeine is readily extracted from plant sources and is very soluble in water, from which it crystallizes as a monohydrate with one molecule of water; from organic solvents it crystallizes as an anhydrous material, melting at 235^{o} to 237^{o}C.; it sublimes at 176^{o}C at atmospheric pressure without decomposition. Pure caffeine is odourless, has a distinctly bitter taste and is stable at temperature, pH and salt concentrations normally encountered in food processing. Caffeine forms unstable salts with acids, but forms stable, water soluble combinations with sodium benzoate and sodium salicylate.

Coffee is by far the most important source of caffeine; it is responsible for about 75% of the total caffeine consumption in the diet. Tea is next in importance, followed by Cola beverages (one half from kola nut and one-half from added caffeine). Thus, dietary caffeine is consumed almost entirely in beverages. A smaller, but for some individuals a highly significant amount, comes from use of caffeine in drugs, usually of the over-the-counter variety.

Ingested caffeine is rapidly absorbed, metabolized and excreted in the urine as methylxanthine derivatives. Within a few minutes after ingestion, caffeine enters all organs and tissues, and reaches peak levels after one hour when it is distributed in proportion to tissue water content. The metabolic

half-life of caffeine in the plasma and most organs is about three hours. Excretion is primarily renal, with little appearing in the faeces. Most of the ingested caffeine is metabolized, with only 3 to 6 per cent appearing in the urine as unchanged caffeine. The major urinary excretion product of caffeine in man is 1-methyl uric acid, formed by demethylation of caffeine. The usual pharmacologically active dose of caffeine is 200mg.

As well as its CNS stimulant effect, other biological effects of caffeine include: elevation of plasma free fatty acids and glucose, diuretic, cardiac muscle stimulant, smooth muscle relaxant, and stimulation of gastric acid secretion (Graham, 1978; MacCornack, 1977 and Ashton, 1987).

The effect of caffeine on the cardiovascular system

Laboratory studies on animals show the intravenous administration of caffeine has paradoxical effects on the cardiovascular system. The heart muscular activity is increased (*via* Ca^{++}), producing an increased heart rate. There is vasodilation through peripheral depression of the vasoconstrictor mechanism. However there is also a central vasoconstrictor stimulation and cardiac irregularities often occur (Chapman & Miller, 1974).

The use of denervation procedures and blocking drugs in animal laboratory studies has shown that the blood pressure fall is due primarily to the peripheral vasodilation effects of caffeine. However, a secondary blood pressure rise occurs, thought to be due to a reflex vasoconstriction and cardiac stimulation. It has been suggested that the secondary pressor response represents a central effect of caffeine (Sollman & Pilcher, 1912a, 1912b and 1912c).

Studies of the effect of caffeine on humans are segregated by therapeutic doses of caffeine and caffeine in coffee. To consider them together is a mistake; cardiovascular effects due to caffeine are duplicated only by heavy doses of coffee ingestion. Experimental studies of coffee consumption by

humans have shown that blood pressure and pulse changes were slight in healthy young volunteers with administration of 3-4mg/kg of caffeine and coffee. Increases of 10mmHg in systolic blood pressure and decreases in pulse averaging 5 per minute have been reported (Horst, 1934). These alterations tended to diminish on repeated testing over a period of weeks. Older men (53-77 years) showed a greater blood pressure rise than young men (21-25 years) after coffee consumption, but half the older subjects had very high control blood pressure levels.

Robertson *et al.*, (1978) looked at the effects of caffeine upon blood pressure. Caffeine (250mg) or placebo was administered in a methylxanthine-free beverage. Although no significant changes in blood pressure followed the placebo, an elevation in both systolic and diastolic pressure was observed after caffeine and reached statistical significance at 30 minutes. The maximum change in blood pressure was seen 60 minutes after caffeine, when a mean increase of 14/10mmHg was measured. Subsequently, blood pressure gradually moderated, but had not quite returned to normal 3 hours later. In addition to its effects on blood pressure Robertson *et al.*, (1978) found that the acute administration of caffeine, in subjects who did not normally ingest methylxanthines, led to increases in heart rate, plasma epinephrine, plasma norepinephrine, plasma renin activity and urinary catecholamines. However, it should be noted, they undertook further experiments which showed that with chronic ingestion of caffeine, tolerance developed (Robertson *et al.*, 1981).

The later study at the Chicago Western Electric Company (LeGrady *et al.*, 1981) did not find blood pressure was affected by the consumption of coffee. These results can be added to a mass of conflicting evidence which surrounds the subject, and serves to highlight the problem. Effectively controlling all variables would seem to the major difficulty in these studies, and further mention of these complicating factors will be made in the Discussion Section.

Essential Hypertension

Approximately 90 per cent of all persons who have hypertension are said to have "essential hypertension", meaning that the hypertension is of unknown origin.

Hypertension can be very damaging because of two primary effects:

1. increased work load on the heart

2. damage to the arteries themselves by the excessive pressure.

METHODS

Note: The experimental set-up described in Section 1 :Part A is common to other experiments in later Sections. For this reason the procedure will not be repeated on each occasion; the reader will be referred back to this Section.

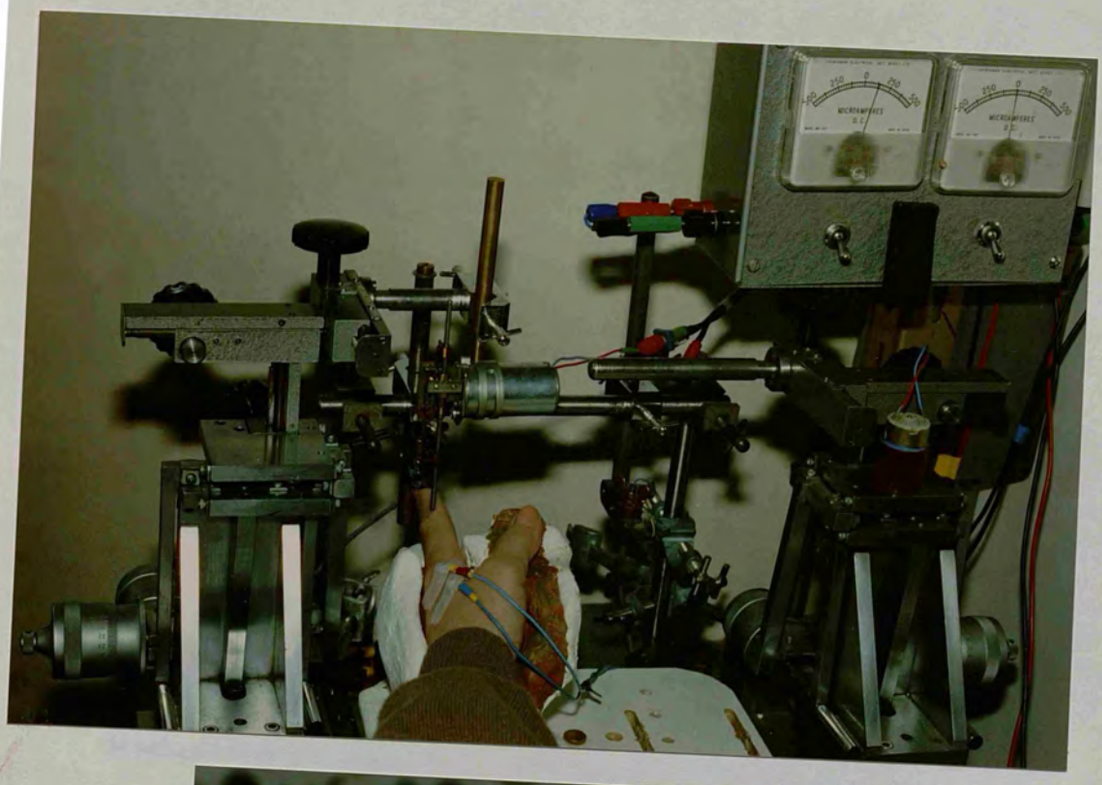
SECTION 1 : M1/M2 RATIO EXPERIMENTS : PART A

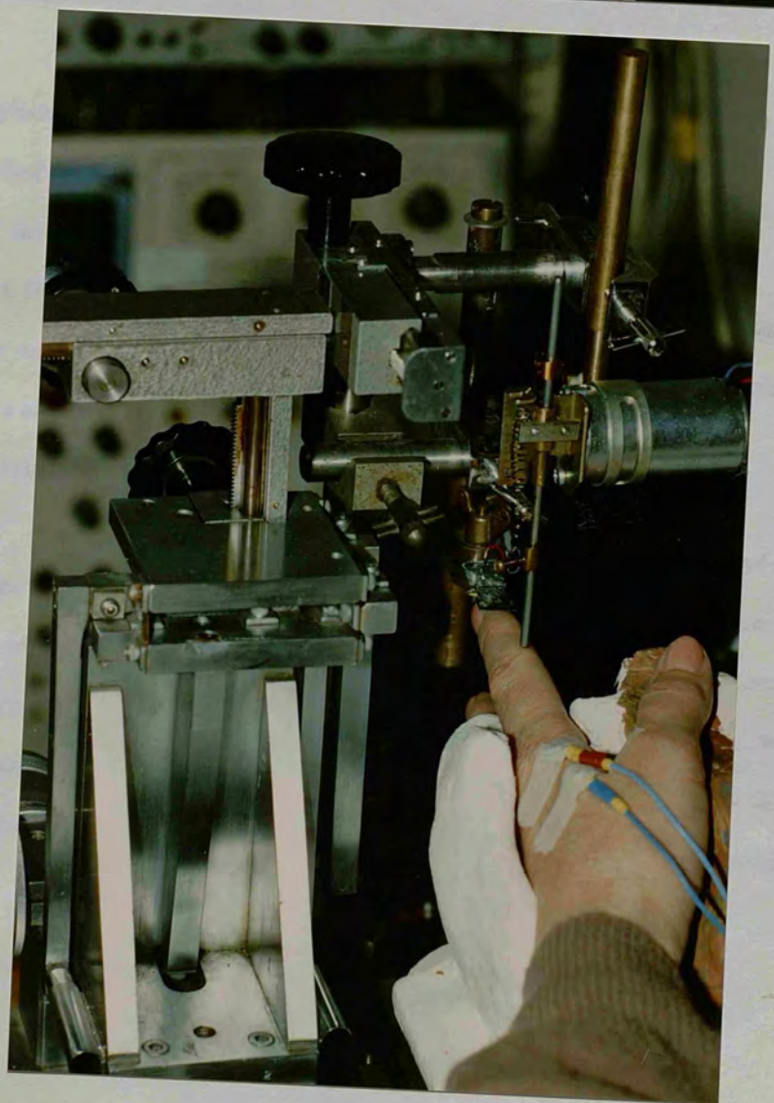
A sudden imposed movement of a limb results in a reflex response in some or all of its muscles. If a small voluntary contraction is being maintained in the muscle being stretched, the electromyographic record usually shows several peaks of activity. The components of this segmented reflex response have been recorded in a series of experiments and a comparison made between the M1 (short-latency) and M2 (long-latency) responses in human subjects of various ages.

To study the reflex response in human subjects the first dorsal interosseous muscle (FDI) of the hand was used. The subjects were seated with the right upper arm in a vertical position. The horizontal forearm was supported by plaster casts and the hand restrained by elastic bands (see Figures 2.1 and 2.2). It was essential that the arm and the hand, other than the index finger, were completely immobilised. The index finger had free range of vertical movement, and the subject was asked to keep as still as possible and to maintain exactly the same position throughout the experiment.

Surface recording electrodes were placed over the belly of the muscle and the subject was asked to maintain a small voluntary contraction of the muscle (about 5-10% of MVC - depending upon the level of MVC of the subject) by raising the index finger against a strain gauge, the output of which was fed to a meter which displayed the force. This steady contraction was maintained by the subject throughout the procedure. With the subject maintaining the small background voluntary contraction, the muscle was stretched briefly and

Figure 2.1 and Figure 2.2 Photographs of experimental set-up. See text for explanation.





repetitively by an electro-mechanical prodder which vertically tapped the finger (see Figure 2.3) The electrical response in the muscle was amplified, rectified and averaged. All records were measured by planimetry.

Subjects

Twenty-four subjects, male and female, ranged in age from 20-63 years. The older subjects were predominantly lecturers from the College, the younger subjects were mainly students. Local Ethical Committee approval was obtained and all subjects gave their informed consent.

Tension measurement

Calibration of the tension exerted by the subject on the strain gauge - to produce the small voluntary contraction - showed that a force of 1.09N was exerted, and was the same in all subjects.

Mechanical stimulation

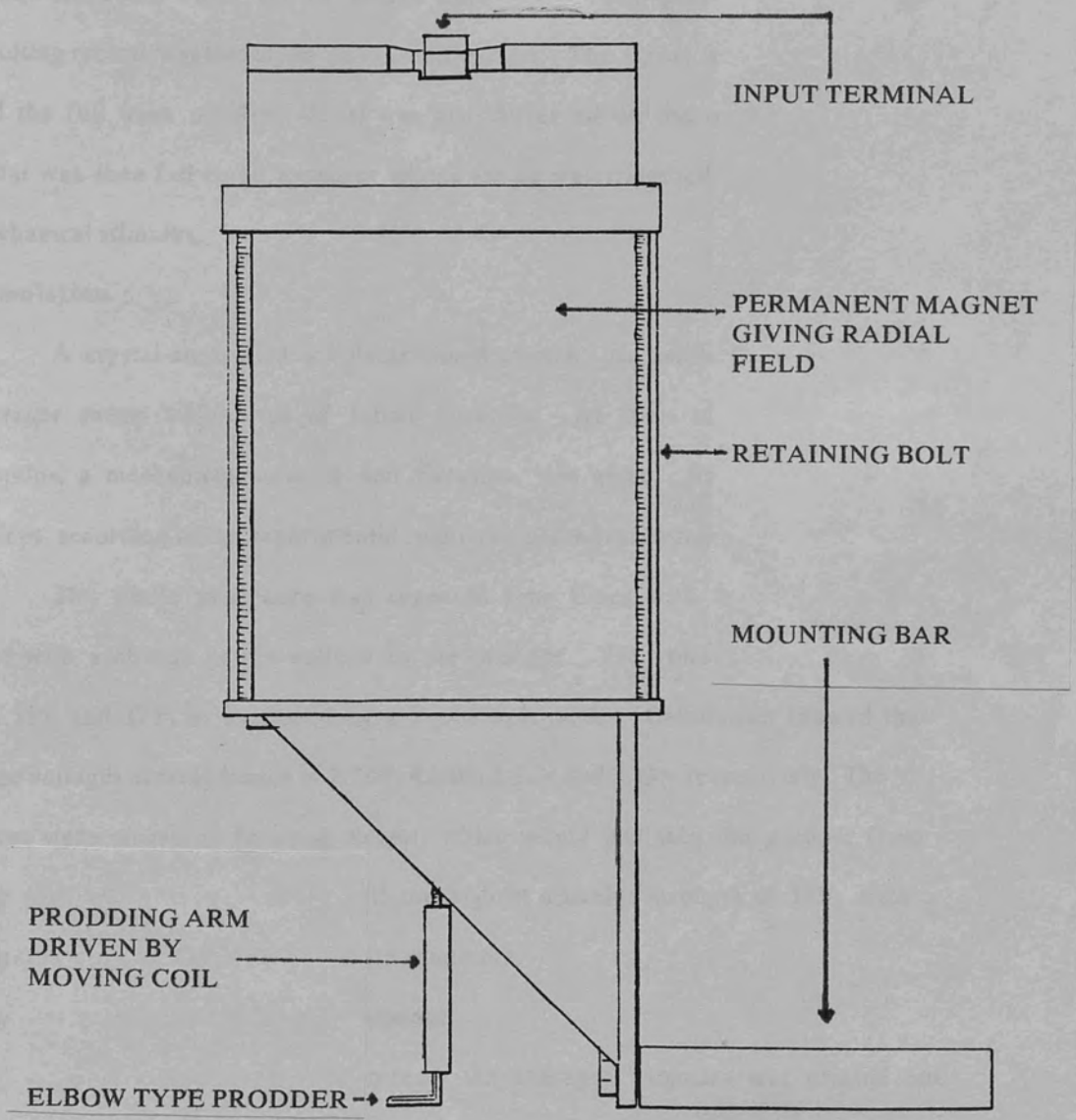
The FDI was stimulated using a mechanical moving-coil prodder whose displacement could be varied between 0 and 2mm according to the voltage applied to it. The prodder was placed at the measured mid-point of the first and second joints of the index finger. A space of 1.0cm was kept between the index finger being stimulated and the rest of the hand. The hand and forearm were immobilised during the period of stimulation by a rig of plaster casts, hooks and elastic bands.

Electrical recording

Recordings of the response of the FDI to stretch were made using two surface electrodes in the form of silver chlorided discs 9.0mm diameter. The electrodes were filled with conducting jelly and stuck with micropore tape to the skin over the belly of the FDI. The inter-electrode distance was 25mm, midpoint to midpoint, and the inter-electrode resistance kept below 20kΩin all subjects. To decrease electrical resistance in the skin, alcohol-soaked swabs

Figure 2.3 Electro-mechanical Prodder used in M1/M2 Series.

Initially the prodder was 1mm above the surface of the skin.



were used to cleanse the skin before the electrodes were applied. An earth electrode was attached to the forearm.

Processing of the electromyographic response

The electromyographic signal recorded by the surface electrodes on the FDI was amplified. A low-frequency filter with its 3-dB point set to 0.8Hz and a high-frequency filter set to 30kHz were used. The gain was x1000. The resulting record was displayed on an oscilloscope. The signal was then rectified and the full wave rectified signal was also displayed on the oscilloscope. This signal was then fed to an averager whose sweep was triggered 20ms prior to the mechanical stimulus.

Stimulation

A crystal-controlled oscillator timed events. An initial pulse started the averager sweep which was of 160ms duration. At 20ms after zero time the stimulus, a mechanical pulse of 4ms duration, was given. Between 32 and 256 sweeps, according to the experimental requirements, were averaged. Repetition rate was 503ms.

The whole procedure was repeated four times with each subject, each time with a change in the voltage to the prodder. The voltages used were 5V, 9V, 13V and 17V, as measured by a digital volt meter. Calibration showed that these voltages exerted forces of 2.73N, 4.18N, 5.62N and 7.19N respectively. The forces were measured by using weights which would just stop the prodder from moving. Each experiment began with the highest stimulus strength of 17V, after which the remaining order was chosen randomly.

Measurement of the averaged response

To provide a permanent record, the averaged response was printed out on an XY recorder. The areas of the M1 and M2 peaks were measured with a planimeter by three persons independently. The peaks were measured from the take off to the return points of the waveform; these points were established by comparison of all the records in a series, using a light box.

A base line representing zero potential difference between the recording electrodes was made on all records at the end of each trace. This was achieved by earthing the signal at the amplifier input during the 147th to 157th ms of each recorded response.

SECTION 1 : PART B

Control Experiments

Changes with increasing age were found in the electromyographic response of the FDI to stretch with increasing age. Control experiments were conducted to check that the findings were not due simply to altered physical properties of the neuromuscular system and/or the limb joints.

I : To investigate muscle and joint stiffness

Increasing muscle and joint stiffness are known to occur with increasing age so it was necessary to discover whether or not such changes were contributing to the changes with age seen in the reflex response to stretch.

In this experiment muscle movement was directly measured. An accelerometer, weighing 13g, (see Appendix page 204) was placed over the belly of the FDI, held in the correct position by double-sided adhesive tape. The index finger of the subject was mechanically stimulated with the prodder at the four different voltages as described in Part A of this section. Records of the muscle displacement which occurred when the muscle was stretched were averaged and printed out on the XY recorder. The responses of ten of the subjects (with a wide age range) were recorded.

II : Neuromuscular Block

This series of experiments was divided into three parts:

i) the experimental set up was the same as in Part A of this section. In addition two 9.0mm diameter surface stimulating electrodes were positioned on the skin over the ulnar nerve at the elbow.

With a sweep time of 40ms, the responses to electrical stimuli were recorded. The maximal response for a 50μs pulse width was found in each subject.The maximal response was usually obtained with around 90V. After 2ms the first electrical stimulus was applied, followed 25ms later by a second identical electrical stimulus. This was repeated eight times and the responses were digitized and stored.. The procedure was repeated, but gradually bringing the stimuli closer together. The initial stimulus was at 2ms and the delay before the second stimulus was progressively reduced by 2ms steps. Below 8ms the delay before the second stimulus was reduced in 1ms steps, the final record being made with a 2ms gap between the two.

In this experiment a larger strain gauge, which was linked to a meter, was used. After the control record, subjects were asked to make a maximum voluntary contraction (MVC) by raising the index finger against the strain gauge. The duration of the MVC varied betweeen subjects; it was sustained for up to 3 minutes. Although there was some subject variability, a maximum voluntary contraction was found to be around 250 divisions on the meter (6.25N). The subject was asked to maintain the MVC. During the last few seconds of the MVC the stimuli were switched on and the responses averaged.

ii) a concentric needle electrode replaced the two surface recording electrodes on the FDI, and one of the 9.0mm diameter electrodes over the ulnar nerve at the elbow was replaced by a plate electrode (5mm x 4mm). Motor unit action potentials were recorded from between the tip of the needle electrode and the shaft. A 40ms sweep was used. The maximal response for a 50μs pulse

width was found in each subject and initially two electrical stimuli were given at 2ms and 24ms. Again a total of eight responses were averaged. The procedure was repeated as described in i) of this section.

The smallest time interval between the two stimuli was then chosen where two distinct responses were obtained.

The subject was asked to make a maximum voluntary contraction for up to three minutes in exactly the same way as described in i) above.

iii) a 0.2mm diameter, insulated tungsten micro-electrode was inserted into the FDI. The micro-electrode was varnished with several layers of Voltalac, the end was exposed for 15μm and electrolytically polished to a tip diameter of approximately 5μm. The electrode resistance was at least 100kΩ. Another bare tungsten wire of the same diameter was inserted into the skin of the back of the hand to act as an indifferent electrode. Single muscle fibre potentials were recorded from the tip of the micro-electrode.

Potentials were identified as originating from single muscle fibres in three ways. First, the action potential duration was not more than 1.0-1.5ms. Secondly, the response was all or nothing as the electrical stimulus strength was varied. And, thirdly, regular trains of identical form were observed.

With a sweep time of 160ms a train of electrical stimuli, 20V and 50μs duration, was applied. There was an interval of 23ms between each stimulus.

The effects of fatigue were investigated. Firstly, responses were recorded after trains of stimulation, which were given for varying lengths of time. Second, the effects of MVCs on the response were recorded.

III : Experiments on nerve conduction

An extremely remote possibility to account for smaller-sized reflex muscle responses in aged persons might be that there is some interference to conduction in the motor or sensory nerve fibres. It must be emphasised that nerve conduction impairment could not explain the differential decline in M1 (as opposed to M2) with age. However, a rough preliminary study was carried out to see if any trends could be observed in nerve conduction parameters and age.

The ulnar nerve was stimulated at the elbow and the resulting compound action potential recorded at the wrist. Eight subjects, aged between 24 and 66 years took part. No obvious relationship holds between the amplitude of the supramaximal nerve volley and the age of the subject.

Obviously, a larger sample of subjects would have to be recorded from, but in the circumstances, eight records would seem to be sufficient to demonstrate that there is no significant age effect on the size of the ulnar compound action potential.

SECTION 2 : FATIGUE OF FDI

The next step was to look at the effect of muscle fatigue on the reflex response of the muscle to stretch, and to see what changes, if any, could be linked to the age of the subject. Again the FDI was used; this time to assess the effect of a strong voluntary contraction on the reflex response. The method here differed from the general procedure in that after the initial control records had been made the subject was asked to make a strong voluntary contraction for 2 minutes. Immediately after this contraction further records were made. The left arm was used in all subjects.

Subjects

The twelve subjects, male and female, ranged in age from 19-43 years.

Tension measurement

Calibration showed that the force exerted by the subject in maintaining the small steady voluntary contraction (50 divisions on the meter) was, in this series of experiments, 1.25N. (A different strain gauge was used in this experiment).

Mechanical stimulation

A different mechanical prodder was used in this experiment, the displacement of which varied between 0 and 6.5mm (see Figure 2.4). The prodder was positioned 1mm above the distal interphalangeal joint of the index finger.

Stimulation

The averager sweep was 160ms as before, but the stimulating mechanical pulse had a duration of 6ms. A total of 128 sweeps were averaged. The voltage to the prodder was 12.2V which, when calibrated, equalled a force of 1.14N. Repetition intervals were 379ms.

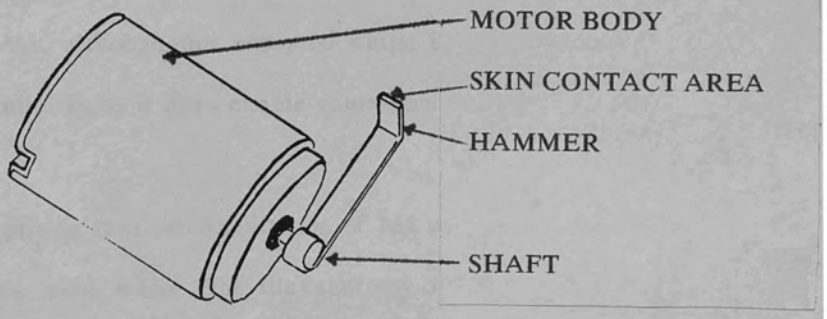


Figure 2.4 Mechanical Prodder used in Fatigue Series.

Units of measurement of action potentials

The areas of the M1 and M2 peaks have been given the units V.s since they represent voltage on one axis and time on the other. Ideally, the current flow generated by the muscle action potentials should be measured (Coulombs). However, paths of current flow vary between subjects and the series or parallel resistances that exist within the muscle, fascia and subcutaneous elements cannot be estimated. The voltage between two points on the skin over the muscle belly was measured; this is a good approximation to the calculated current flow, provided that tissue and electrode impedance does not change. Presenting the results as V.s, although not accepted units, is preferable to the use of cm^2 or "arbitrary units" since it does enable some comparison to be made among different subjects.

It was, in fact, surprising that the amplitudes of M1 were comparable in different subjects, and this must mean that the anatomy of the small hand muscles does not vary too much among typical subjects.

SECTION 3 : NEUROMUSCULAR BLOCK

The FDI was used to investigate the possibility that neuromuscular block can occur in fatigued muscle. The subject was seated with the left forearm and hand horizontal and supported by plaster casts in the usual way. Action potentials were recorded from single motor units in the FDI (see below) using surface electrodes placed over the belly of the muscle, using electrical stimulation of the ulnar nerve at the elbow.

After the recording of controls the subject was asked to sustain a two minute strong voluntary contraction of the FDI by raising the index finger against the strain gauge. The subject was asked to sustain a force of 12.5N, (500 divisions on the meter).

Immediately after the strong contraction a further record was taken of the response of the single motor unit to the same electrical stimulation. The frequency of electrical stimulation at which neuromuscular block (NMB) occurred was also investigated.

Subjects

Fifteen subjects, male and female, age range 17-44 years, took part in the experiment.

Electrical stimulation

The ulnar nerve of the left arm was electrically stimulated by applying one 9.0mm diameter chlorided silver disc electrode to the skin over the olecranon fossa at the elbow and one large plate electrode placed proximally on the lateral surface of the upper arm. The inter-electrode distance was 60mm. The precise location of the nerve stimulating electrode was adjusted until a record from a single motor unit was obtained on the oscilloscope. It was necessary to investigate a single motor unit that responded to each electrical stimulus in an all or nothing fashion with a wide range of stimulating voltage free of a second one. Sometimes this was difficult but usually it was possible

to record an action potential from a single motor unit using the surface electrodes. Initally a roving electrode was used to find the best position for the stimulating electrode. To ensure the electrode position did not alter during the strong voluntary contraction the electrode had to be firmly and immovably fixed to the skin using tape and cotton wool pads. An array of electrodes was used, and the two electrodes that provided the best record were employed.

Stimuli were of 50μs duration and a single motor unit was usually found at about 45V. Needle electrodes could not be used as it was necessary to use the same single motor unit action potential throughout the MVC It is not possible to do this with needle electrodes; the MVC causes the needle tip to move relative to the motor unit..

In the first part of the experiment the subject received electrical stimulation at different frequencies; 3Hz, 10Hz, 20Hz, 40Hz and 60Hz. On each occasion the stimulation lasted for 1min; there was 5 minutes rest allowed between each frequency of stimulation. The frequency of electrical stimulation which resulted in the loss of the action potential was noted.

After a five minute rest period a control record was again taken at 3Hz. When the action potential had fully recovered from the earlier stimulation the subject was asked to make a strong voluntary contraction of various forces, maintained using the strain gauge, for two minutes; no electrical stimulation was given during this contraction. Immediately after the strong contraction, with the electrical stimulation frequency set at the 3Hz necessary to record action potentials, a further record was taken. Additional records were then taken until the action potential returned, indicating that NMB was no longer present.

Electromyographic recording

In this experiment the recording electrodes were 35mm apart and a 20mm wide band of aluminium foil around the forearm acted as an earth.

Electromyographic processing

The action potentials recorded from the single motor unit were amplified using a low frequency filter with its 3-dB point set to 80Hz and a high frequency filter set to to give the best record, but remained the same during any one experiment. The gain was x1000. The signals were displayed on an oscilloscope and stored digitally to capture the response at a given moment.

SECTION 4 : REFLEXES IN BICEPS

The electromyographic response which can be recorded in FDI in response to stretch also produces a response in the biceps muscle. The ulnar nerve was stimulated electrically, and the EMG response in biceps was recorded. It has already been shown that the area of the M1 component of the EMG in older people is reduced. If this reduction is the result of impaired reflex sensitivity i.e., the change lies in the muscle receptors, then eliciting the same reflex response by stimulating afferent nerves directly should show no such diminution.

Subjects

Twenty two subjects, male and female, ranged in age from 19-65 years.

Electrical recording

Chlorided silver disc recording electrodes of 9.0mm diameter were placed over the belly of the left biceps muscle 60mm apart, and a large plate electrode placed on the forearm acted as an earth.

Electrical stimulation

Two stimulating electrodes were applied to the ulnar nerve at the left wrist; again using silver disc electrodes as described above. The inter-electrode distance was 30mm and the electrode resistance was kept below 40kΩ. The EMG response in the biceps muscle to stimulation at various voltages was recorded. Electrical stimulation ranged from 25-60V, and the pulse width was 50μs.

Stimulation

An initial pulse started the averager sweep which was of 160ms duration. At 20ms the electrical stimulus, which was of 50μs duration was given. 128 sweeps were averaged.

SECTION 5 : TREMOR

The tremor of the hand, rotating about the wrist joint, and the tremor of the middle finger were measured using an accelerometer. Tremor was examined in subjects taken from a wide age range to find out if there were any age-related changes.

Subjects were seated comfortably and the left elbow and forearm supported at a natural height, with the arm held in a horizontal position by a closely fitting plaster mould which was rigidly mounted on to a small recording stage. The forearm was further stabilized at a point immediately proximal to the wrist joint by the pressure of a metal bar also mounted on the recording stage. The arrangement permitted free wrist flexion and extension movements while eliminating, or minimizing, movements about other joints in the limb. Finger tremor was recorded from the middle finger of the hand, which was supported up to the meta-carpo-phalangeal joint.

Subjects

Twenty six subjects, male and female, ranged in age from 20-70 years.

Accelerometry

Tremor was recorded with an accelerometer (see Appendix page 204) which was attached to a plastic ring and placed over the middle finger of the hand. The output of the accelerometer was subjected to spectral analysis.

Analysis

Frequency analysis of the signal was carried out in real time using the Hewlett-Packard 3582A spectrum analyser, remotely programmed with a type 9528A desk-top computer and automatically plotted on a type 7225 graphics plotter. The frequency span was 0-25Hz, which gave a time record length ($N\delta t$) of 10s, and a calculated point spacing (δf) of 0.1Hz. A Hann pass-band shape was used, to minimize leakage, giving 0.15Hz equivalent noise band width. Since the sampling frequency was 102.4Hz (i.e., Nyquist frequency = 51.2Hz) alias contamination did not occur within the specified frequency range. Four

separate, consecutive 10s power spectra were averaged to give 90% confidence limits between +4.7 and -2.9dB for each spectral point.

The smoothed spectra were obtained by the method of thirds. For each spectral power point the computer summed its value with that of the adjacent two points and calculated the mean. This process was repeated thirty two times. Before display, the square root of each smoothed point was extracted to produce the amplitude spectrum.

Calibration

For accelerometry the calibration curves supplied with the transducer were employed. It will be noted that all spectral components are given as an amplitude in mV. This is so because the spectral values are expressed as the square root of their power when they are plotted (for reasons given in Gottlieb & Lippold, 1983).

The amplitude scales are referred to mV at the electrodes and were obtained by using a 3Hz sine wave of 1mV peak-to-peak amplitude applied to the input plugs (with the electrodes disconnected and time constant set to 0.2s), the source impedance being 4MΩ. Gains were adjusted to give a full scale deflexion peak in the spectrum (= 40mV/spectral point) with the 1mV calibrating signal. The accelerometer gave 31.6mV input to the analyser for a linear acceleration of $1m/s^2$ and had 3dB cut-off points in the charge amplifier at 0.1kHz and 0.2Hz. Gains were adjusted to give full scale deflexion (= 40mV/spectral point) for an acceleration of $5m/s^2$.

SECTION 6 : TRAINING IN FDI

The reduction in area of the M1 component of the EMG from the FDI in response to stretch in older people could be the result of muscle disuse. To investigate this possibility the finger of a 44 year old subject was trained for eight weeks.

The experimental set up was as given in Section I :A.

Training

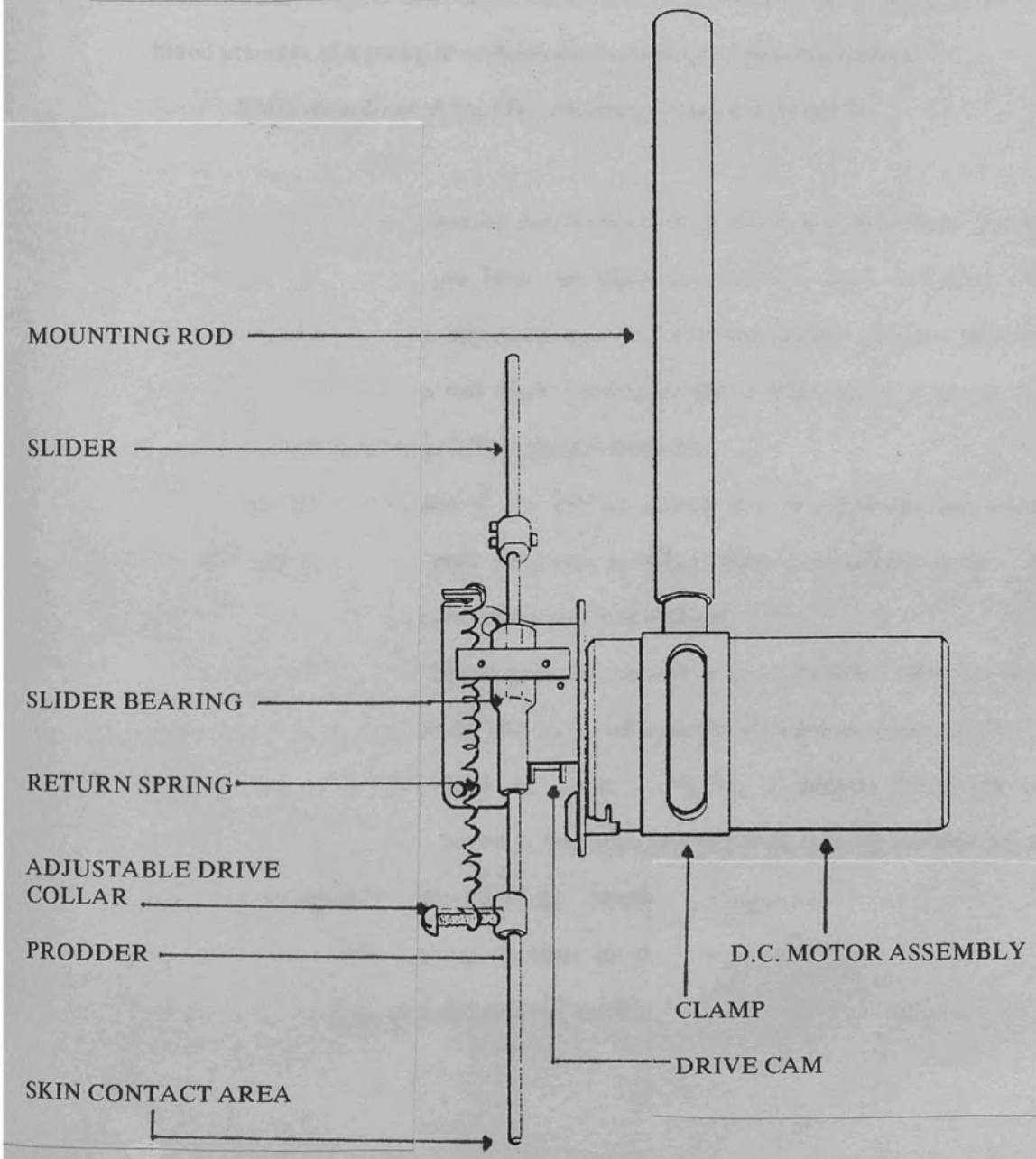
Each day for four weeks the subject lifted a 1.0kg weight, using FDI, suspended from the index finger and maintained a 2 min MVC. In the second four weeks of the programme, in addition to the 2 min MVC each day, the FDI was made to raise and lower the index finger 30 times with the 1.0kg weight suspended.

Electromyographic recording

9.0mm diameter surface recording electrodes, 35mm apart were placed on the belly of the FDI, and 128 responses were averaged. EMG records were made before, during and after the training programme. The mechanical prodder used to stretch the FDI is shown in Figure 2.5. At each recording session three records were made, and the average area of M1, the average area for M2, the M1 amplitude and the Aspect Ratio were measured.

Figure 2.5 Mechanical Prodder used in Training Series.

Repetition rate for stimulus was 379ms.



SECTION 7 : COFFEE AND HYPERTENSION

If the change in the stretch reflex in older people is the result of an impaired reflex sensitivity of stretch receptors, it might be expected that other stretch receptors in the body would be similarly affected. The impaired reflex sensitivity could contribute to hypertension, for example, if the stretch receptors controlling blood pressure changed with age.

To investigate this possibility the effects of the caffeine in coffee on the blood pressure of a group of subjects with a wide age range was studied.

EMG recordings of the FDI response to stretch were made.

Protocol

The subject was seated comfortably on a chair and the blood pressure was taken. Fifteen minutes later the blood pressure was again recorded. The subject was then given a measured quantity of strong coffee. Fifteen minutes later the blood pressure was again recorded. Three more blood pressure readings were then taken at fifteen minute intervals.

The EMG response of the FDI to stretch was recorded and processed in the usual way. Subjects gave their age, smoking habits and caffeine intake. In addition their blood pressure history was investigated.

The technique of blood pressure recording has subjective elements in it, although the magnitude of the effects found in this study were most unlikely to be the result of this kind of error. Ideally, a hidden (random) zero sphygomanometer should be used; however, it was found entirely satisfactory to achieve double-blind readings by employing two persons to make the measurement. One person listened to the Korotkow sounds without visual monitoring; the other took the mercury reading.

RESULTS

SECTION 1 : PART A

Comparison of M1, M2 and the M1/M2 ratio in subjects of different ages.

The short-latency component - M1

The spinal stretch reflex (M1) in the FDI is smaller in older people. Figure 3.1 shows records of the electromyographic response to a brief and repetitive stretch of the FDI by an electro-mechanical prodder. The top trace shows the response recorded from a 20 year old subject; the M1 peak has a greater area than the M1 peak in the 42 year old (bottom trace). The results of all 24 experiments showed a consistently smaller area for the M1 peak in older people (see Table 3.1).

The experimental set up, and the care taken to reproduce exactly similar conditions for each subject was of paramount importance. Without these precautions the results would have been so variable that comparison of EMG components would have been impossible. The rig, which had been specially constructed for the experiment, completely immobilised the arm of the subject. It was lined with cotton wool so that the arm was as comfortable as possible, for it was important for the subject to feel completely relaxed. The prodder was positioned in exactly the same place with each subject, and the position on the skin marked with a pen. The subject was asked to keep as still as possible during the entire experiment, and to ensure that the prodder remained on exactly the same spot throughout the experiment.

REPRESENTATIVE ELECTROMYOGRAPHIC RECORD SHOWING THE SMALLER SIZE OF M1 IN OLDER PEOPLE

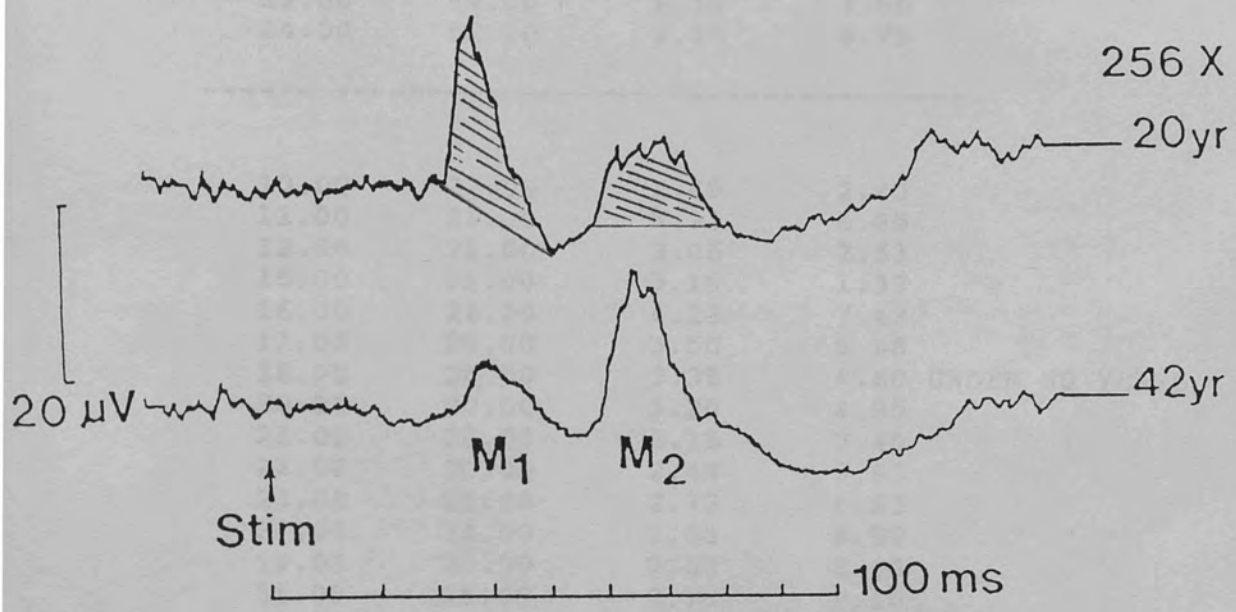


Figure 3.1 The averaged rectified surface EMG of the first dorsal interosseous (FDI) to a brief stretch. The upper record represents the EMG recorded from a 20 year old subject. The lower record shows the response of a 42 year old subject. 256 responses were averaged.

Top trace shows method for delineating areas to be measured.

TABLE 3.1

VALUES FOR M1 AND M2 cm^2

EXP. #	AGE	M1	M2	
8.00	38.00	1.80	4.18	
13.00	51.00	2.13	6.38	
14.00	42.00	0.55	2.75	
19.00	60.00	0.05	4.50	
23.00	63.00	0.45	3.58	OVER 30 YEARS
26.00	46.00	1.20	3.85	
30.00	43.00	0.80	2.55	
32.00	59.00	0.95	1.58	
33.00	49.00	1.48	3.50	
34.00	52.00	1.85	6.75	
10.00	22.00	2.45	2.43	
11.00	21.00	3.33	6.85	
12.00	21.00	3.05	2.53	
15.00	21.00	3.10	1.33	
16.00	28.00	4.23	7.43	
17.00	20.00	3.50	5.48	
18.00	24.00	3.38	4.60	UNDER 30 YEARS
20.00	20.00	3.20	4.85	
21.00	20.00	2.15	3.40	
22.00	20.00	2.48	3.60	
24.00	21.00	2.73	4.83	
27.00	24.00	3.05	4.50	
29.00	20.00	2.80	2.03	
31.00	25.00	2.75	4.10	

Using a planimeter, the areas of the M1 and M2 peaks for each subject were measured from the takeoff to the return points of the waveform. The areas were measured by three people independently. The start and end points of the M1 and M2 components were decided upon by visual inspection of all the records in a series, i.e., all records from one subject. Measurement of the records in this way provided consistent results when the independently measured values were compared.

When these results were studied, the subjects appeared to fall naturally into two groups - those under 30 years and those over 30 years. Because of this, it was decided that the "young group" should be those below 30 and the "older group" those over 30 years old. Thirty is the cut-off level that best divides the results into two groups.

The mean area of M1 at each stimulus strength was plotted against the voltage applied to the prodder. Regression analysis gives the "best fit" line to the data in terms of having the least scatter. The results of such an analysis of the M1 values shows a statistically significant difference between the area of M1 in the young and the old subjects at all forces of stimulation (Figure 3.2). The regression lines on Figure 3.2 indicate, by the significant difference in their slopes, that the sensitivity to muscle stretch is significantly different between young and old subjects. The difference in the intercepts of the two regression lines indicates that there is a higher stimulation threshold in the older subjects. Table 3.2 gives values for M1 at all stimulus strengths for both groups, and the results of the regression analysis of those values. Full details of the analysis can be found in the Appendix page 216.

The long-latency component - M2

When the area of M2 is measured in the same way, no such difference between young and old subjects is found. When the area of M2 is plotted against

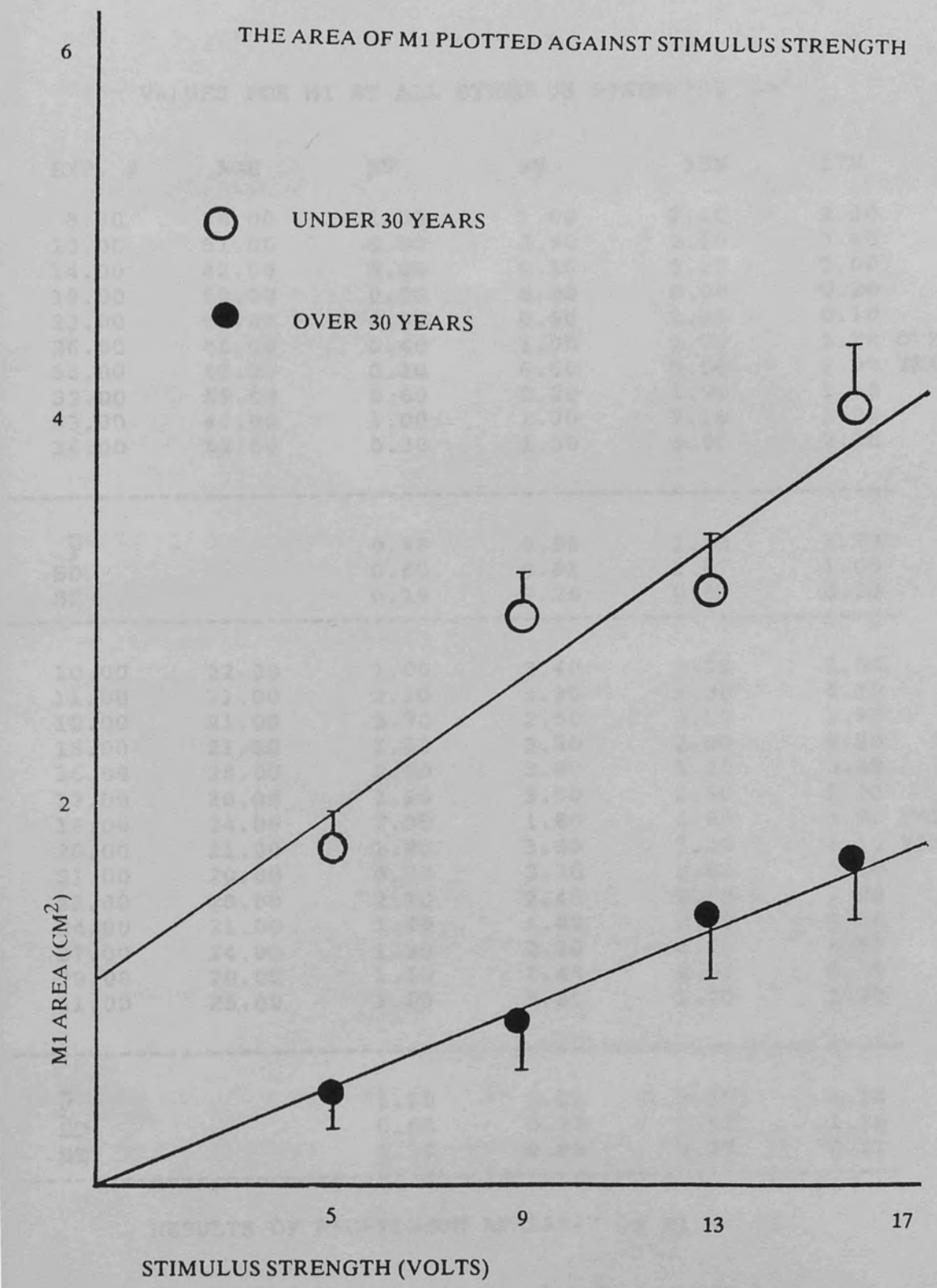


Figure 3.2 A graph showing the difference in the area of M1 in the two age groups. The area of M1 is plotted against stimulus strength.

VALUES FOR M1 AT ALL STIMULUS STRENGTHS cm^2

EXP. #	AGE	5V	9V	13V	17V	
8.00	38.00	1.90	1.00	2.00	2.30	
13.00	51.00	0.00	2.80	2.10	3.60	
14.00	42.00	0.00	0.10	0.10	2.00	
19.00	60.00	0.00	0.00	0.00	0.20	
23.00	63.00	0.50	0.60	0.60	0.10	
26.00	46.00	0.40	1.00	1.70	1.70	OVER 30
30.00	43.00	0.10	0.60	0.50	2.00	YEARS
32.00	59.00	0.60	0.20	1.90	1.10	
33.00	49.00	1.00	1.00	2.10	1.80	
34.00	52.00	0.30	1.30	3.30	2.50	
$\bar{y}$		0.48	0.86	1.43	1.73	
SD		0.60	0.81	1.07	1.05	
SE		0.19	0.26	0.34	0.33	
10.00	22.00	1.00	2.40	2.90	3.50	
11.00	21.00	2.10	3.90	3.20	4.10	
12.00	21.00	2.70	2.50	3.10	3.90	
15.00	21.00	1.50	3.20	2.80	4.90	
16.00	28.00	2.00	3.80	5.30	5.80	
17.00	20.00	2.20	3.00	2.60	6.20	
18.00	24.00	2.90	1.80	4.90	3.90	UNDER 30
20.00	21.00	1.90	3.60	3.20	4.10	YEARS
21.00	20.00	0.50	3.20	2.60	2.30	
22.00	20.00	2.10	2.40	2.10	3.30	
24.00	21.00	1.90	4.00	2.90	2.10	
27.00	24.00	1.30	2.20	4.20	4.50	
29.00	20.00	1.10	2.40	2.60	5.10	
31.00	25.00	1.80	3.80	1.70	3.70	
$\bar{y}$		1.79	3.01	3.15	4.10	
SD		0.66	0.73	1.01	1.16	
SE		0.18	0.20	0.27	0.31	

RESULTS OF REGRESSION ANALYSIS ON M1 VALUES

OVER 30 YEARS Slope = 1.02 Intercept = - 0.06
UNDER 30 YEARS Slope = 2.84 Intercept = 1.08
(when x = 10)

the voltage applied to the prodder the regression lines show no significant difference between the young and older subjects (Figure 3.3). The least squares regression analysis of the M2 values can be found in the Appendix page 216.

M1 and M2 have different physiological origins. The M1 component is the spinal stretch reflex receiving its excitation from the primary endings of the muscle spindles, whereas M2 is the result of activation of predominantly skin afferents. Because they have different origins it is, perhaps, not surprising to find that the two components are not changed by age in the same way.

The M1/M2 ratio

Because factors such as inter-electrode distance, skin resistance, electrode position and hand size could have introduced an unwanted variability between subjects, the ratio of the areas of M1 and M2 was calculated. In each subject M1 and M2 would probably be affected equally by such variables. In Figure 3.4 the M1/M2 ratio has been plotted against age in years. All the subjects under 30 years old had a ratio above 0.45 whilst all but one of those over 30 years were below that level.

Because values which are ratios are not normally distributed it is not possible to use parametric statistics in their analysis. In comparing two separate sets of observations the Wilcoxon rank sum test is an appropriate non-parametric (or distribution free) statistical analysis. This test is a very simple test of significance. Full details of the analysis can be found in the Appendix page 218, and the summarized results are in Table 3.4 together with the M1/M2 ratio values for the two age groups. There is a highly statistically significant difference in the M1/M2 ratio between the two age groups ($p < 0.001$).

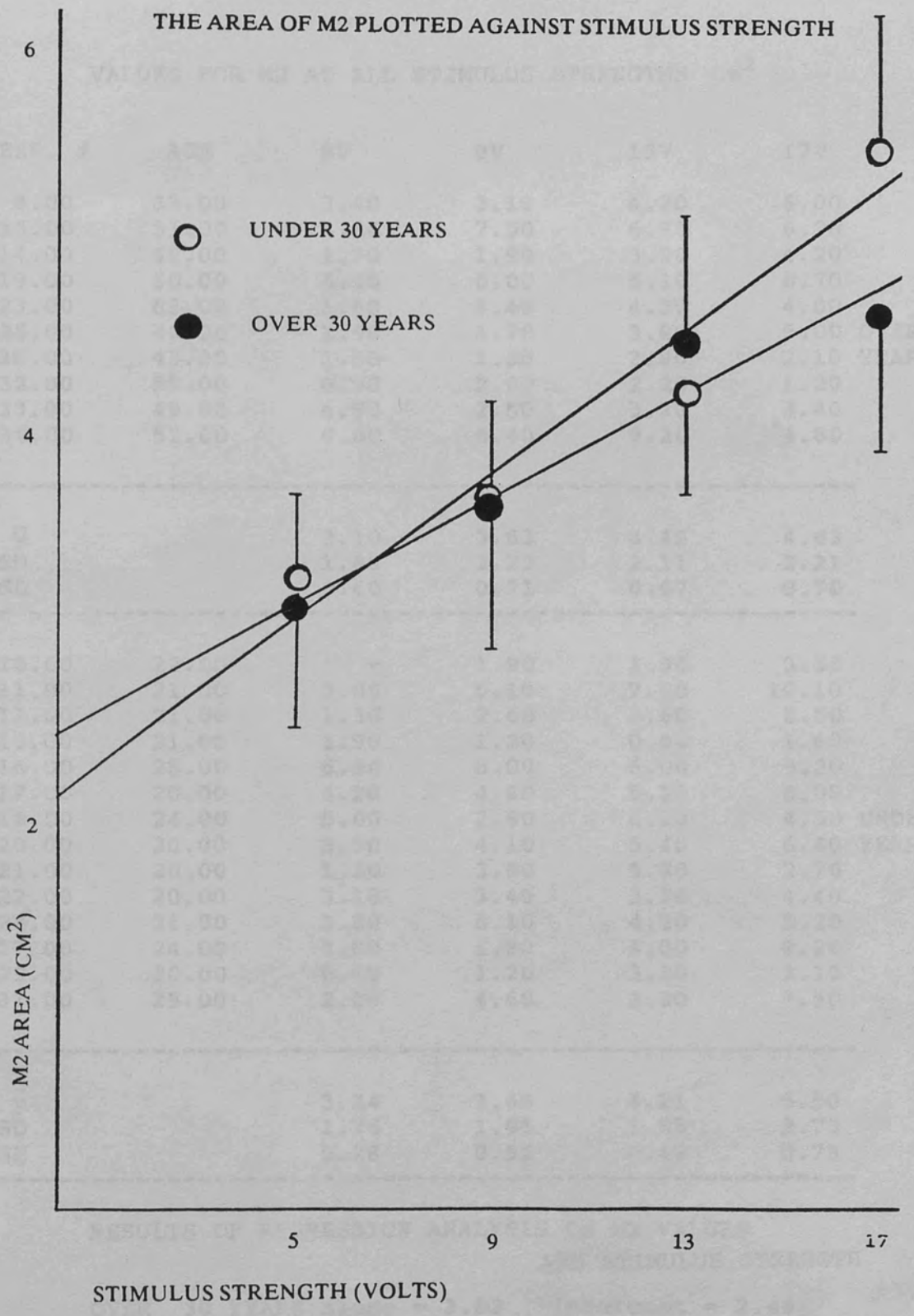


Figure 3.3 A graph of the area of M2 plotted against stimulus strength. There is no significant difference between the two age groups.

TABLE 3.3

VALUES FOR M2 AT ALL STIMULUS STRENGTHS cm^2

EXP. #	AGE	5V	9V	13V	17V	
8.00	38.00	3.40	3.10	4.20	6.00	
13.00	51.00	4.30	7.50	6.80	6.90	
14.00	42.00	1.70	1.90	3.20	4.20	
19.00	60.00	4.20	0.00	5.10	8.70	
23.00	63.00	1.60	4.40	4.30	4.00	
26.00	46.00	1.90	4.70	3.80	5.00	OVER 30
30.00	43.00	1.50	3.80	2.80	2.10	YEARS
32.00	59.00	0.90	2.00	2.20	1.20	
33.00	49.00	4.90	2.50	3.20	3.40	
34.00	52.00	6.60	6.40	9.20	4.80	
$\bar{y}$		3.10	3.63	4.48	4.63	
SD		1.86	2.23	2.11	2.21	
SE		0.60	0.71	0.67	0.70	
10.00	22.00	-	1.90	1.90	3.50	
11.00	21.00	5.00	5.10	7.20	10.10	
12.00	21.00	1.30	2.60	3.60	2.60	
15.00	21.00	1.90	1.20	0.60	1.60	
16.00	28.00	6.50	8.00	6.00	9.20	
17.00	20.00	4.20	4.60	5.10	8.00	
18.00	24.00	5.00	2.80	6.10	4.50	UNDER 30
20.00	20.00	3.50	4.10	5.40	6.40	YEARS
21.00	20.00	1.20	3.90	5.80	2.70	
22.00	20.00	3.10	3.40	3.50	4.40	
24.00	21.00	3.80	6.10	4.20	5.20	
27.00	24.00	4.00	1.80	4.00	8.20	
29.00	20.00	0.60	1.20	3.20	3.10	
31.00	25.00	2.00	4.60	2.30	7.50	
$\bar{y}$		3.24	3.66	4.21	5.50	
SD		1.76	1.95	1.85	2.73	
SE		0.28	0.52	0.49	0.73	

RESULTS OF REGRESSION ANALYSIS ON M2 VALUES AND STIMULUS STRENGTH

OVER 30 YEARS Slope = 3.82 Intercept = 2.46
UNDER 30 YEARS Slope = 3.98 Intercept = 2.13
(when x = 10)

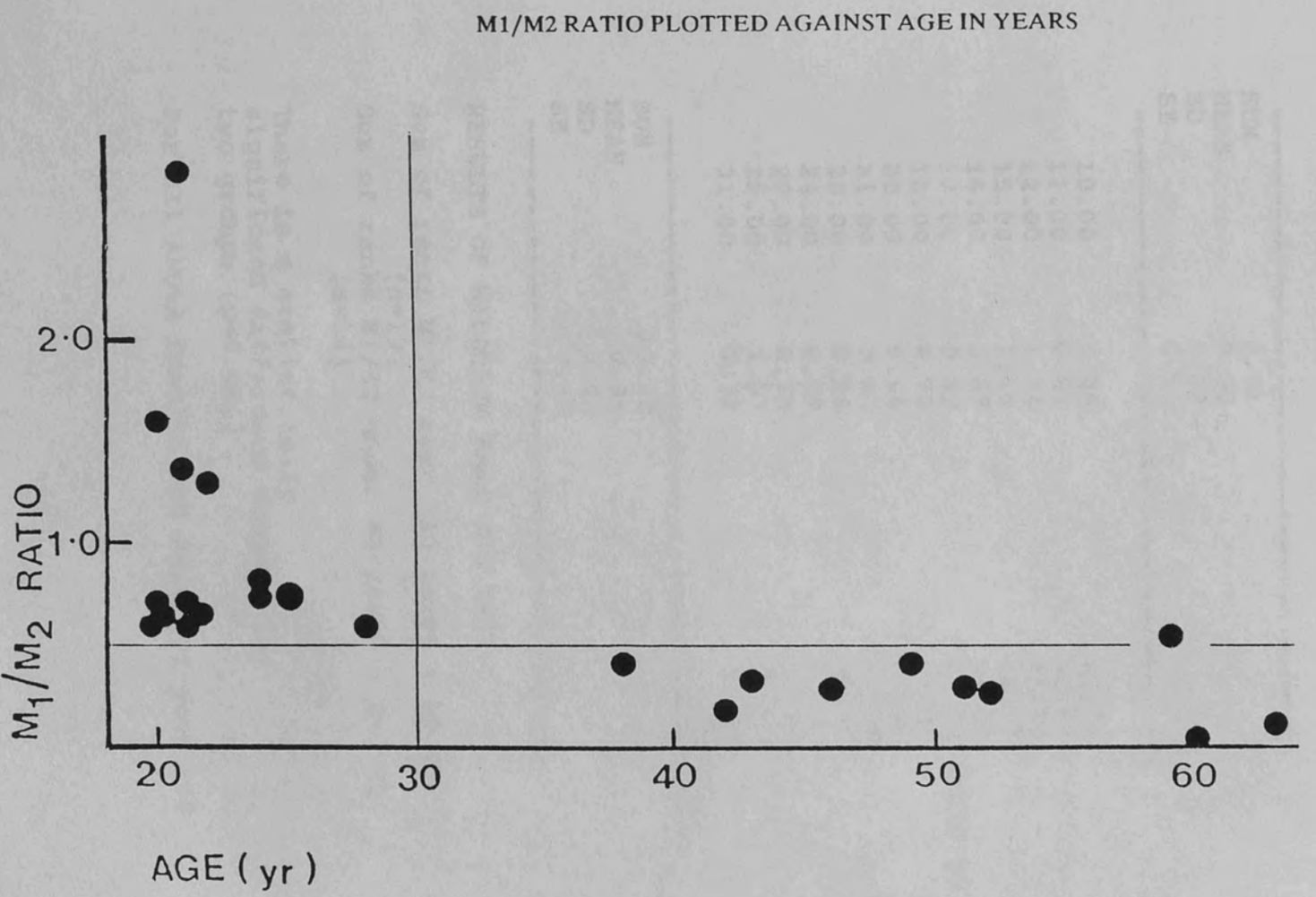


Figure 3.4 The M1/M2 ratio is plotted against the age of the subject. All subjects under 30 years of age have a ratio above 0.45. All but one of the subjects over 30 years of age lie below that level.

M1/M2 RATIO VALUES FOR THE TWO AGE GROUPS

EXP #	M1/M2 cm^2	AGE	
8.00	0.44	38.00	
13.00	0.30	51.00	
14.00	0.14	42.00	
19.00	0.01	60.00	OVER 30 YEARS
23.00	0.15	63.00	
26.00	0.30	46.00	
30.00	0.30	43.00	
32.00	0.64	59.00	
33.00	0.45	49.00	
34.00	0.28	52.00	
SUM	3.01		
MEAN	0.30		
SD	0.18		
SE	0.06		
10.00	0.26	22.00	
11.00	0.51	21.00	
12.00	1.35	21.00	
15.00	2.80	21.00	
16.00	0.57	28.00	
17.00	0.62	20.00	UNDER 30 YEARS
18.00	0.72	24.00	
20.00	0.66	21.00	
21.00	0.64	20.00	
22.00	0.68	20.00	
24.00	0.57	21.00	
27.00	0.79	24.00	
29.00	1.57	20.00	
31.00	0.74	25.00	
SUM	13.48		
MEAN	0.96		
SD	0.62		
SE	0.17		

RESULTS OF WILCOXON RANK SUM TEST

Sum of ranks M1/M2 over 30 years = 59.50
(n=10)
Sum of ranks M1/M2 under 30 years = 240.50
(n=14)

There is a statistically
significant difference between the
two groups ($p<0.001$)

For all ANOVA results see Appendix page 208

Blood Pressure

The casual blood pressure of each subject was recorded whilst at rest. Since a rough guide to normal systolic blood pressure, in mm Hg, can be made by adding the age of a subject to 100, the subjects were divided into two groups: those with a systolic blood pressure (SBP) <130mmHg and those with SBP >130mmHg.

Figure 3.5 is a graph of the M1/M2 ratio plotted against systolic blood pressure for all subjects. Full details of the statistical treatment of the results (Wilcoxon Rank Sum Test) can be found in the Appendix page 219. A summary of the results, together with all M1/M2 ratio values and SBP for the two age groups can be found in Table 3.5. There is a statistically significant difference ($p < 0.01$) between the two blood pressure groups. As the M1/M2 ratio falls the SBP rises. Since the size of the ratio is a reflection of the area of M1, the results show that a smaller stretch reflex response is associated with a rise in SBP.

Each subject completed a questionnaire. This provided the following details:

1. Smoker or non-smoker
2. Caffeine intake
3. Diet - vegetarian or non-vegetarian
4. Amount of exercise
5. Musical instrument - play or not
6. Hypertensive relatives

A preliminary unpaired, two-tailed t-test, comparing the means of subjects above and below 30 years of age, showed that their M1/M2 ratios were highly significantly different. However, type I errors are introduced if data is not normally distributed, as is the case with ratios.

The experiment involved 189 measures across 16 conditions for 24 subjects (see Appendix Table 5.1). The data were analysed by Analysis of Variance appropriate for a randomized blocks design where each variable formed a separate block in which between 5 and 19 observations were made. Post-hoc testing for significant differences among the means was performed using the method of Tukey and Snedecor (1967 and see Plutchick, 1983). The fixed range test (using LSR) gave the same result.

The F-value from the ANOVA was significant at the level $p<0.0001$. Comparison of the group means after the ANOVA, revealed that the interactions between groups A & B (old and young) and A & H (young and non-coffee drinkers) just failed to reach significance at the $p=0.05$ level. The other interactions were not significant (see Table 5.2)

This can be taken to indicate that the highly significant difference ($p<0.0001$) found in the ANOVA carried out solely on the groups A & B (young and old subjects) is not completely independent of all the other factors investigated. In particular, there is a strong interaction between non-coffee-drinking and age. The details of the statistical methods employed can be found in Appendix pages 209-214.

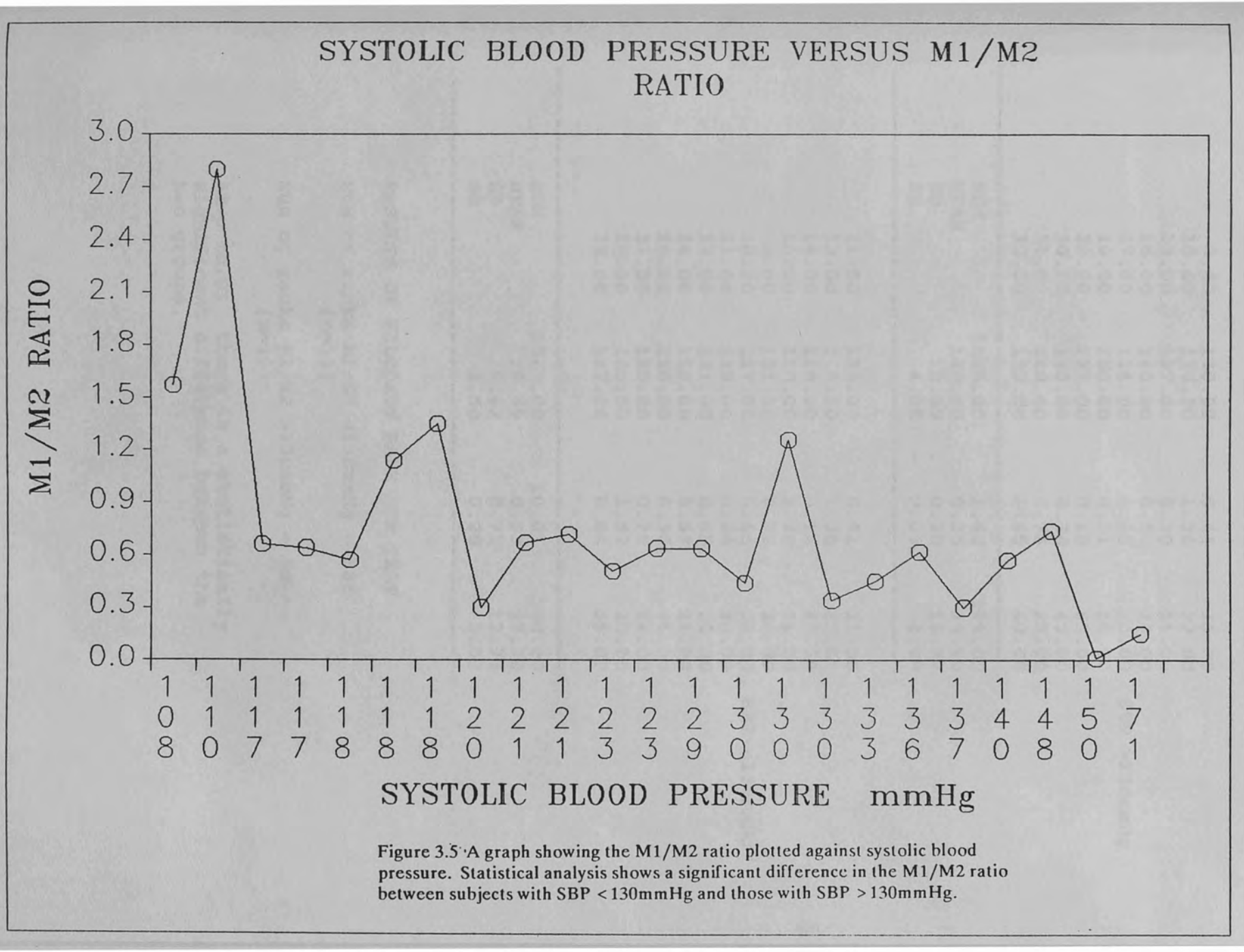


Figure 3.5 A graph showing the M1/M2 ratio plotted against systolic blood pressure. Statistical analysis shows a significant difference in the M1/M2 ratio between subjects with SBP < 130mmHg and those with SBP > 130mmHg.

TABLE 3.5

M1/M2 RATIO FOR THE 2 BLOOD PRESSURE GROUPS

EXP #	SBP	M1/M2	AGE	cm^2
8.00	130.00	0.44	38.00	
10.00	130.00	1.26	22.00	
13.00	137.00	0.30	51.00	
16.00	140.00	0.57	28.00	
17.00	136.00	0.62	20.00	SBP >130mmHg
19.00	150.00	0.01	60.00	
23.00	171.00	0.15	63.00	
30.00	130.00	0.34	43.00	
31.00	148.00	0.74	25.00	
33.00	133.00	0.45	49.00	
SUM	1405.00	1.68	399.00	
MEAN	140.50	0.35	39.90	
SD	12.89	0.28	15.77	
SE	4.08	0.09	4.99	
11.00	123.00	0.51	21.00	
12.00	118.00	1.35	21.00	
14.00	118.00	0.14	42.00	
15.00	110.00	2.80	21.00	
18.00	121.00	0.72	24.00	
20.00	117.00	0.66	21.00	SBP <130mmHg
21.00	129.00	0.64	20.00	
22.00	121.00	0.68	20.00	
24.00	118.00	0.57	21.00	
26.00	120.00	0.30	46.00	
27.00	123.00	0.79	24.00	
29.00	108.00	1.57	20.00	
32.00	117.00	0.64	59.00	
SUM	1543.00	10.01	360.00	
MEAN	118.69	0.83	27.70	
SD	5.42	0.71	12.74	
SE	1.50	0.20	3.53	

RESULTS OF WILCOXON RANK SUM TEST

Sum of ranks M1/M2 <130mmHg = 186
(n=13)

Sum of ranks M1/M2 >130mmHg = 90
(n=10)

At $p < 0.01$ there is a statistically significant difference between the two groups.

SECTION 1 : PART B

Control experiments

The aim of the control experiments was to check that the change in M1 area in the older subjects was not the result of altered physical properties of the neuromuscular system and/or the limb joints.

I : Investigation of muscle and joint stiffness in the FDI.

An accelerometer placed over the belly of the FDI was used to measure the mechanical behaviour of the muscle during stretching. Figure 3.6 is a representative record of the traces recorded; the height from the zero displacement level of the first peak (displacement) was measured for each voltage and the peak displacement calculated. Not all traces had as many as 6 die-away oscillations. On the first of the two graphs in Figure 3.7 the peak displacement of the muscle has been plotted against the voltage applied to the prodder. The relationship was linear, the greater the stimulus the larger the displacement. The second graph (Figure 3.8) shows the peak displacement of the muscle against age in years. There was no correlation between peak displacement of the muscle and age. Table 3.7 gives the accelerometer values. It seemed unlikely from these results that the difference in the stretch reflex between the young and the older subjects was caused by age-related factors that altered the mechanical response of the muscle to the stimulus prod (e.g. arthritis, fibrosis etc.).

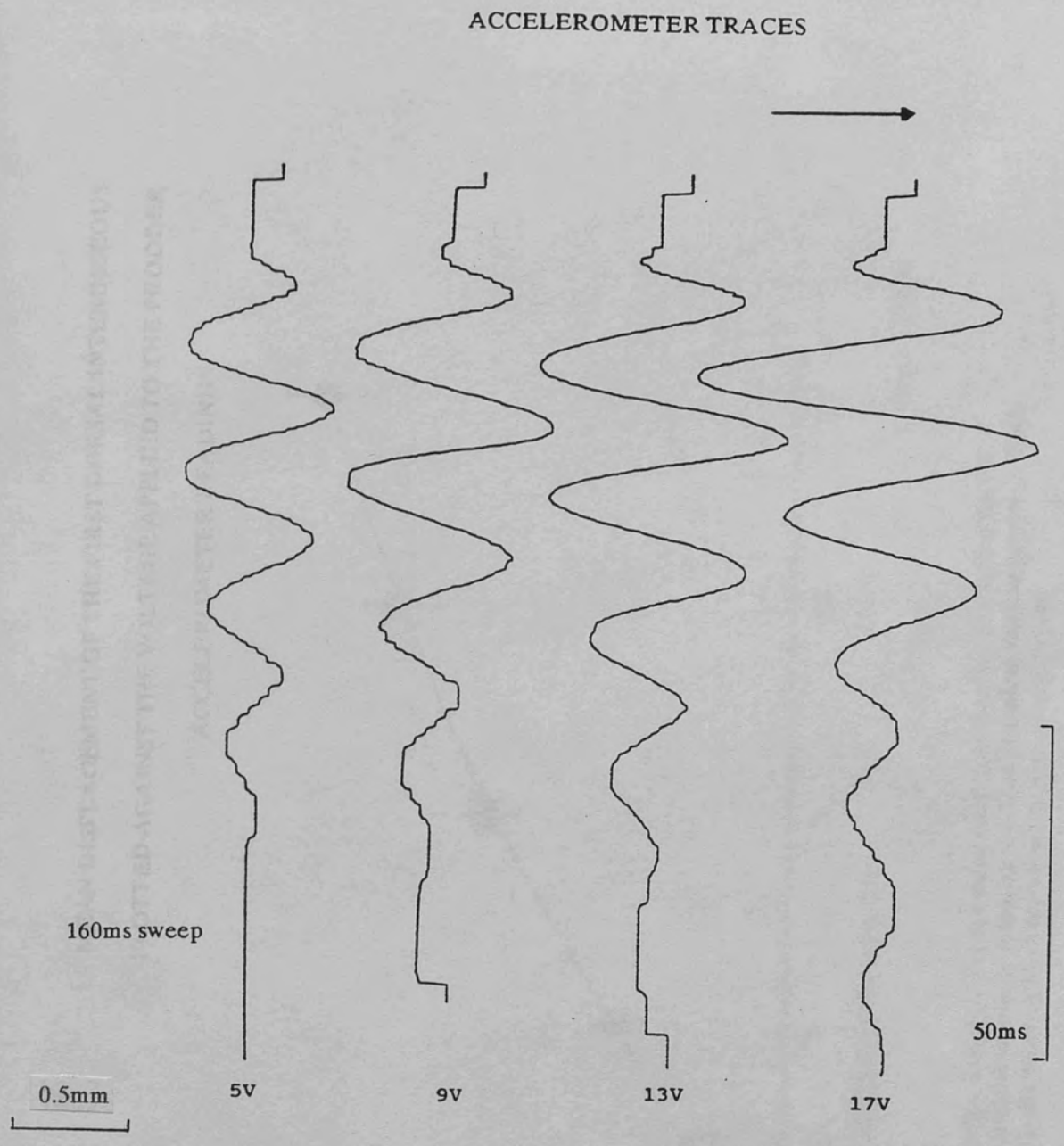


Figure 3.6 Typical traces recorded from an accelerometer placed on the belly of the first dorsal interosseous (FDI) in response to four stimulus levels.

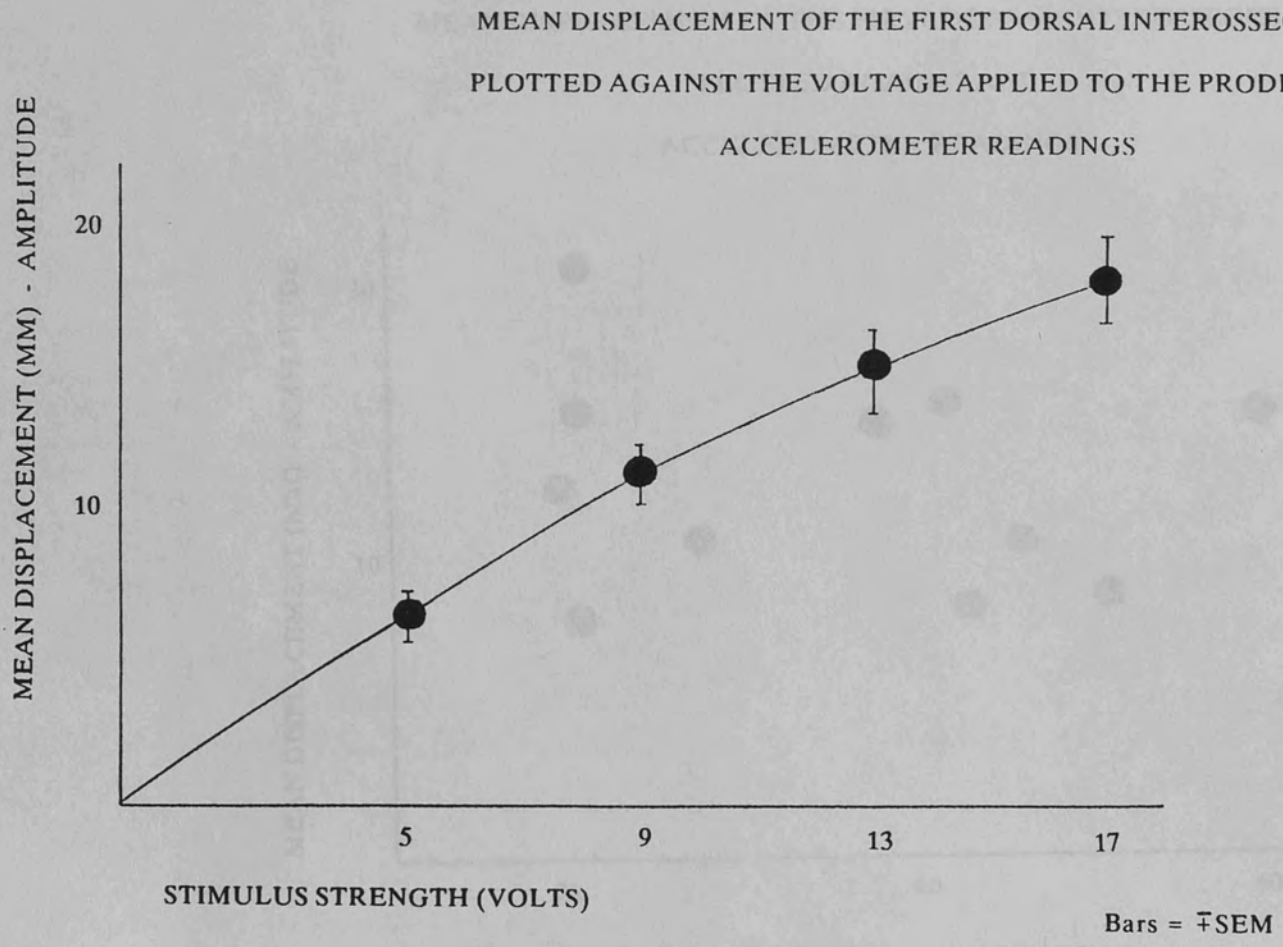


Figure 3.7 Graph shows the mean peak displacement of the first dorsal interosseous muscle in response to a brief stretch of varying intensity. Each point is the mean of 11 observations of peak displacement.

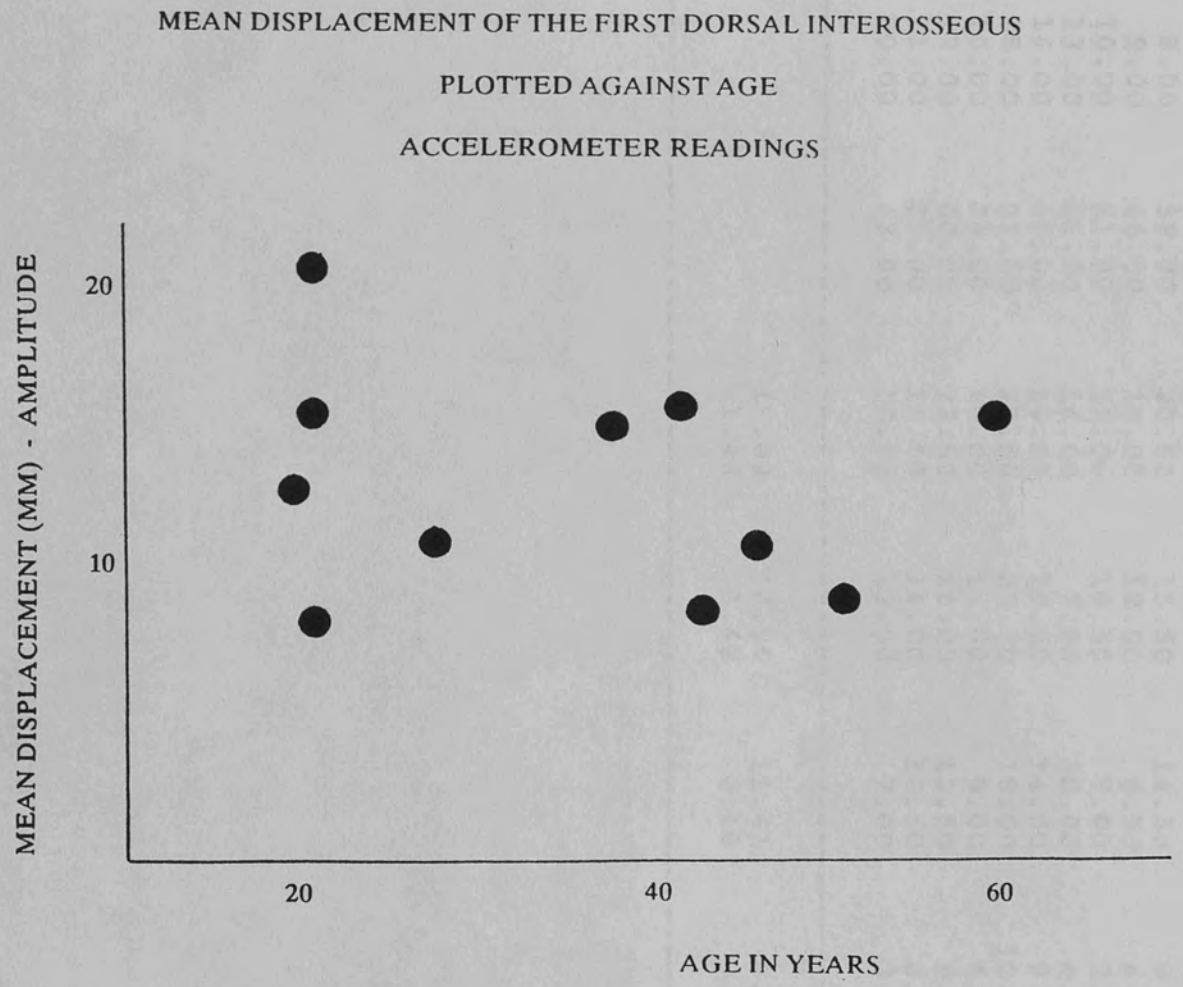


Figure 3.8. Showing the mean peak displacement of FDI plotted against the age of the subject in years. There is no correlation between displacement and age.

ACCELEROMETER VALUES mm

EXP. #	AGE	17V	13V	9V	5V	x
7.00	21.00	22.00	18.00	12.50	8.50	15.25
8.00	38.00	20.50	15.50	14.50	8.50	14.75
9.00	46.00	18.00	12.00	8.50	4.00	10.63
10.00	21.00	13.00	10.50	7.00	2.00	8.13
13.00	51.00	14.00	7.00	10.00	4.00	8.75
14.00	42.00	19.50	19.50	14.00	9.00	15.50
15.00	21.00	27.50	25.50	18.00	10.50	20.38
16.00	28.00	16.00	14.00	9.00	4.00	10.75
19.00	60.00	22.50	16.00	12.50	9.00	15.00
21.00	20.00	15.50	14.00	12.50	8.50	12.63
30.00	43.00	10.50	12.50	7.00	3.50	8.38
	$\bar{x}$	18.09	14.96	11.41	6.50	
	SE	1.42	1.42	0.10	0.90	

II : Neuromuscular Block

The presence of neuromuscular block (NMB) during the course of the experiment might be responsible for part or all of the change in the M1 component of the reflex response. The following experiments were conducted in order to exclude this possibility.

i) The ulnar nerve at the elbow was electrically stimulated with two identical stimuli and the responses of the whole muscle, recorded with surface electrodes, were averaged. A stimulus strength, usually obtained with around 90V, which produced a maximal response was used. After 2ms the first electrical stimulus was applied, followed 25ms later by the second stimulus. This was repeated 8 times and the responses averaged. The procedure was then repeated, but gradually bringing the stimuli closer together. The time between the stimuli was varied until the time interval was only 1ms - see Figure 3.9. At this point the first response became muddled with the second and it was impossible to say if block had occurred or not.

The smallest time interval between the two stimuli was chosen where two distinct responses were obtained, and the subject was asked to make a MVC. The length of the MVC was 2min 45s. The electrical stimuli were switched on for the last few seconds of the contraction and the responses averaged. The MVC had the effect of decreasing the amplitude of the first action potential of the muscle, increasing its width and slightly increasing its latency so that the first action potential occurred later when compared with the control trace recorded before the MVC (Figure 3.10). The second peak was also reduced in amplitude, and in some cases was lost completely. The muscle action potentials (M-waves) were smaller presumably because the action potential of each individual muscle fibre was reduced in amplitude. The width of the peak probably increases due to the prolongation of the external increase in the concentration of potassium ions

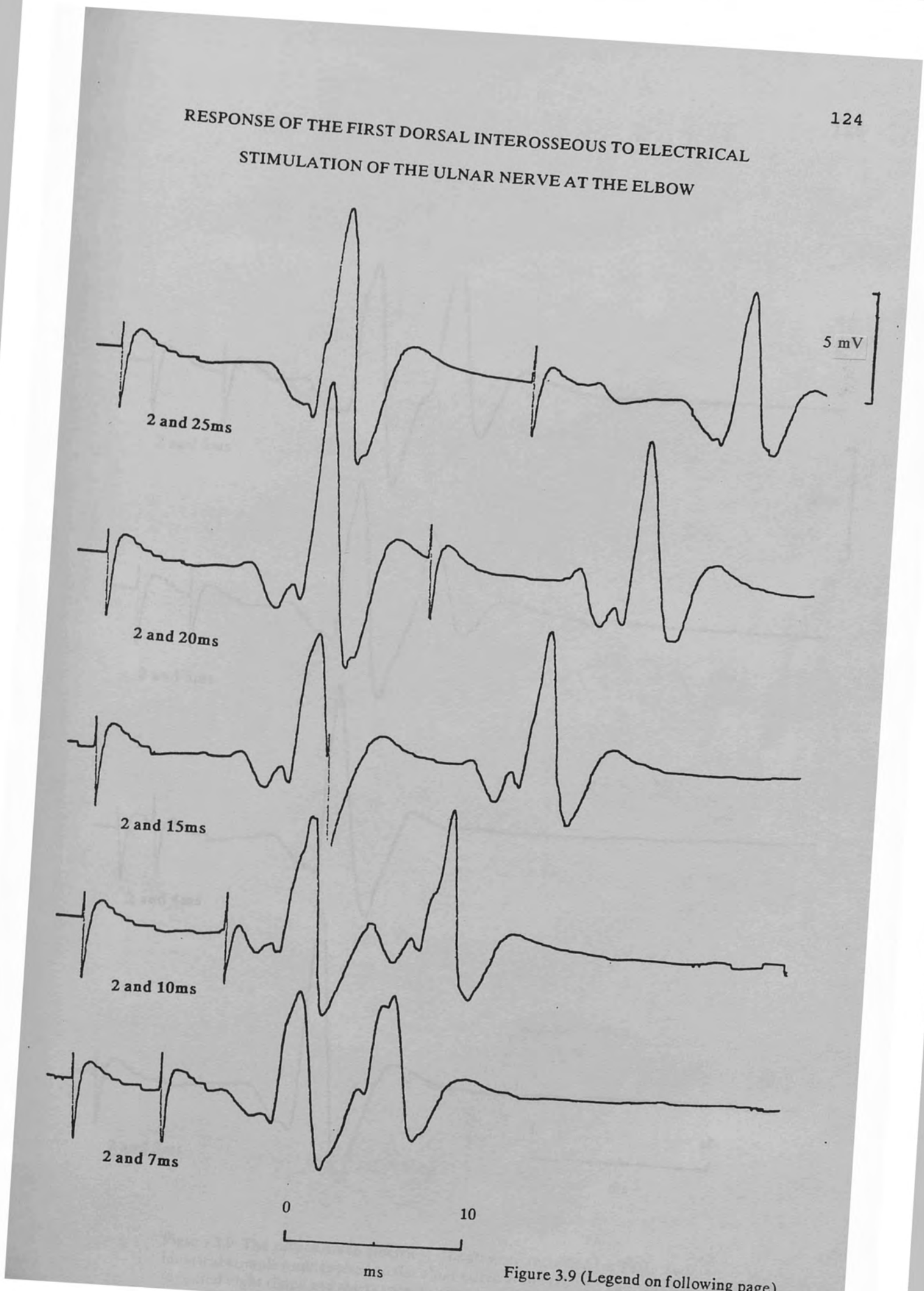


Figure 3.9 (Legend on following page)

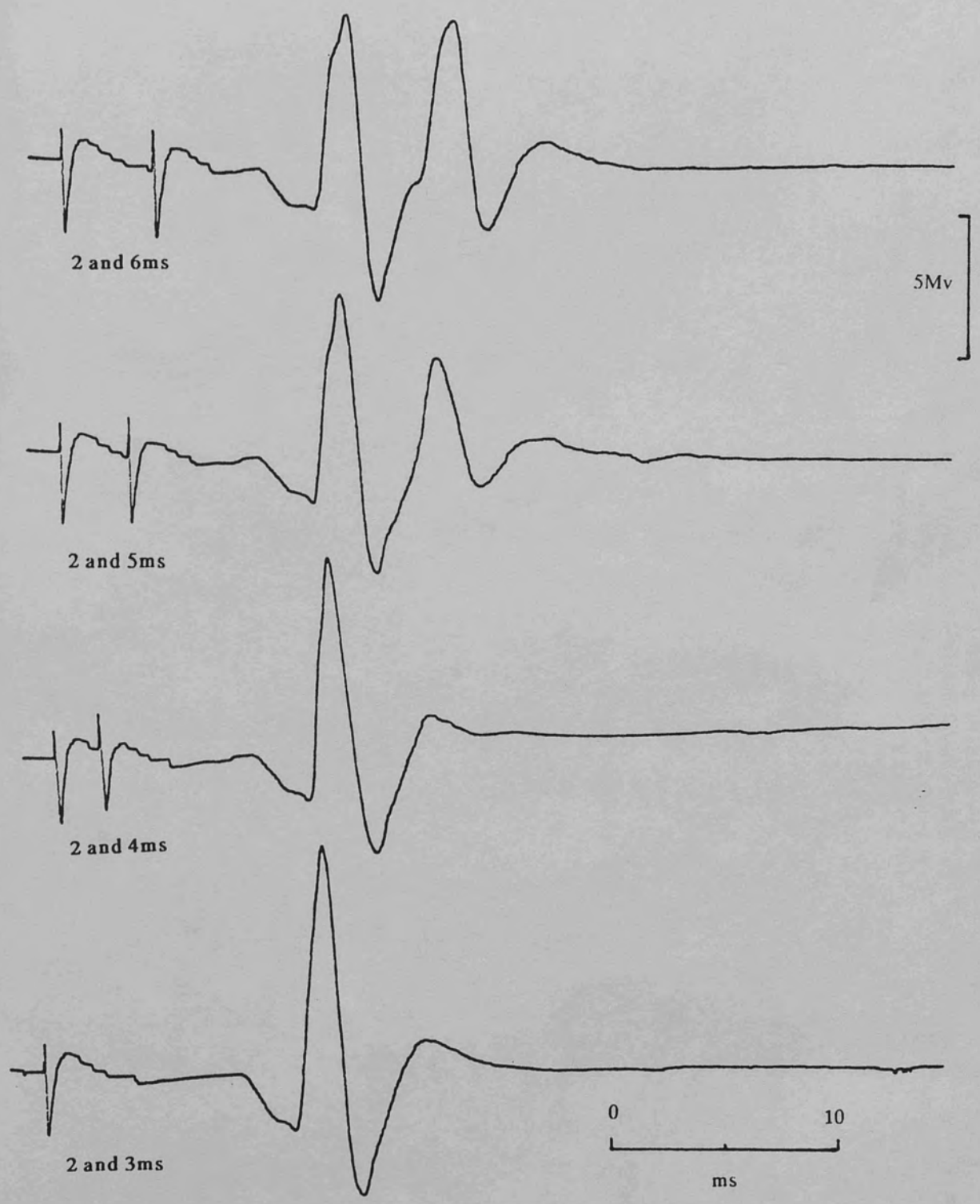


Figure 3.9 The responses to electrical stimuli were recorded for FDI. Two identical stimuli were applied to the ulnar nerve at the elbow. This was repeated eight times and the responses averaged. The procedure was repeated, but gradually bringing the stimuli closer together. There was a 40ms sweep.

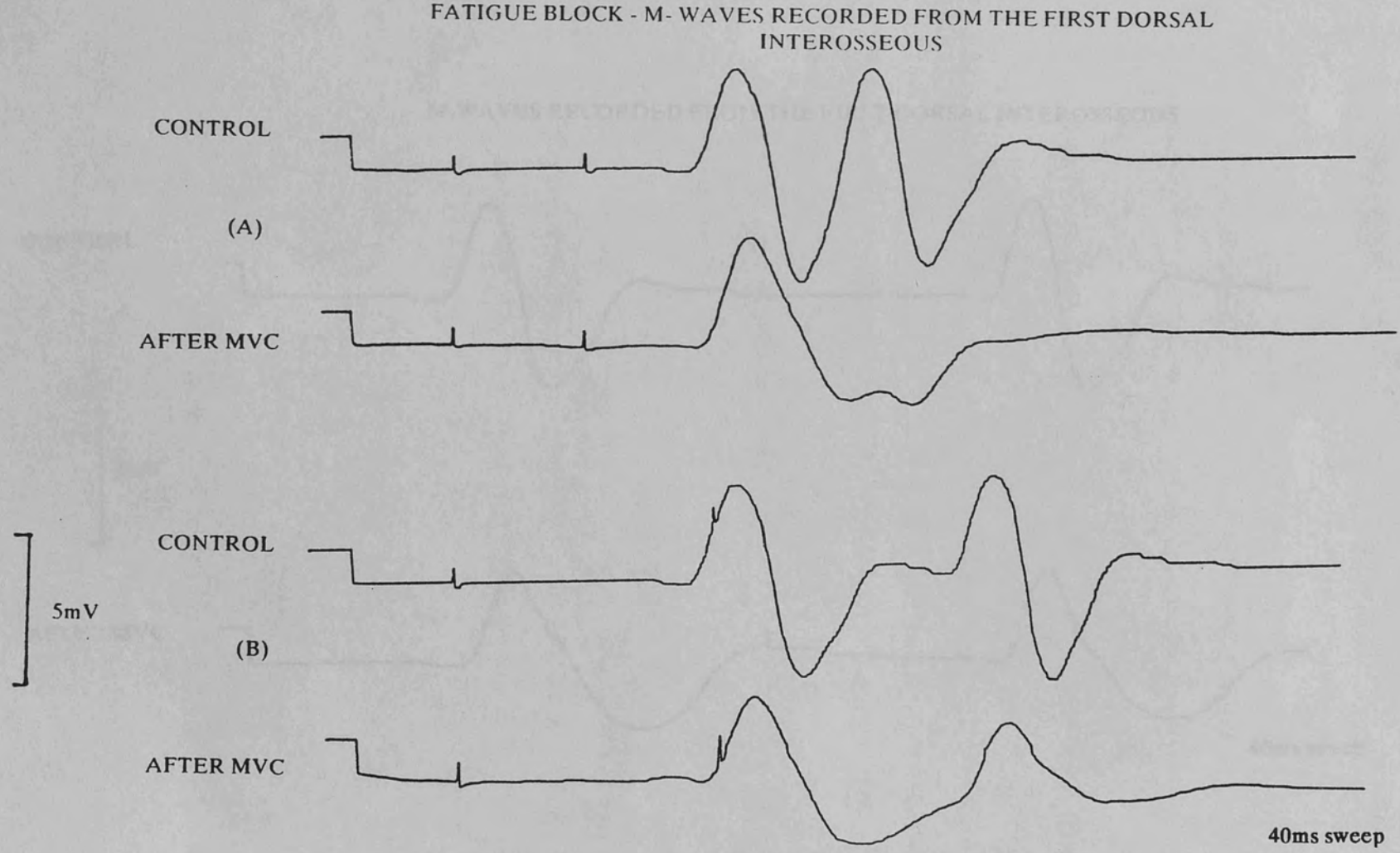


Figure 3.10 is a record of M-waves recorded in FDI after a MVC (2min 45s). (A) shows the response to two identical electrical stimuli given 5ms apart introduced during the last few seconds of the MVC. (B) is the response when the stimuli were 10ms apart.

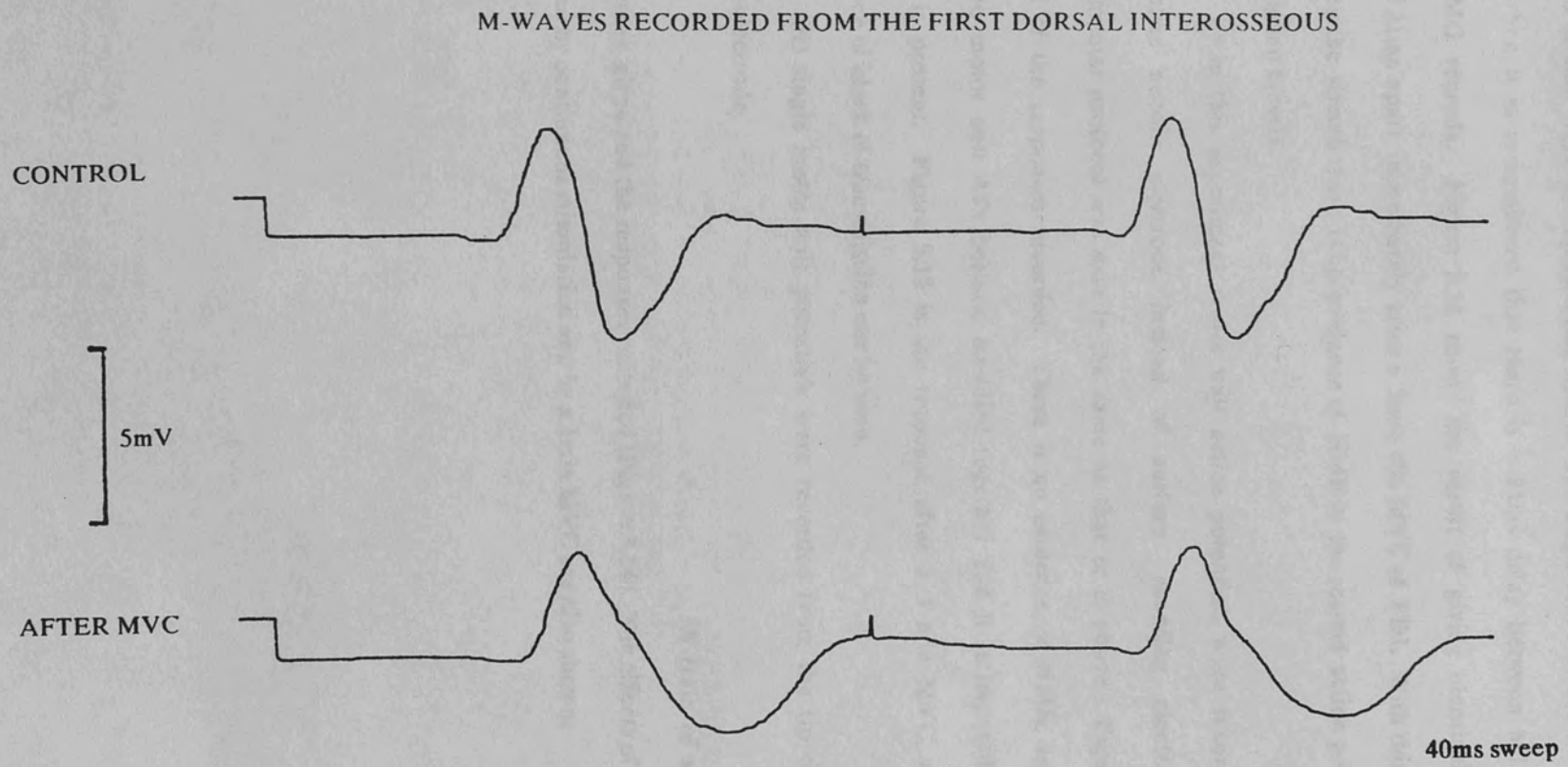


Figure 3.11 This record shows the effect of a MVC (2min 45s) on electrically elicited M-waves in the FDI when the stimuli were separated by 21ms. There was no fatigue block.

which occurs with fatigue. The prolongation may depend on increased external potassium ion concentration or interference with a potassium carrier mechanism.

The main point of this experiment was to look for evidence of NMB when the two stimuli were presented 21ms apart. The importance of the result becomes clear when it is remembered that there is a 21ms delay between M1 and M2 on the EMG records. Figure 3.11 shows the result of giving identical electrical stimuli 21ms apart, immediately after a 2min 45s MVC of FDI. With this interval between the stimuli there is no evidence of NMB in the second action potential in the fatigued muscle.

ii) in this experiment motor unit action potentials were recorded using a concentric needle electrode instead of surface recording electrodes. The experimental protocol was exactly the same as that in i) above. Figure 3.12 is a record of the responses recorded. There is no evidence of NMB, and eventually the two motor unit APs become muddled together and it is impossible to tell if block is present. Figure 3.13 is the response after a 3 min MVC, and again no evidence of block of transmission can be seen.

iii) single motor unit potentials were recorded from the tip of a tungsten micro-electrode. A train of stimuli, 23ms apart were given and the responses recorded (Figure 3.14). The effects of fatigue, induced by continuous stimulation and by a 1min MVC are also shown.

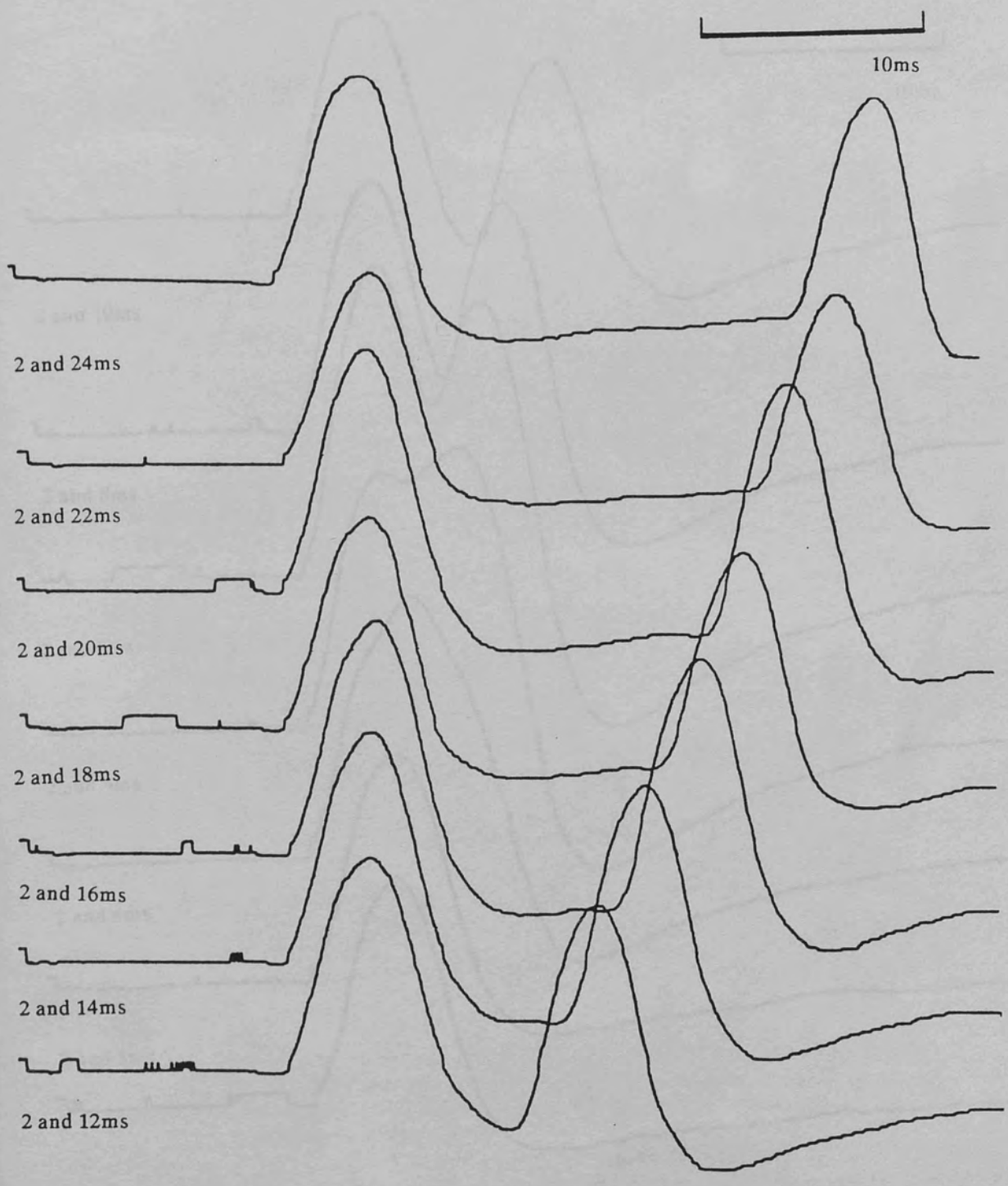


Figure 3.12 shows the motor unit action potentials recorded in response to electrical stimuli using a concentric needle electrode. (Full legend on next page)

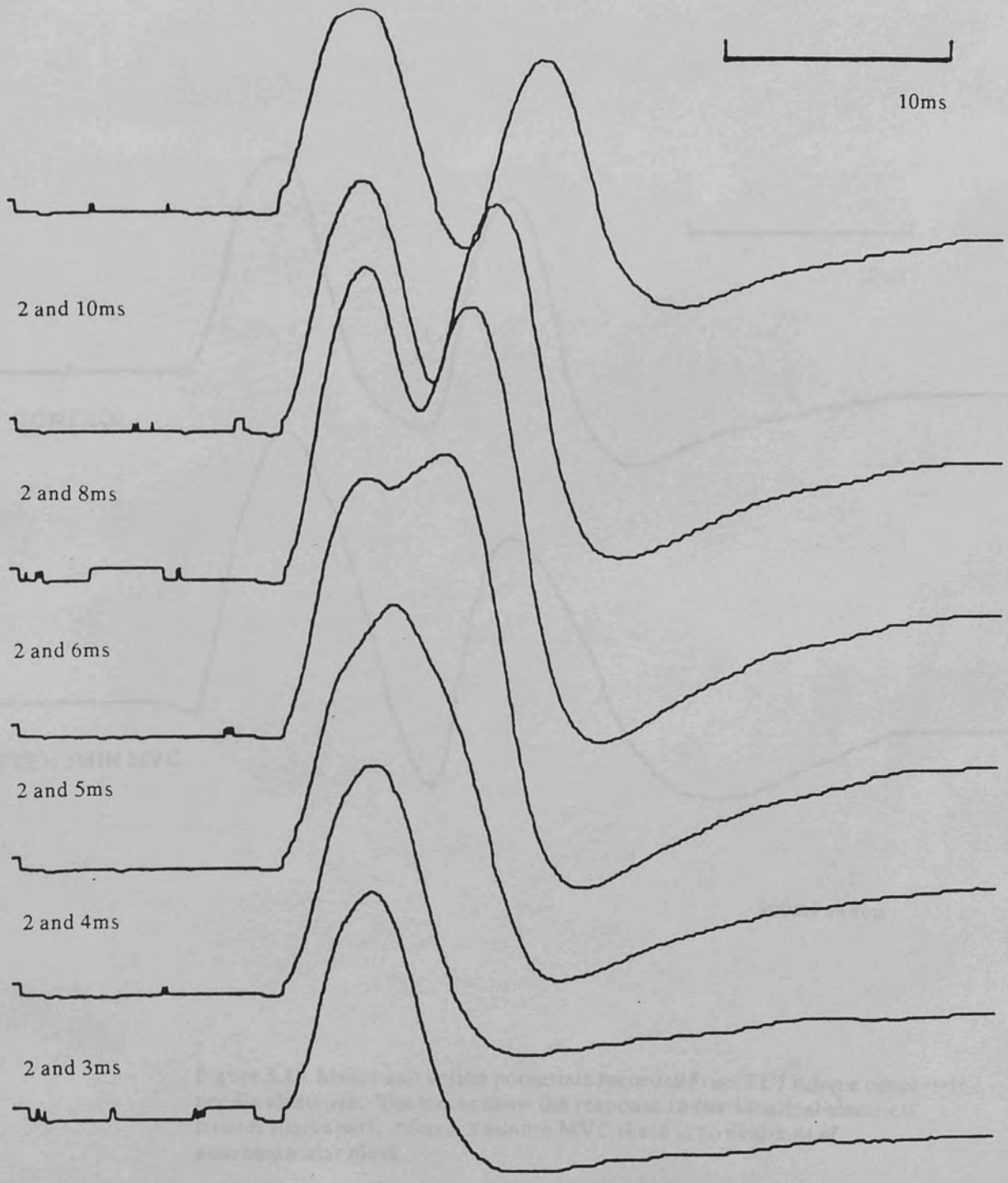


Figure 3.12 The responses to electrical stimuli were recorded from the FDI using a concentric needle electrode. Two identical stimuli were applied to the ulnar nerve at the elbow. This was repeated eight times and the responses averaged. The procedure was repeated, but gradually bringing the stimuli closer together. There is no evidence of neuromuscular block.

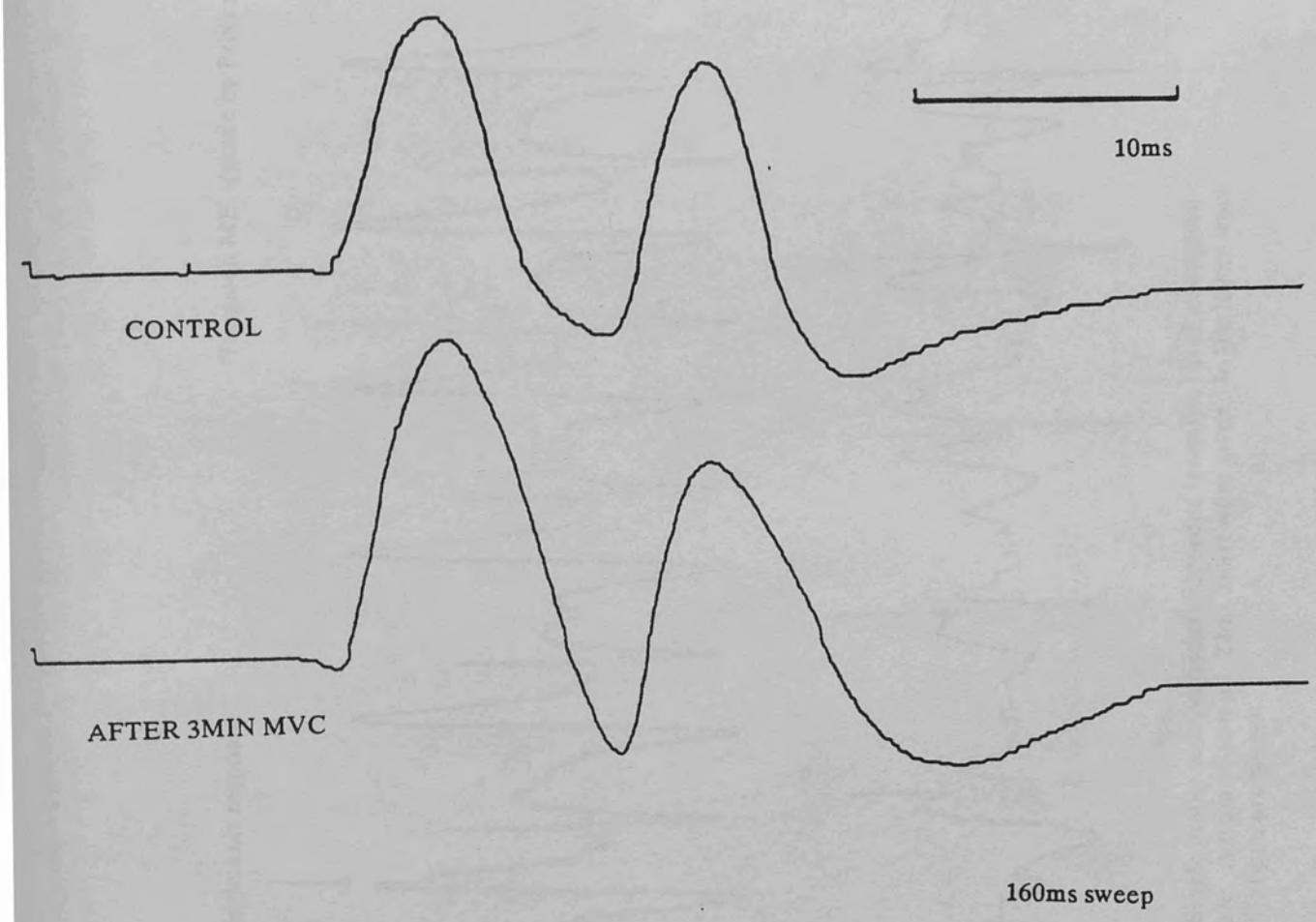


Figure 3.13 Motor unit action potentials recorded from FDI using a concentric needle electrode. The traces show the response to two identical electrical stimuli 10ms apart. After a 3 minute MVC there is no evidence of neuromuscular block.

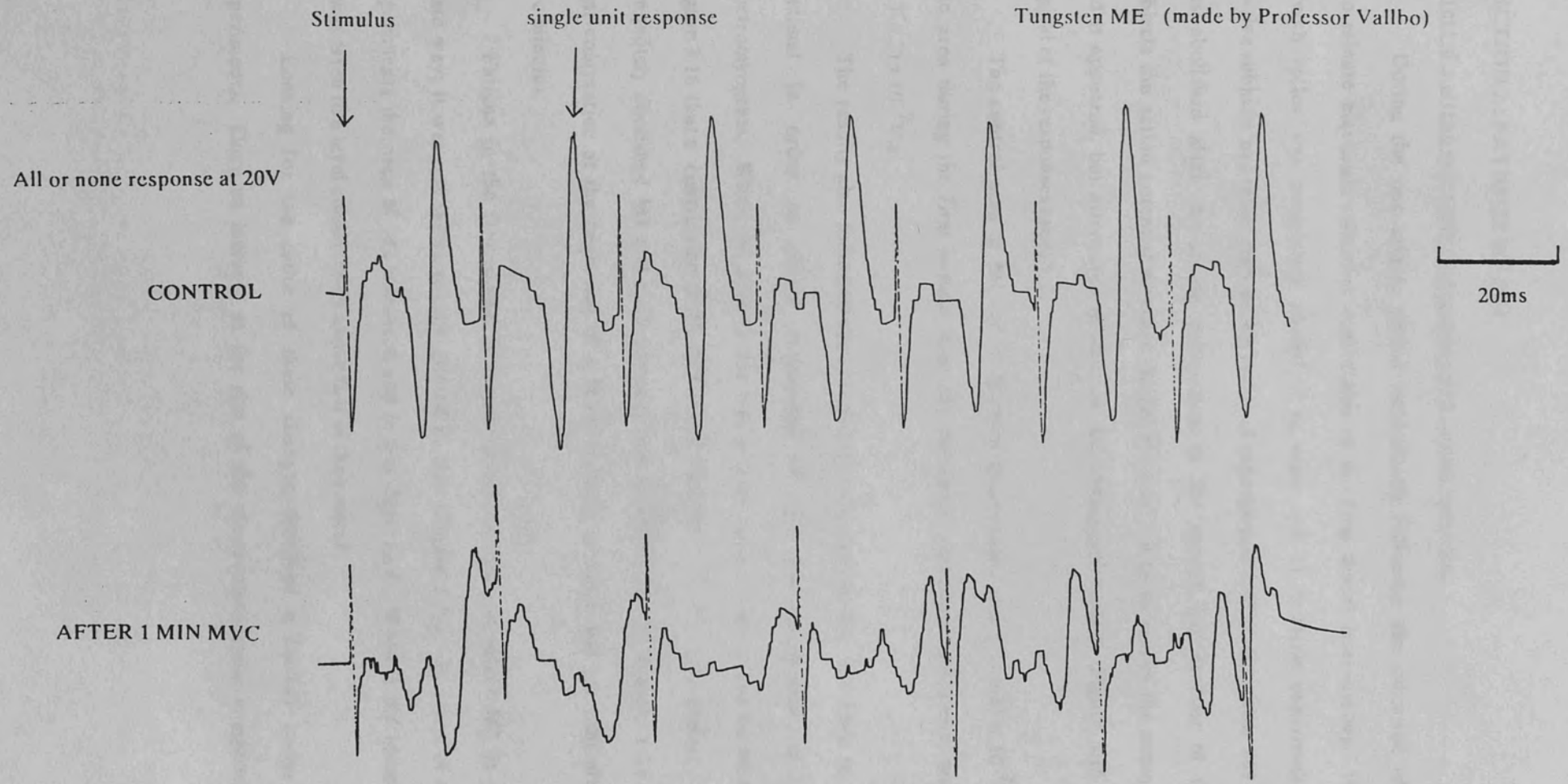


Figure 3.14 Single motor unit potentials recorded from the tip of a tungsten microelectrode. A train of stimuli, 23ms apart were given. In the lower trace the effects of fatigue are shown.

SECTION 2 : FATIGUE OF FDI

Effect of a strong voluntary contraction on the reflex response.

During the one minute period immediately following the cessation of a two minute maximum voluntary contraction of the first dorsal interosseous, the stretch reflex was completely abolished in eight out of thirteen experiments. Twelve subjects had taken part in this series of experiments and in every case M1 was abolished after the strong contraction of the muscle but in four of the subjects the action potential returned during the time taken to record the average and it appeared, but attenuated in size, on the permanent record. Figure 3.15 is typical of the responses recorded.

The control area of M1 for all thirteen experiments was $(5.3 \pm 0.3) \times 10^{-7}$ V.s. The area during the first minute after the maximum voluntary contraction was $(0.7 \pm 0.2) \times 10^{-7}$ V.s.

The results also indicated that a voluntary contraction did not have to be maximal in order to obtain diminution of the M1 component of the electromyogram. When the area of M1 was plotted against time it can be seen in Figure 3.16 that a contraction of 25 MVC for 2 minutes almost completely abolished M1 and a 75 per cent one abolished it. Of course, a 25 per cent contraction at the beginning of a MVC is likely to reach 100 per cent after two minutes.

Fatigue in the first dorsal interosseous muscle did not affect M2 in the same way; it was not systematically altered in size (Figure 3.17). In seven of the experiments the area of M2 increased and in 6 it decreased. When it did increase it was often to a level considerably above that of the control.

Looking for the cause of these changes, involved a further series of experiments. Since an increase in the size of the electromyographic components

THE EFFECT OF A MAXIMUM VOLUNTARY CONTRACTION ON THE EMG OF THE FIRST DORSAL INTEROSSEOUS

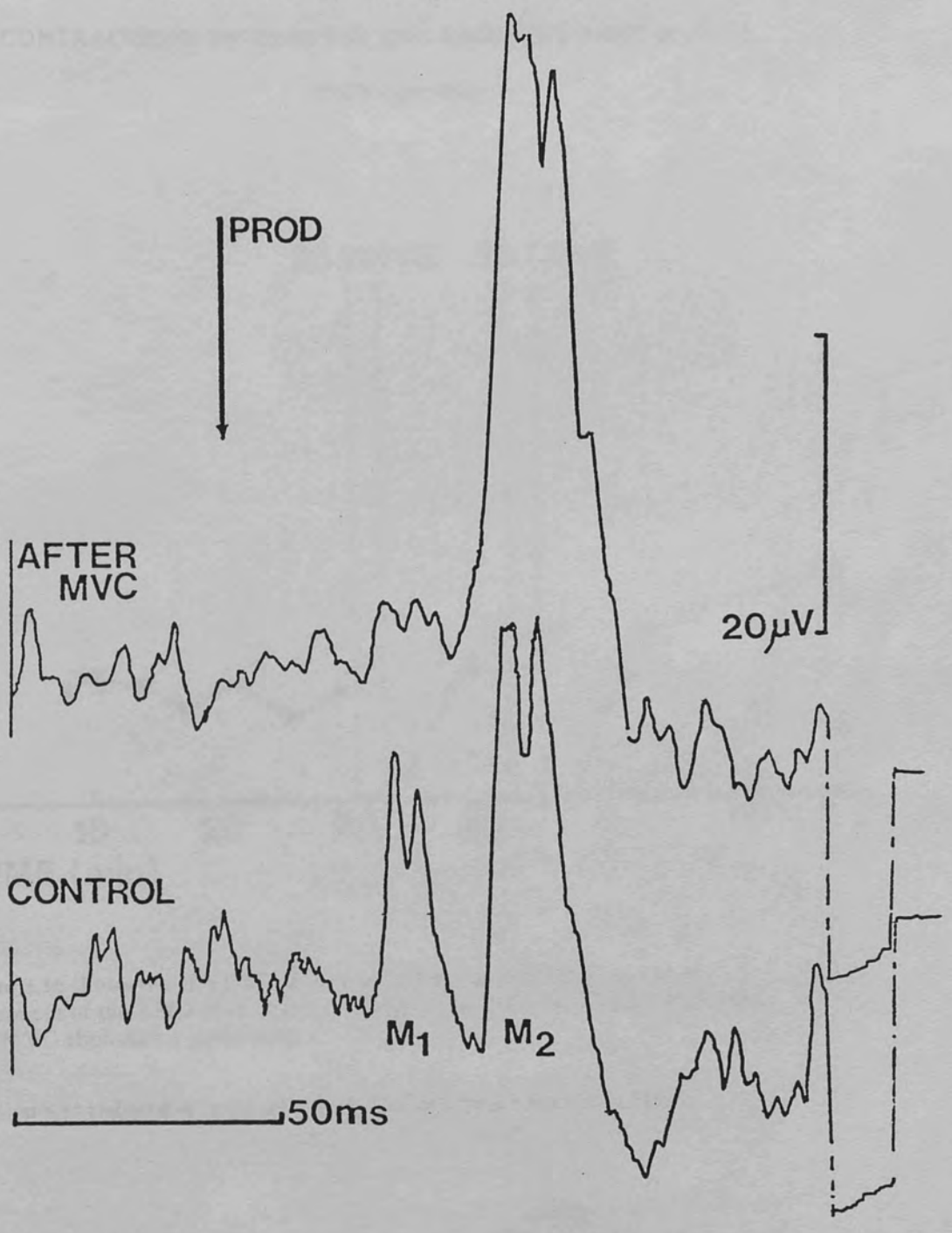


Figure 3.15 shows the effect of a 2 minute MVC on the EMG response in the first dorsal interosseous. In the control M1 and M2 are both present. After the MVC, M1 is almost abolished.

Note that the shorting pulse is large after the MVC; a fact indicating that the integrated electrical activity required to maintain the 10% MVC background contraction was increased. This would explain the larger amplitude of M2 after the MVC.

A GRAPH SHOWING THE EFFECT OF MAXIMUM VOLUNTARY CONTRACTIONS ON M1 IN THE EMG FROM THE FIRST DORSAL INTEROSSEOUS

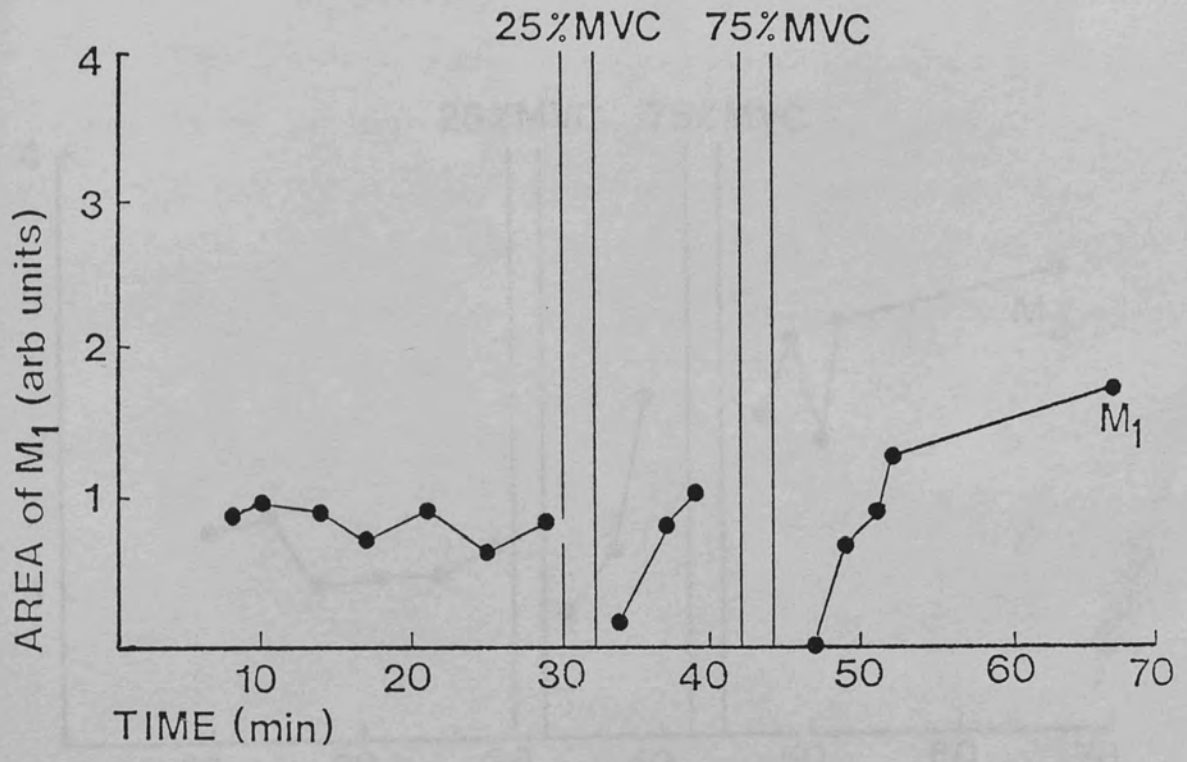


Figure 3.16 shows the effect of a 25% and a 75% 2 minute MVC on the M1 component of the EMG of the FDI. It is almost abolished by a 25% MVC and a 75% MVC abolishes it completely.

Tension was reduced in most subjects by 30-50% by a two minute MVC.

A GRAPH SHOWING THE EFFECT OF MAXIMUM VOLUNTARY CONTRACTIONS ON M2 IN THE EMG FROM THE FIRST DORSAL INTEROSSEOUS

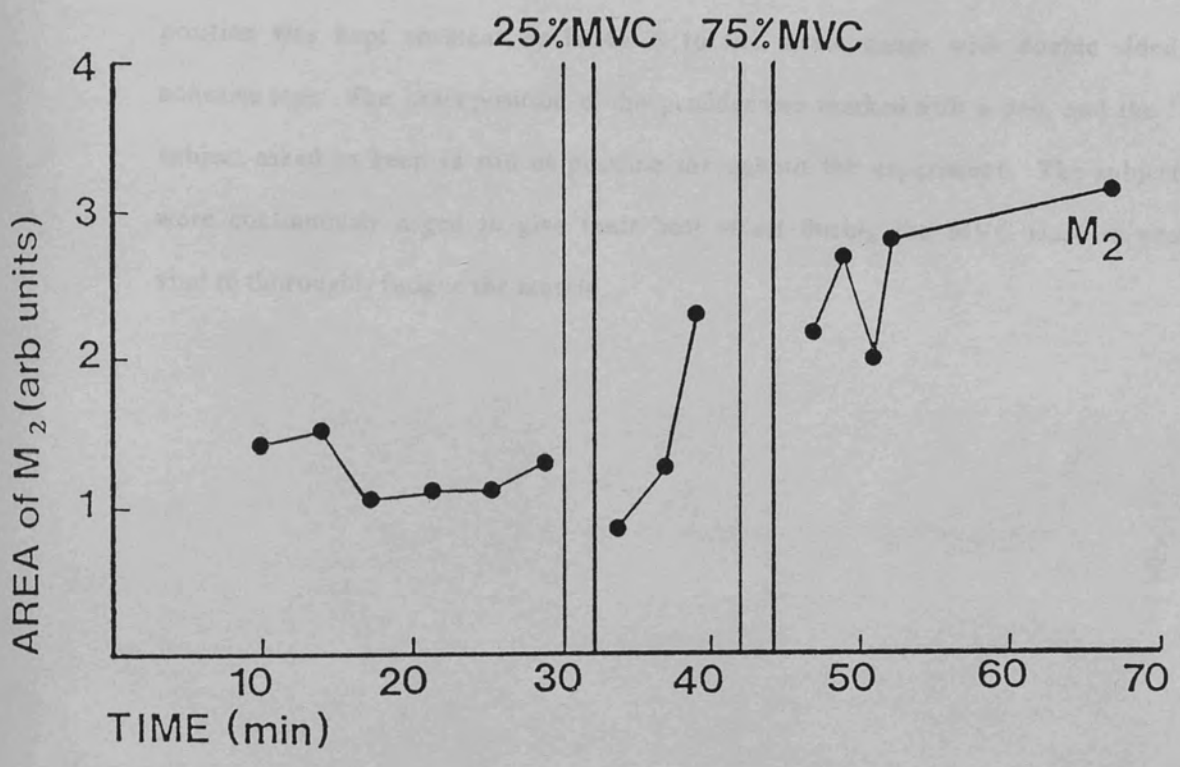


Figure 3.17 shows the effect of a 25% and a 75% 2 minute MVC on the M2 component of the EMG of the FDI. It is not abolished.

is known to be caused by an increase in the force of background activity records were taken with the subject having increasing levels of background contraction, the prod remaining the same. Figure 3.18, in which is plotted M1, M2 and the M1/M2 ratio against increasing force of background contraction, showed that both M1 and M2 increased in area. At each level of force, M2 area increased more than M1; the ratio, after a small reduction at the lower force levels, remained unaltered. In fatigue the contractile mechanism gradually fails, so an increased voluntary drive is necessary to maintain the required tension.

Every effort was made to immobilise completely the arm, and the finger position was kept constant by fixing it to the strain gauge with double sided adhesive tape. The exact position of the prodder was marked with a pen, and the subject asked to keep as still as possible throughout the experiment. The subjects were continuously urged to give their best effort during the MVC since it was vital to thoroughly fatigue the muscle.

A GRAPH OF THE AREA OF M1, M2 AND THE M1/M2 RATIO VERSUS FORCE

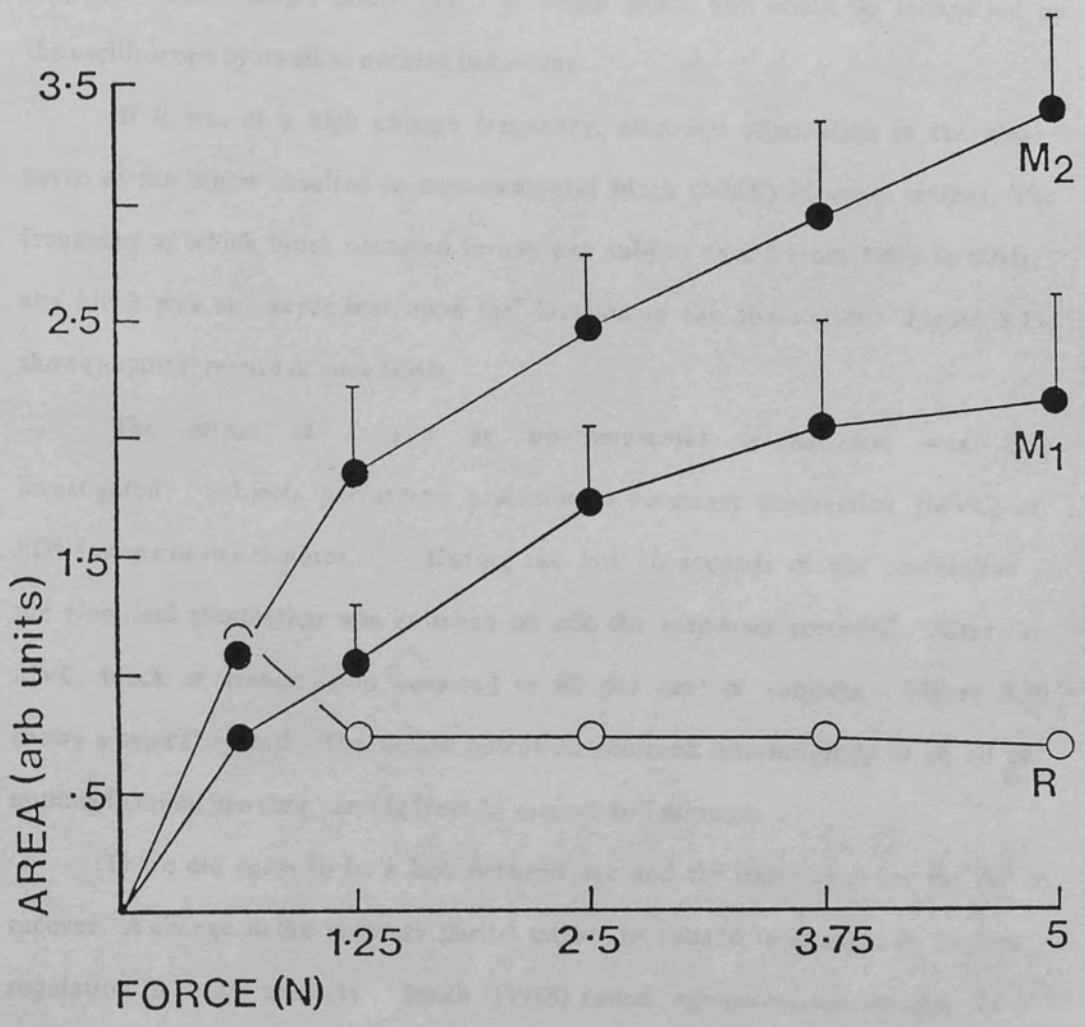


Figure 3.18 shows the effect of increasing the force of the background contraction on M1, M2 and M1/M2 ratio

SECTION 3 : NEUROMUSCULAR BLOCK

The ulnar nerve was electrically stimulated at the elbow at various frequencies and the responses in the first dorsal interosseous were recorded. Action potentials (AP) were recorded from single motor units in the FDI using surface electrodes. The ulnar nerve was stimulated at a voltage which produced a response from a single motor unit. A single motor unit could be recognised on the oscilloscope by its all or nothing behaviour.

If it was at a high enough frequency, electrical stimulation of the ulnar nerve at the elbow resulted in neuromuscular block (NMB) in every subject. The frequency at which block occurred in any one subject varied from 10Hz to 60Hz, and block was not dependent upon the duration of the stimulation. Figure 3.19 shows a typical record of such NMB.

The effect of fatigue on neuromuscular transmission was then investigated. Subjects performed a maximum voluntary contraction (MVC) of FDI for one or two minutes. During the last 10 seconds of the contraction the electrical stimulation was switched on and the responses recorded. After the MVC, block of transmission occurred in 80 per cent of subjects - Figure 3.20 shows a typical record. The action potentials returned intermittently in an all or nothing fashion, in a time varying from 15 seconds to 7 minutes.

There did seem to be a link between age and the time taken for the AP to recover. A change in the recovery period might be related to changes in calcium regulation in older subjects. Smith (1988) found age-associated changes in calcium regulation for extensor digitorum longus muscles of old rats. Rates of calcium clearance from synaptic release sites were lower in the aged muscle. He suggested that this may be related to progressive disuse of the muscle, and a consequent decrease in the expression of calcium regulatory enzymes.

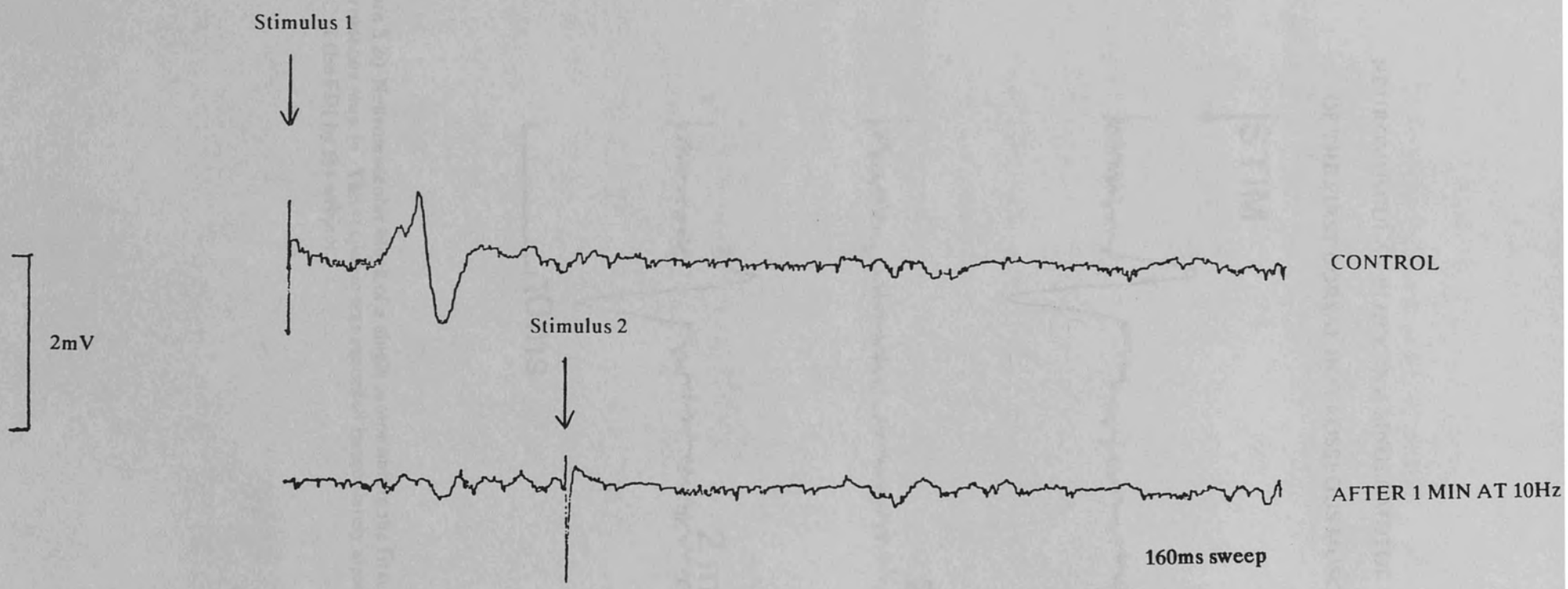


Figure 3.19 Neuromuscular block of a single motor unit in the first dorsal interosseous muscle recorded using surface electrodes. The ulnar nerve was electrically stimulated at the elbow. The lower trace is a record of the response after 1 minute of 10Hz stimulation. The stimulus strength was 35 volts.

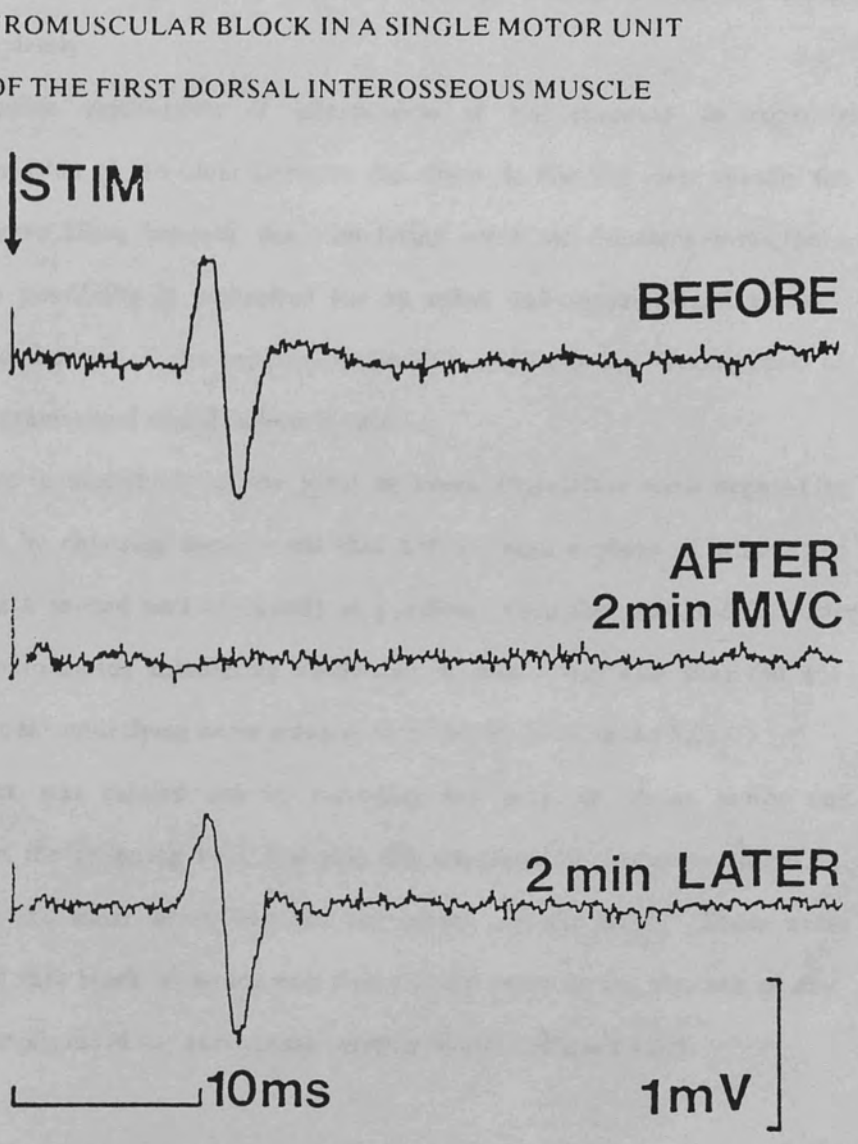


Figure 3.20 Neuromuscular block of a single motor unit in the first dorsal interosseous muscle. The response was recorded immediately after a 2 minute MVC of the FDI by the subject.

Sometimes the response recorded represented more than one motor unit. At the same latency, it was found that some units blocked and others did not (see Figure 3.21). The action potential on the oscilloscope became smaller but did not disappear completely.

A possible explanation of interruption of the response to repetitive electrical stimulation of the ulnar nerve at the elbow, is that for some reason, the appropriate nerve fibre beneath the stimulating electrode becomes inexcitable. Normally, this possibility is controlled for by using well-supramaximal stimuli. However, since the aim of the experiments in this section is the investigation of single units, supramaximal stimuli cannot be used.

Changes in excitability at the point of nerve stimulation were negated as far as possible by choosing motor units that had as large a range of stimulating voltage (before a second unit obtruded) as possible; often this was 20-30V. Also care was taken to attach stimulating electrodes in such a way that they did not move relative to the underlying nerve trunk even during an MVC of the FDI.

A check was carried out by recording not only the single motor unit potentials from the fatiguing FDI, but also the simultaneous nerve potentials in the arm, from the ulnar nerve between the elbow and the hand. These nerve records showed that block of motor unit firing could occur in the absence of any change in the amplitude of the nerve trunk action potentials (Figure 3.22).

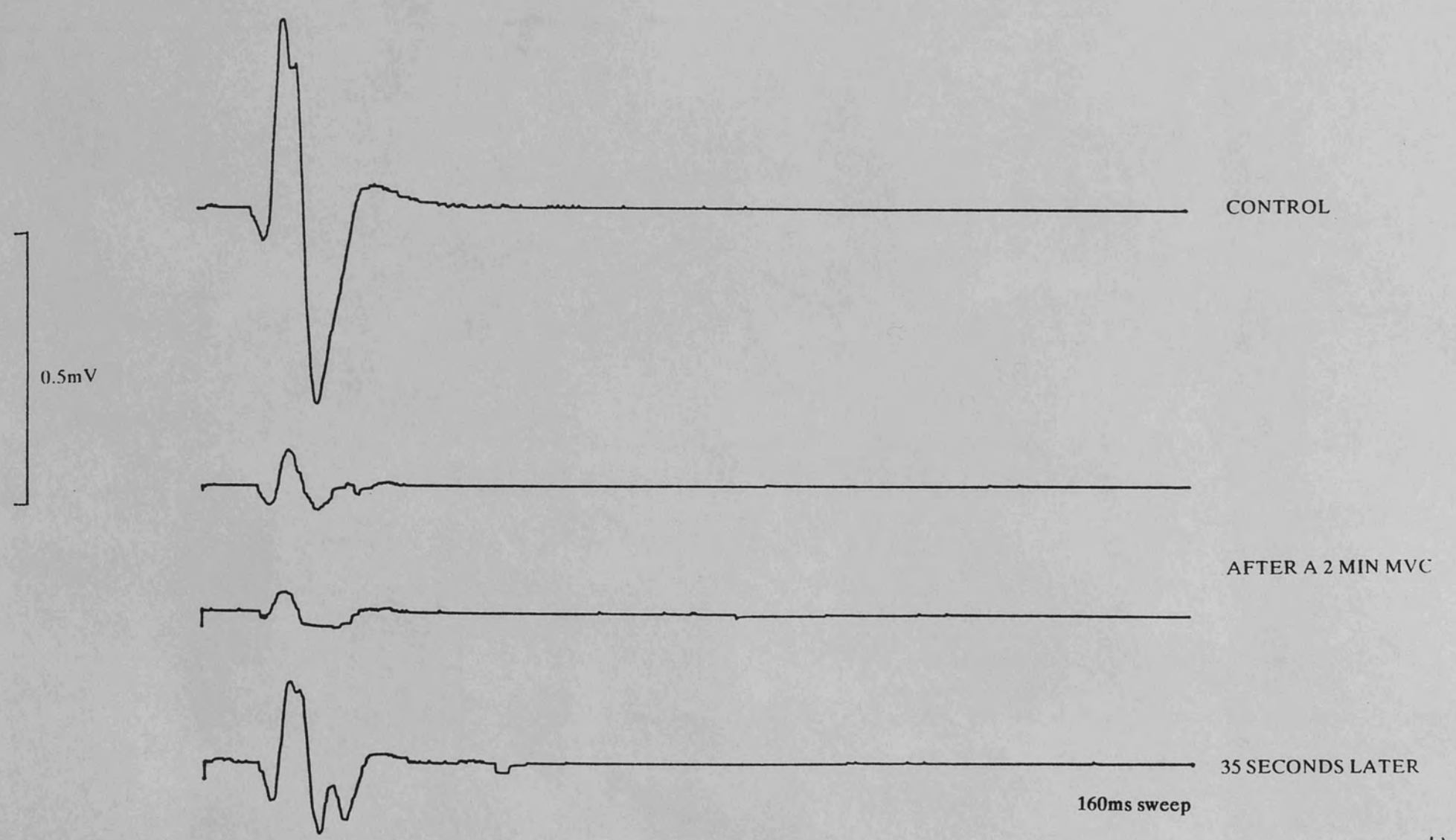


Figure 3.21 The partial neuromuscular block recorded from an action potential consisting of more than one motor unit immediately after a 2 minute MVC of the FDI. The action potential began its recovery after 4 minutes rest. The motor units were of the same latency: some units blocked and others did not.

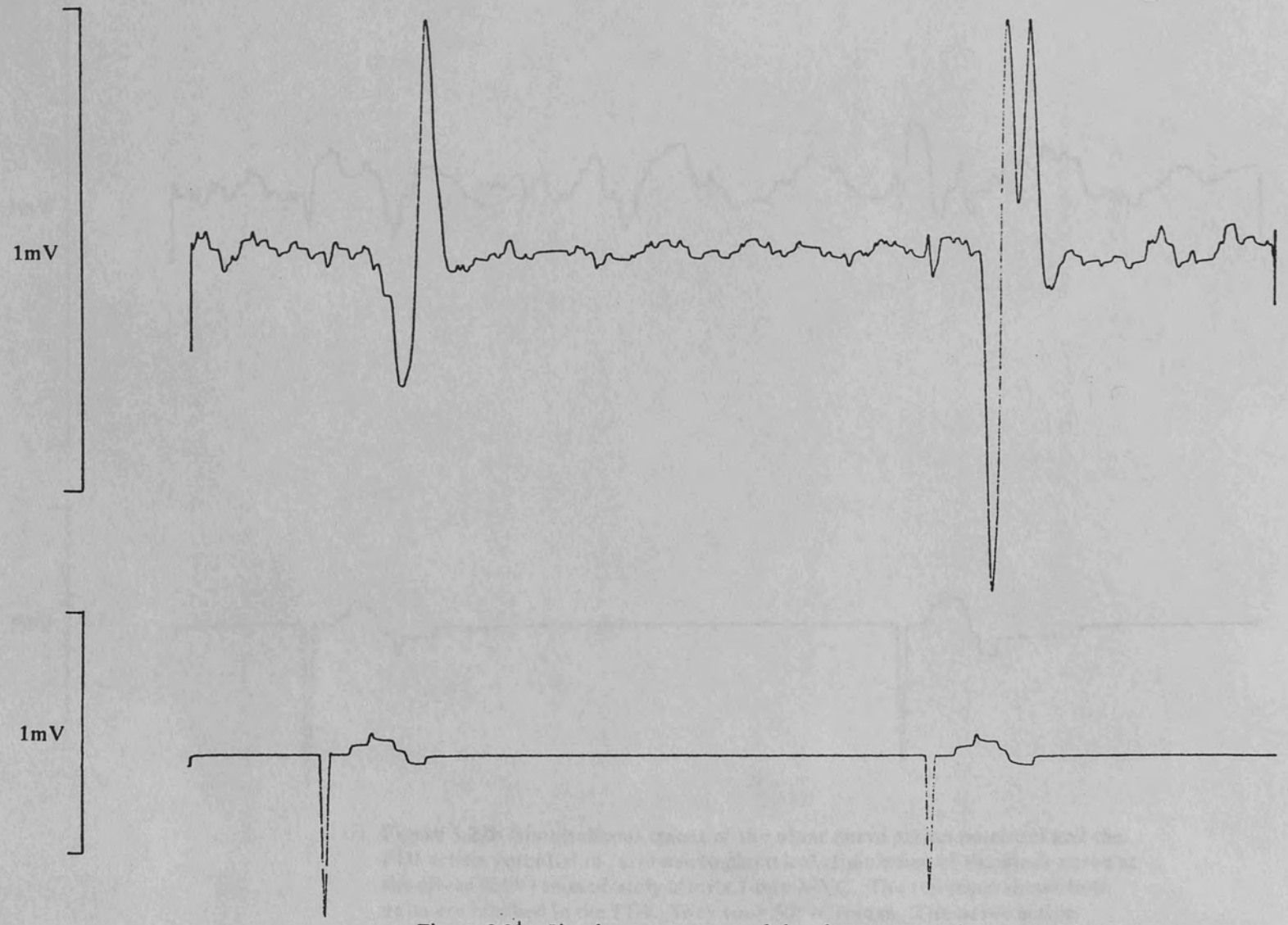


Figure 3.22a Simultaneous traces of the ulnar nerve action potential and the FDI action potential in response to electrical stimulation of the ulnar nerve at the elbow (30V).

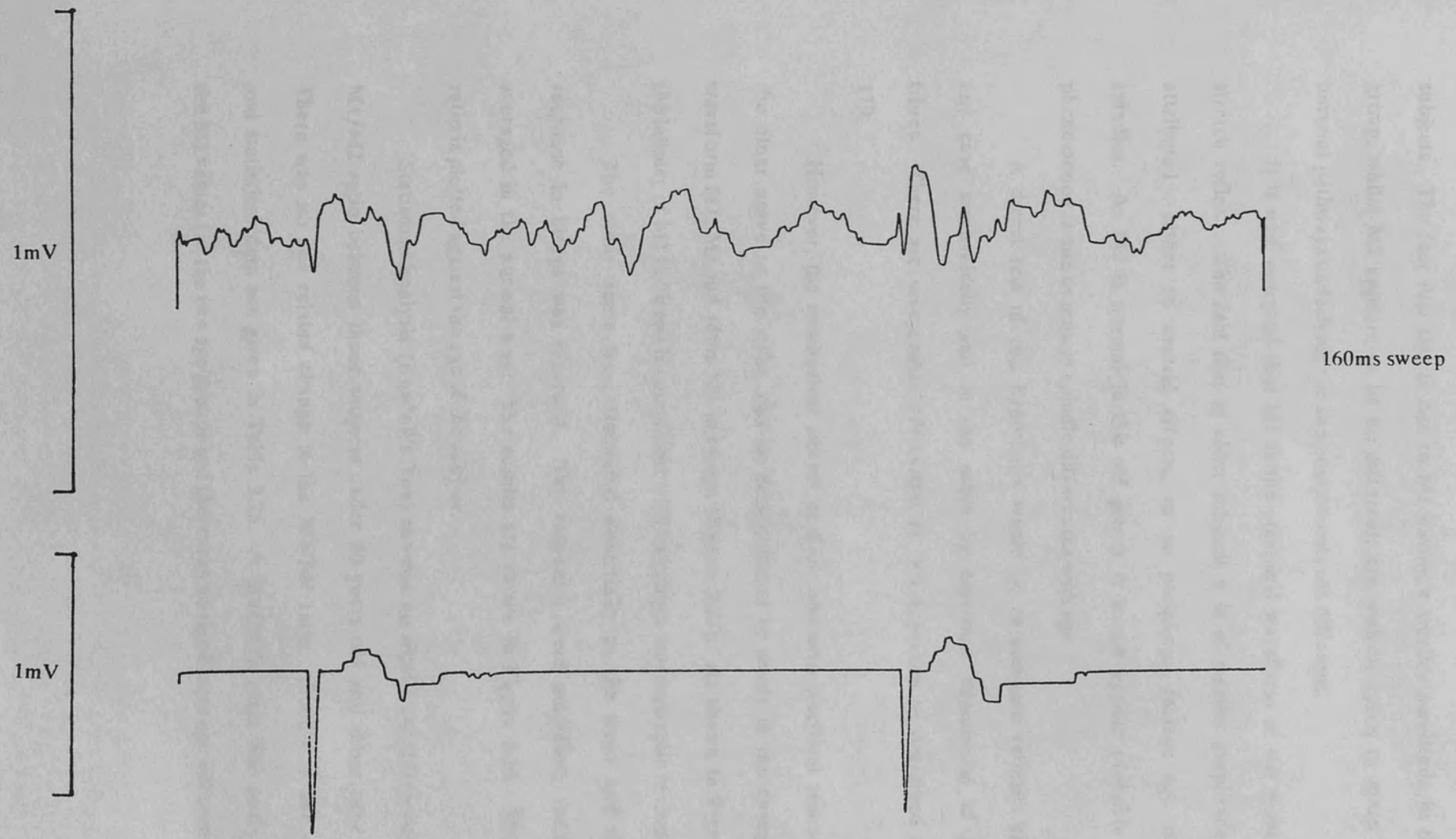


Figure 3.22b Simultaneous traces of the ulnar nerve action potential and the FDI action potential in response to electrical stimulation of the ulnar nerve at the elbow (30V) immediately after a 1 min MVC. The top trace shows both units are blocked in the FDI. They took 50s to return. The nerve action potential shows no change in amplitude.

SECTION 4 : REFLEXES IN BICEPS

As has been described already, the M1/M2 ratio in FDI is smaller in older subjects. The fact that this is due to M1 having a smaller amplitude in the older group, whilst M2 appears to be no different, can well be taken to mean that the nervous pathways underlying the two components are different.

It is now accepted that M1 is the electrical waveform of the monosynaptic stretch reflex. The fact that in older subjects it is of smaller amplitude can be attributed either to central effects, or to peripheral factors e.g. in muscle spindles. As M2 is normal in the old group, it would appear probable that the phenomenon is due to muscle spindle differences with age.

A direct test of this hypothesis would be to compare reflexes elicited in one case mechanically and in the other by electrical stimulation of afferent fibres. There are insuperable difficulties in this approach as described on page 179.

However, the mechanical stretch of FDI, and also electrical stimulation of the ulnar nerve at the wrist, can be demonstrated to result in the characteristic waveform M1, M2 and often M3 in biceps (Figure 3.23). As shown in Figure 3.24, the latency of M1 in biceps is compatible with its being a monosynaptic response.

The ulnar nerve was stimulated electrically at the wrist and the EMG response in biceps was recorded. The responses were amplified, rectified and averaged in the normal way. The results are shown in Figure 3.25. The M1/M2 ratio is plotted against the age of the subject.

Statistical analysis (Kendall's Tau) showed no significant difference in the M1/M2 ratio between those subjects under 30 years old and those over 30 years. There was no age related change in the M1/M2 ratio. Details of the numerical and statistical data are given in Table 3.25. A Student's t-test was performed on the M1 values for the two age groups and there was no significant age difference.

THE ELECTRICAL RESPONSE TO MECHANICAL STRETCH OF THE FIRST DORSAL INTEROSSEOUS RECORDED IN BICEPS AND FDI

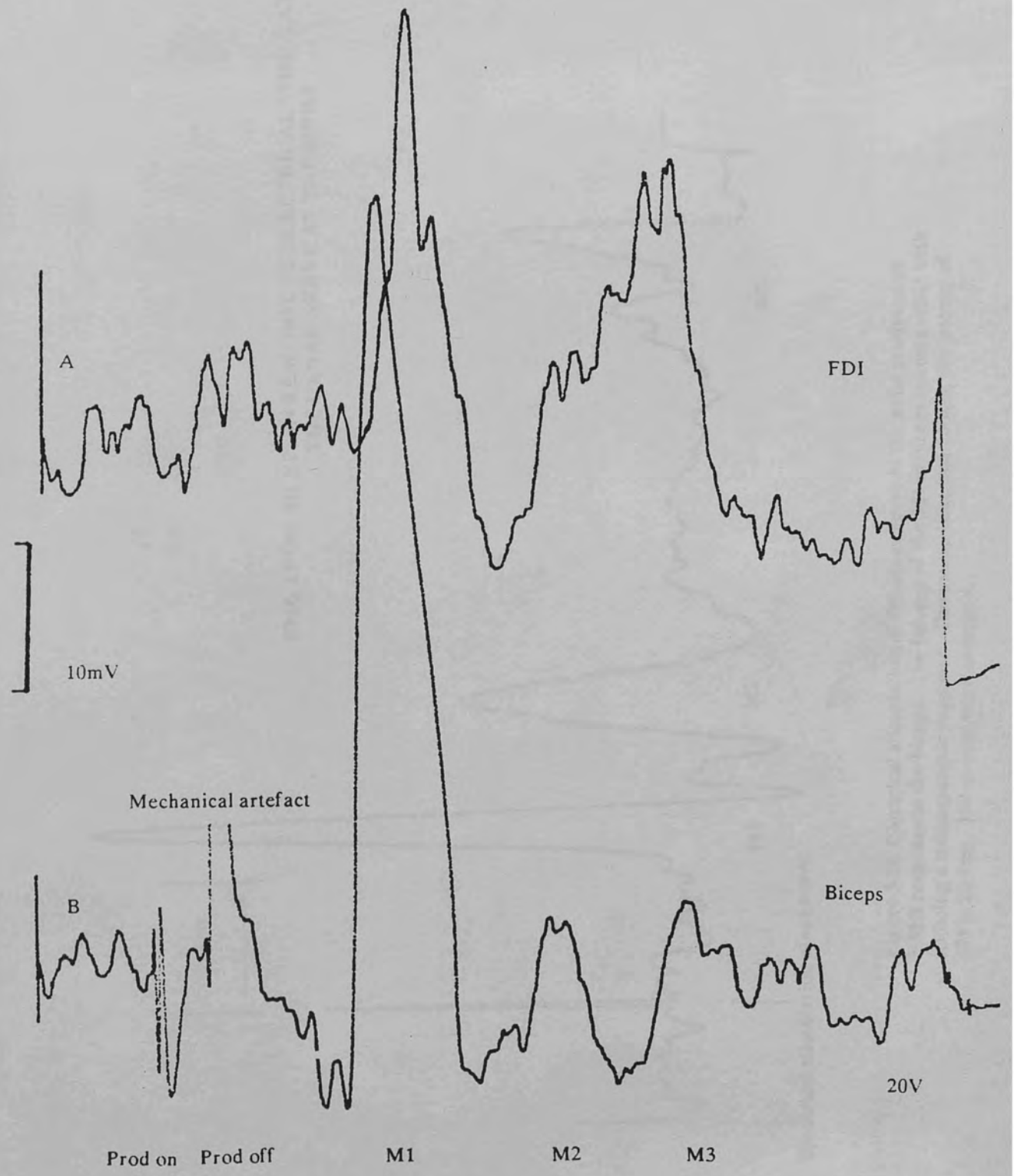


Figure 3.23 EMG records from FDI and biceps in response to mechanical stimulation. The EMGs have a characteristic wave form; M1, M2 and often M3. There is a difference in the latency of the M1 peaks of about 5ms, that of biceps being the shorter, as would be expected. The mechanical artefact in record B has been cut off. The sweep was 160ms duration; 128 sweeps of the rectified EMG were averaged.

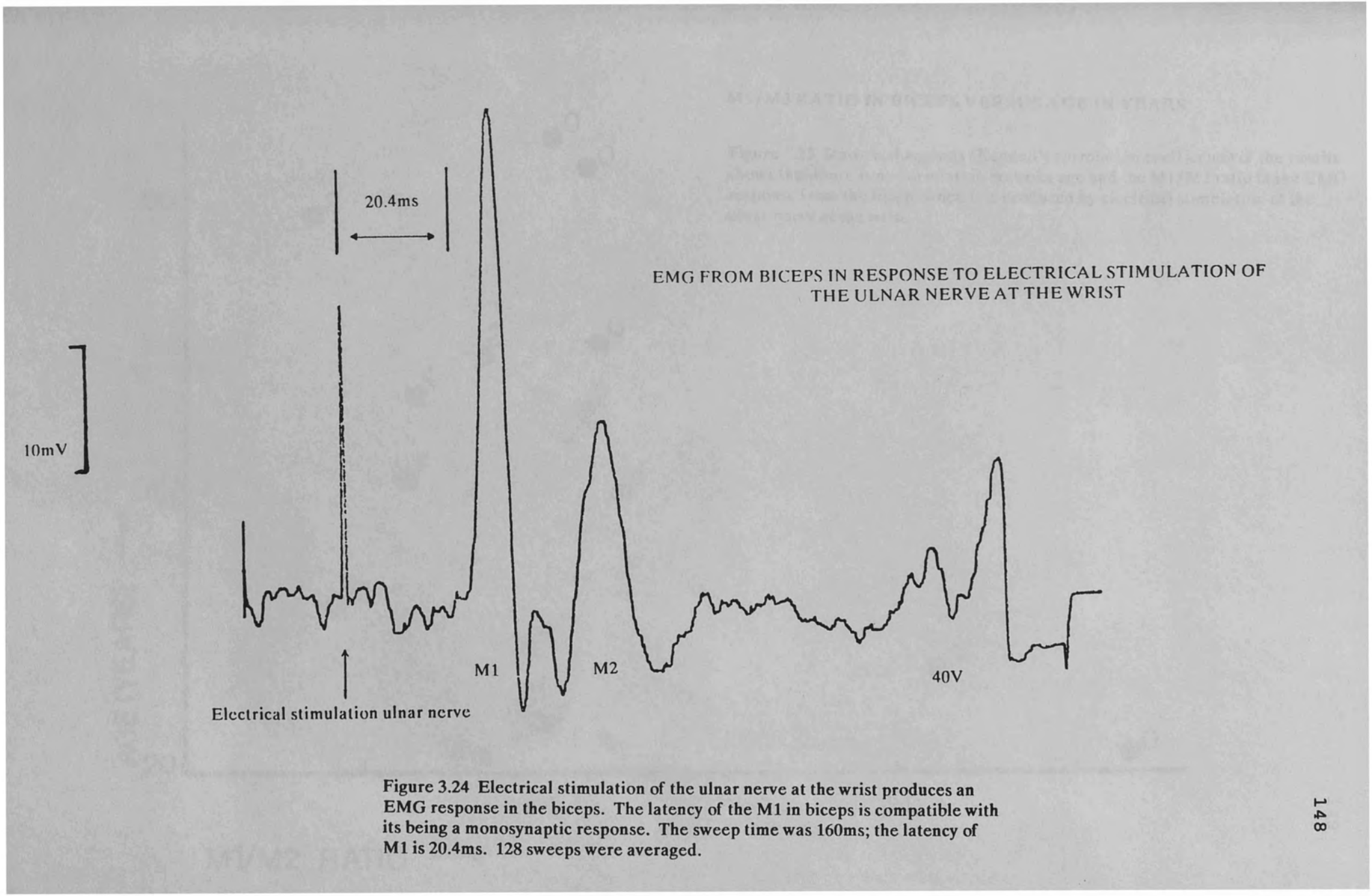


Figure 3.24 Electrical stimulation of the ulnar nerve at the wrist produces an EMG response in the biceps. The latency of the M1 in biceps is compatible with its being a monosynaptic response. The sweep time was 160ms; the latency of M1 is 20.4ms. 128 sweeps were averaged.

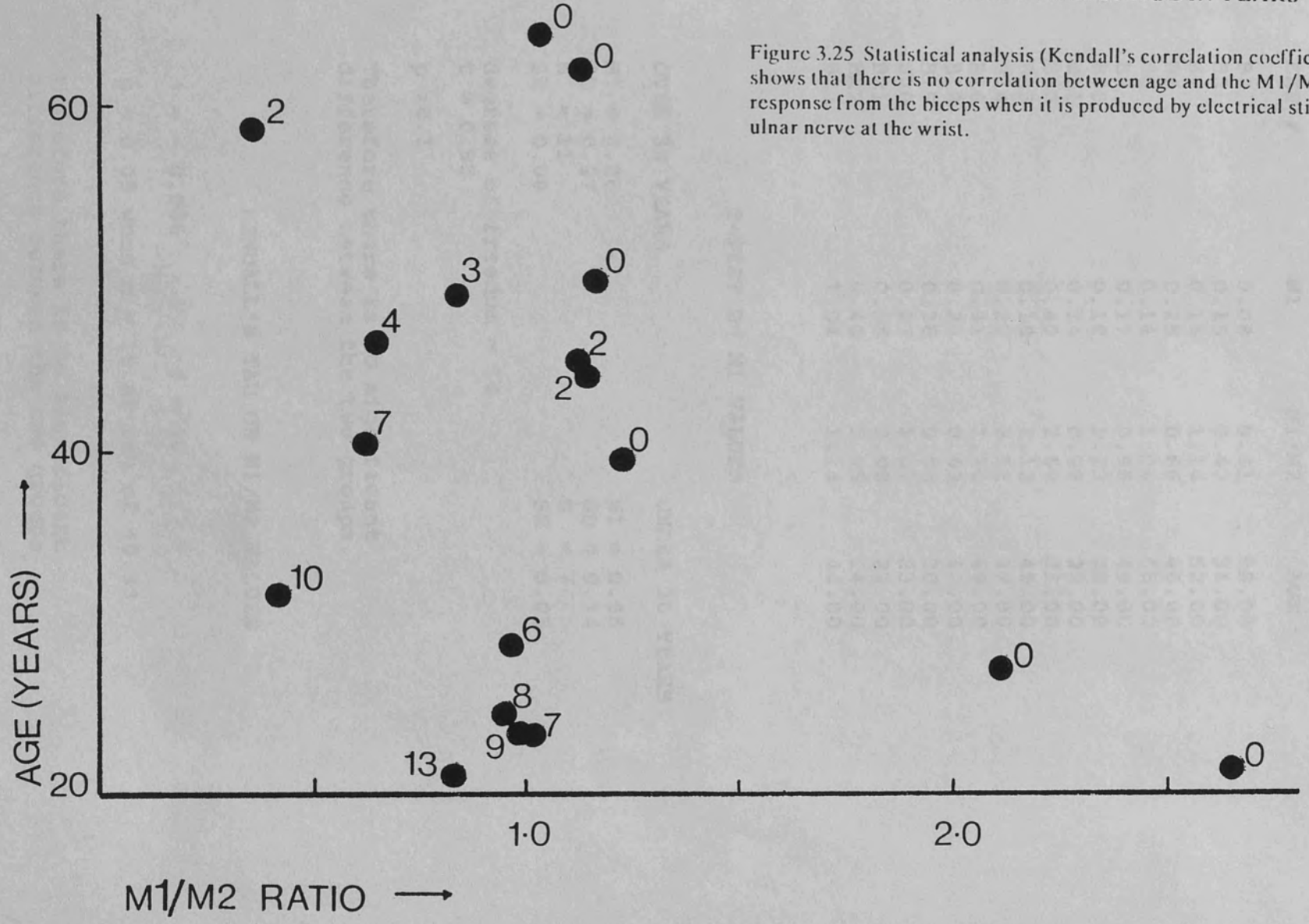


Figure 3.25 Statistical analysis (Kendall's correlation coefficient) of the results shows that there is no correlation between age and the M1/M2 ratio in the EMG response from the biceps when it is produced by electrical stimulation of the ulnar nerve at the wrist.

VALUES FOR THE BICEPS SERIES

EXP #	M1	M1/M2	AGE
B2	0.08	0.41	58.00
B3	0.15	0.42	31.00
B4	0.15	1.14	62.00
B6	0.25	0.66	46.00
B8	0.14	1.04	65.00
B9	0.17	0.95	49.00
B10	0.18	1.23	39.00
B11	0.14	0.98	23.00
B12	0.40	2.69	21.00
B13	0.15	1.12	45.00
B14	0.27	2.11	27.00
B16	0.31	1.16	49.00
B18	0.25	0.63	40.00
B19	0.38	0.83	20.00
B20	0.27	1.01	23.00
B21	0.55	0.98	29.00
B22	0.46	0.95	24.00
B23	1.04	1.14	44.00

T-TEST ON M1 VALUES

OVER 30 YEARS	UNDER 30 YEARS
M1 = 0.26	M1 = 0.35
SD = 0.27	SD = 0.14
n = 11	n = 7
SE = 0.08	SE = 0.05

degrees of freedom = 16
t = 0.95

p >0.1

Therefore there is no significant difference between the two groups.

KENDALL'S TAU ON M1/M2 VALUES

τ = - 0.046 # = 18

p = 0.05 when n = 18 at tau of +0.33

Therefore there is no significant difference between the two groups

For details of statistical analysis see Appendix page 215

SECTION 5 : TREMOR

It might be predicted that if physiological tremor is due to oscillation in the reflex arc at 8-12Hz (Lippold, 1973) there will be some difference in the tremor recorded from young or old people. On the basis that spindle sensitivity becomes less with age, it would be expected that older people would exhibit less tremor than young ones.

Wrist and finger tremor were measured with an accelerometer, and the output of the accelerometer subjected to spectral analysis (Figures 3.26a and 3.27a). The results are plotted in Figures 3.26 and 3.27. The subjects were divided into two groups by age and the results subjected to statistical analysis (Student's t-test; see Table 3.26). No significant difference in tremor amplitude was found between the two groups of subjects.

Note that tremor in the 8-12Hz range is rapidly abolished by ischaemia; testing at this time shows that there is no change in reflex sensitivity produced by the ischaemia.

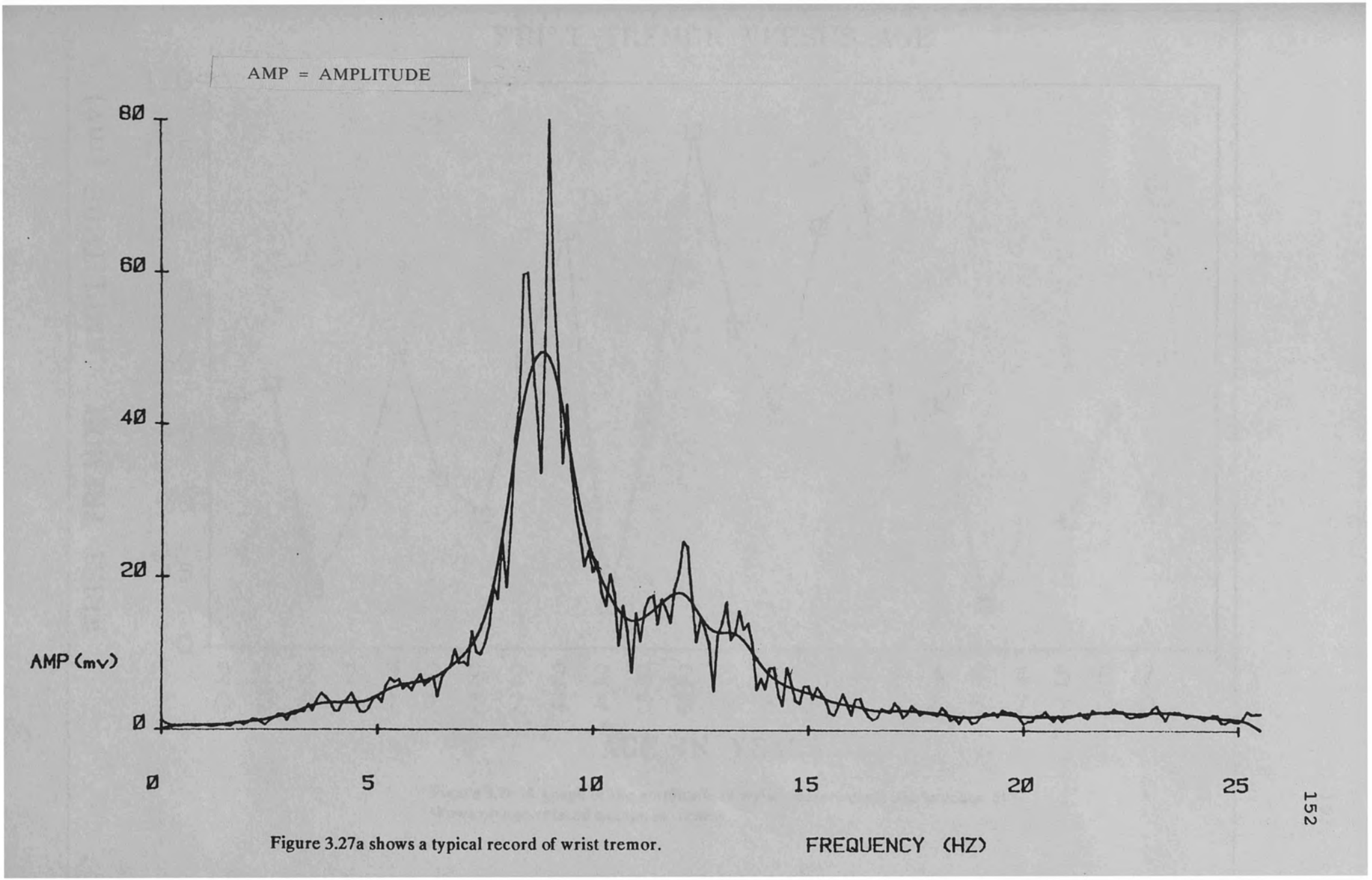


Figure 3.27a shows a typical record of wrist tremor.

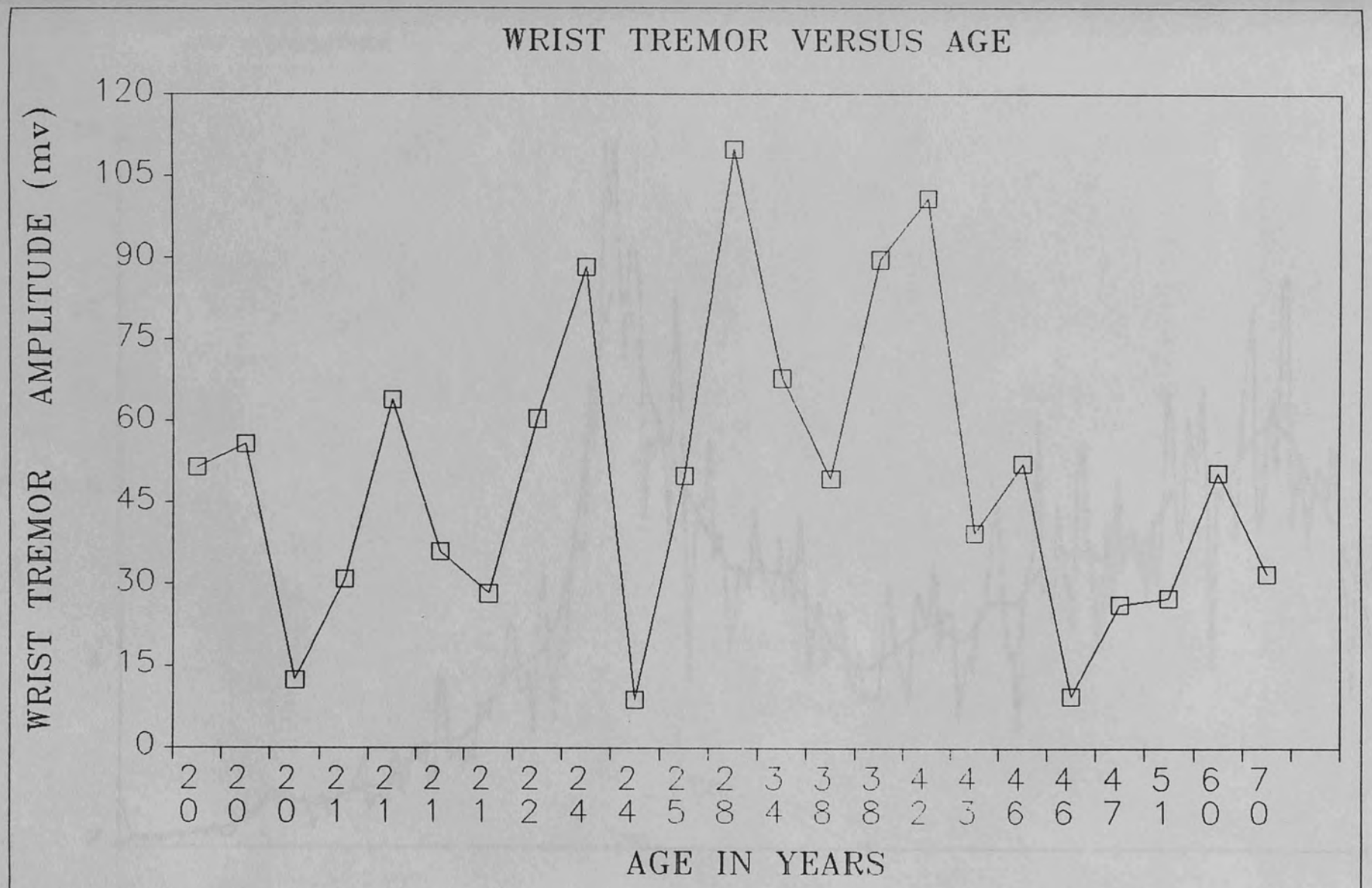


Figure 3.26 A graph of the amplitude of wrist tremor versus age in years. It shows no age-related change in tremor.

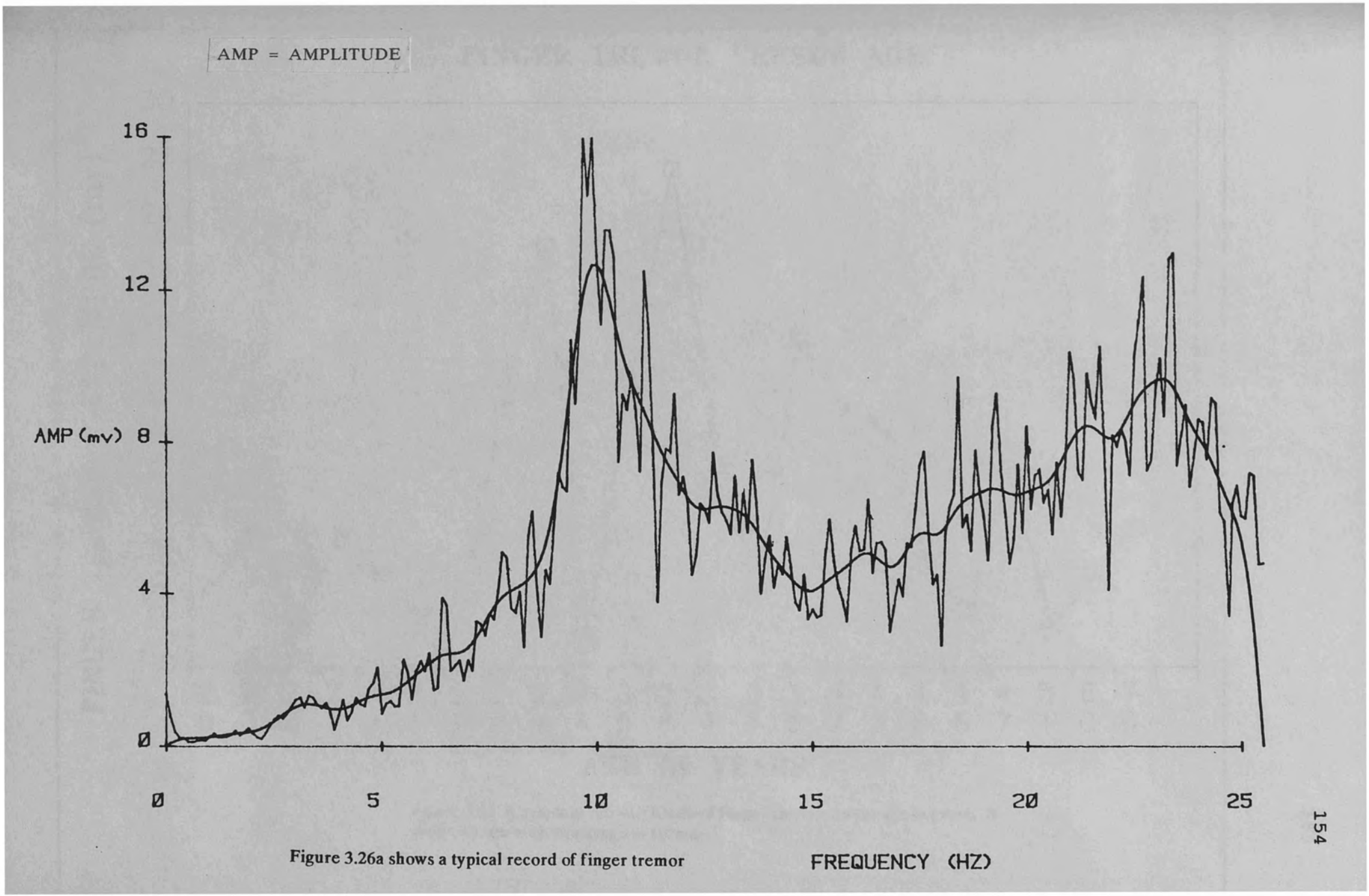


Figure 3.26a shows a typical record of finger tremor

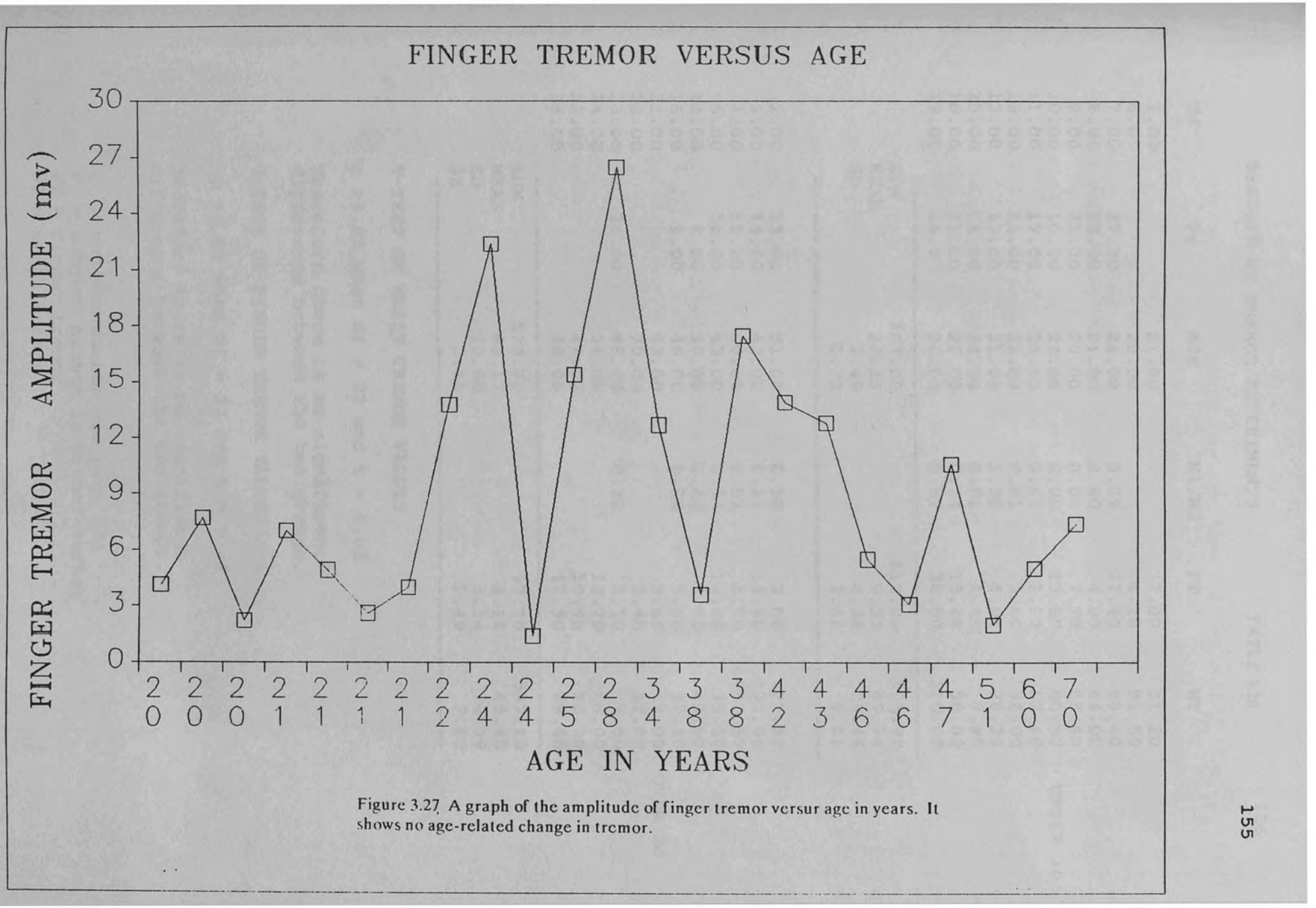


Figure 3.27 A graph of the amplitude of finger tremor versur age in years. It shows no age-related change in tremor.

RESULTS OF TREMOR EXPERIMENTS TABLE 3.26

T#	P#	AGE	M1/M2	FT	WT	
1.00		21.00		7.00	31.20	
6.00		20.00		4.10	51.50	
7.00	27.00	24.00	0.79	22.40	88.40	
8.00	15.00	21.00	2.80	4.90	64.00	
9.00	21.00	20.00	0.64	7.70	55.80	
10.00	10.00	22.00	0.95	13.80	60.50	UNDER 30
11.00	17.00	20.00	0.61	2.20	12.40	
12.00	11.00	21.00	0.51	2.60	36.00	
13.00	12.00	21.00	1.35	4.00	28.30	
15.00	18.00	24.00	0.81	1.40	8.80	
16.00	31.00	25.00	0.74	15.40	50.00	
19.00	16.00	28.00	0.57	26.50	110.00	
	SUM	267.00		112.00	596.90	
	MEAN	22.25		9.33	49.74	
	SD	2.49		8.34	29.46	
		0.72		2.41	8.51	
2.00	13.00	51.00	0.30	2.00	27.50	
3.00	14.00	42.00	0.14	13.90	101.00	
4.00	19.00	60.00	0.01	5.00	50.50	
5.00	30.00	43.00	0.34	12.80	39.50	
14.00	8.00	38.00	0.44	3.60	49.50	
18.00	9.00	46.00	0.06	5.50	52.20	
21.00		63.00		3.60	47.00	OVER 30
22.00		70.00		7.40	32.00	
23.00	26.00	46.00	0.30	3.10	9.50	
24.00		34.00		12.70	68.00	
25.00		47.00		10.60	26.30	
26.00		38.00		17.50	89.80	
	SUM	578.00		97.70	592.80	
	MEAN	48.17		8.14	49.40	
	SD	10.00		5.14	26.39	
	SE	2.89		1.49	7.63	

T-TEST ON WRIST TREMOR VALUES

p >0.05 when df = 22 and t = 0.03

Therefore there is no significant difference between the two groups.

T-TEST ON FINGER TREMOR VALUES

p >0.05 when df = 22 and t = 0.42

Therefore there is no significant difference between the two groups.

T = subject number see page 108
P = subject number in Tremor series
FT = finger tremor
WT = wrist tremor

SECTION 6 : TRAINING IN FDI

The first dorsal interosseous muscle was trained for two months. There was a training effect in the EMG of the muscle (Figure 3.28a) The amplitude of M1 was greater after the two month training regime; some of the improvement was lost when training was discontinued (Figure 3.28). The amplitude of M1 before training began and the mean M1 amplitude at the end of training were statistically analysed (Student's t-test). The results showed a significant difference in M1 amplitude before training and the M1 amplitude that was recorded after training ($p<0.0005$). If the pre-training responses were compared to responses recorded some time after the training regime ended, there was still a significant difference between the two groups ($p<0.025$). The amplitude of M1 was still greater than the pre-training levels two months after training was stopped.

It should be noted that this experiment was performed by only one subject. The subject must have considerable motivation. The training regime must be adhered to conscientiously, and constant EMG records are necessary throughout the period. Such subjects are not easy to find!

THE EFFECT OF TRAINING ON THE EMG RESPONSE OF THE FIRST DORSAL INTEROSSEOUS

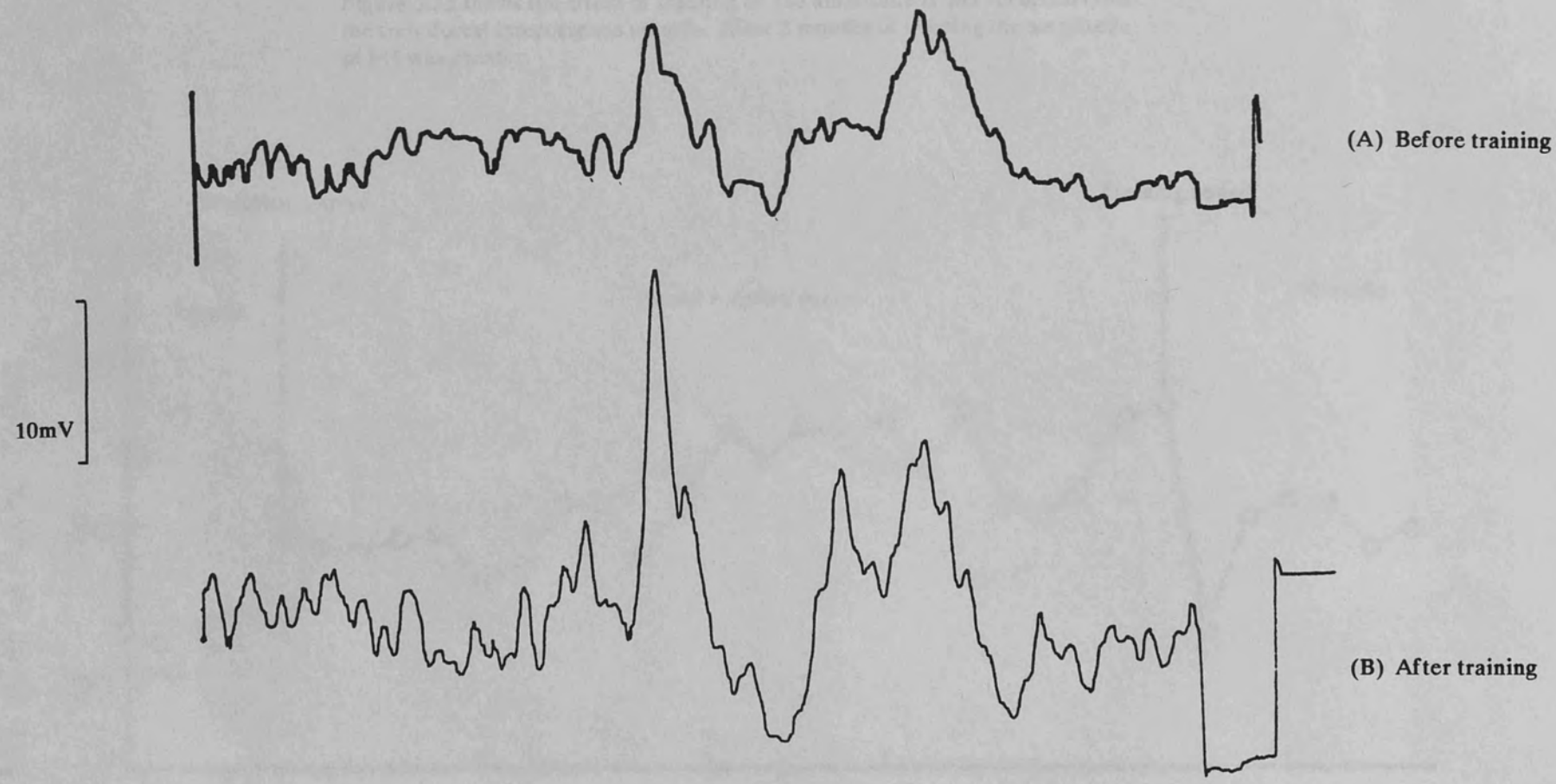
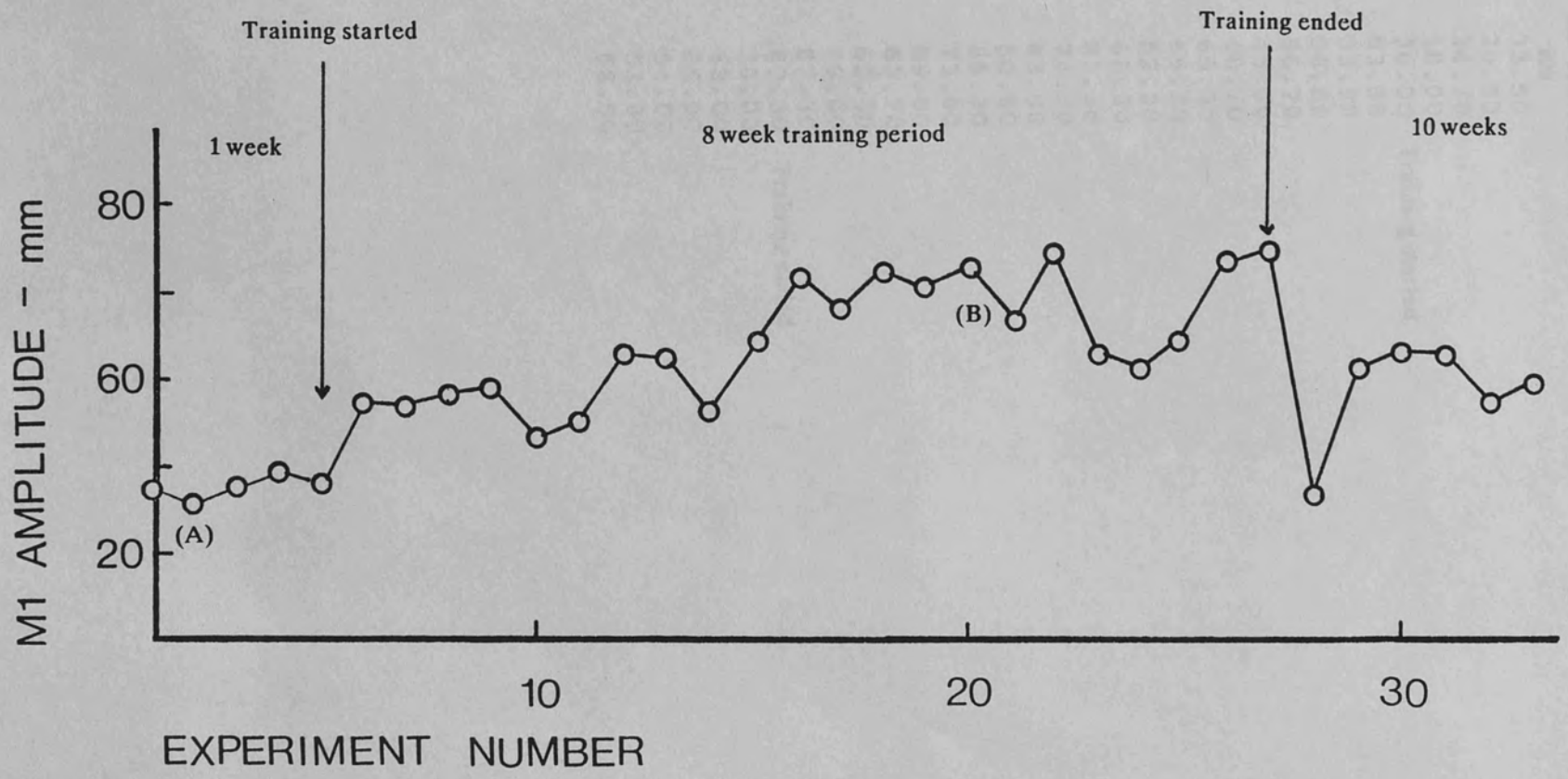


Figure 3.28a show the EMG recorded from the FDI - (A) before training, and (B) after training of the muscle. There was a 160ms sweep and 128 sweeps were averaged. The voltage to the prodder was 10V.

Figure 3.28 shows the effect of training on the amplitude of M1 recorded from the first dorsal interosseous muscle. After 2 months of training the amplitude of M1 was greater.



RESULTS OF TRAINING SERIES

EXP. #	M1 AMPLITUDE mm	
1.00	33.50	
2.00	30.50	
3.00	34.70	
4.00	38.00	
5.00	36.00	Training started
6.00	53.80	
7.00	53.30	
8.00	56.00	
9.00	56.70	
10.00	46.00	
11.00	48.70	
12.00	65.00	
13.00	65.30	
14.00	52.20	
15.00	68.30	
16.00	83.30	
17.00	76.30	
18.00	83.80	
19.00	80.80	
20.00	86.30	
21.00	73.00	
22.00	89.00	
23.00	63.70	
24.00	62.30	
25.00	69.00	
26.00	87.30	
27.00	89.30	Training ended
28.00	33.00	
29.00	62.00	
30.00	66.00	
31.00	64.00	
32.00	53.00	
33.00	58.00	

SECTION 7 : COFFEE AND HYPERTENSION

The results provide preliminary evidence of a significant difference in the effects of the caffeine in coffee on the systolic blood pressure in people of different ages.

Sixteen subjects took part in the experiment, and their blood pressure was monitored before and after drinking strong coffee. The subjects were divided into two groups, those under 30 years and those over 30 years old. The results are presented in Table 3.29. A Student's t-test on the rise in blood pressure versus age showed that there is a significant difference ($p<0.0005$) between the two groups. The young group have a mean blood pressure rise of 4.38; the older group a mean of 20.75. Any minus values are treated as zeros, and no Bessel's correction has been done. Details of the statistical analysis can be found in the Table.

Control experiments (done blind) with de-caffeinated coffee and tea showed that the effects were likely to be due to the action of caffeine and not to any placebo effects or observer bias.

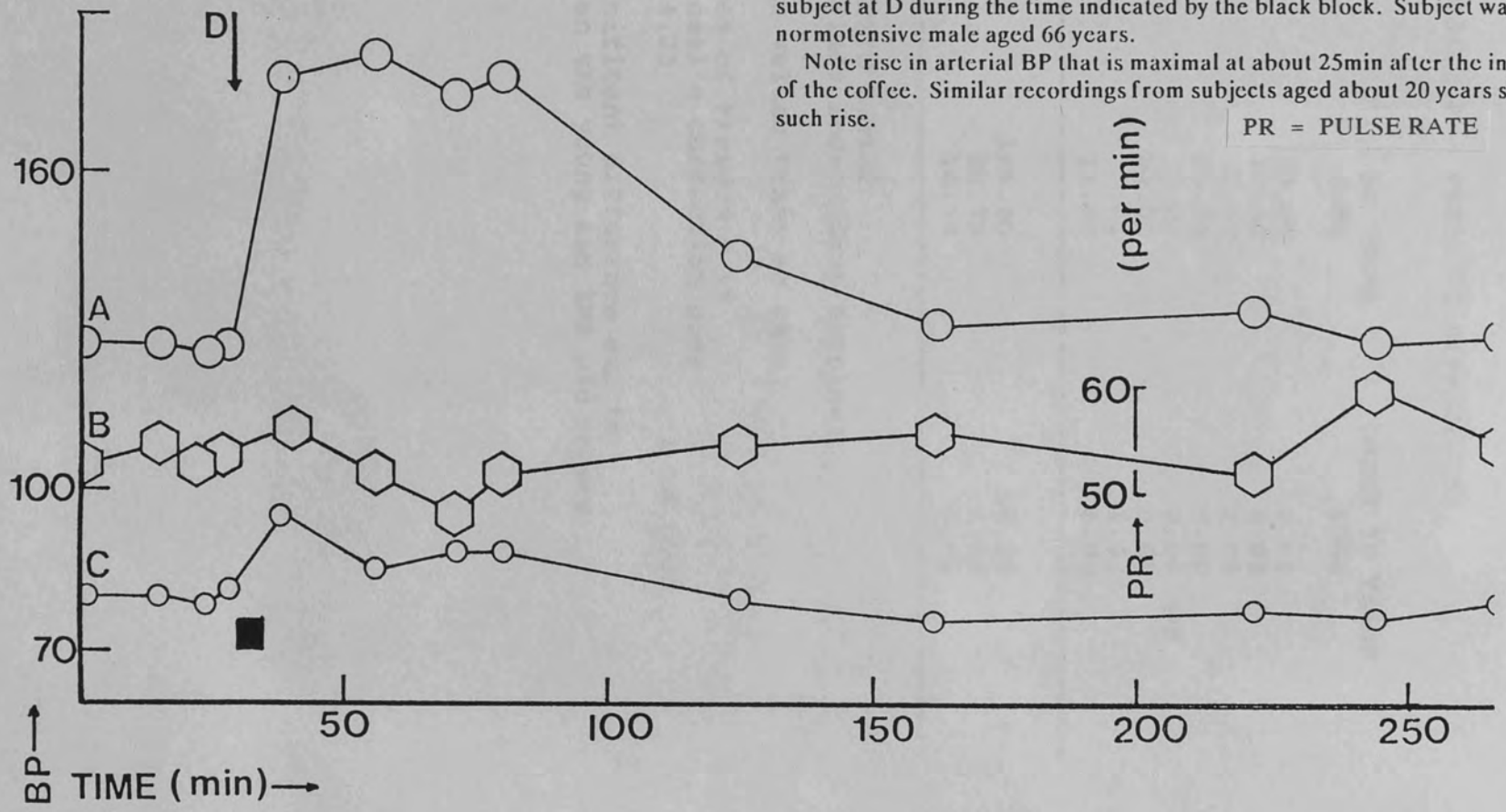


Figure 3.29 Graph shows the effects of drinking 1 cup filter coffee (approximately 200mg caffeine) upon, (A) systolic blood pressure, (B) heart rate and (C) diastolic pressure. After four control observations coffee was drunk by subject at D during the time indicated by the black block. Subject was a normotensive male aged 66 years.

Note rise in arterial BP that is maximal at about 25min after the ingestion of the coffee. Similar recordings from subjects aged about 20 years showed no such rise.

PR = PULSE RATE

COFFEE EXPERIMENT : BLOOD PRESSURE VALUES

SYSTOLIC BLOOD PRESSURE DIFFERENCES

	OVER 30 YEARS mmHg	UNDER 30 YEARS mmHg	
	29.00	0.00	
	20.00	0.00	
	32.00	2.00	
	20.00	9.00	
n=8	0.00	0.00	n=8
	54.00	0.00	
	0.00	16.00	
	11.00	8.00	
SUM	166.00	35.00	
MEAN	20.75	4.38	
SD	16.79	5.61	

STUDENT'S t-TEST
(1-tailed; independent samples)

(minus values taken as zero)

Degrees of Freedom = 14
No Bessel's correction done
t = 4.23 $p < 0.0005$

A significant difference exists
between the young and the old groups

DISCUSSION

The discussion is divided into sections that correspond to those in Methods and Results. The main experimental work was to investigate the EMG response to a brief stretch of the first dorsal interosseous, in particular the short latency response, M1 and the second long latency response M2. Firstly, the EMG responses of groups of subjects in two age groups were recorded, and second the implications of the changes in the stretch reflex were examined.

The remainder of the experimental work was to look for the possible causes of the changes in the stretch reflex in older people. The effect of fatigue on M1 and M2 was investigated, and the possibility that neuromuscular block might occur was examined. Changes in the EMG in response to training of the FDI highlighted the role played by muscle disuse in the observed changes in the stretch reflex in elderly people. Finally, pilot studies were conducted on the effects of drinking ordinary coffee on the blood pressure and heart rate of normal subjects. The theoretical basis for this last series rests on the premise that the syndrome of impaired stretch reflex sensitivity in older people involves stretch reflexes throughout the body and not only muscle stretch reflexes. In the circulatory system this impairment could result in reduced control of blood pressure changes, because of the effects upon the sensitivity of baroreceptors.

SECTION 1 : M1/M2 RATIO EXPERIMENTS

It is already well known that the reflex response in human muscle is slower in older people. This change has been explained by an increase in conduction time through the reflex. Prolongation of contraction time, latency, and relaxation by about 13 per cent and a decrease of maximal rate of tension development in muscles have been described in the rat (Gutmann *et al* ., 1971) and in man (Campbell, McComas & Petito 1973).

Our studies have shown that there is a smaller reflex response in older people, in addition to it being slower. It is likely that this is the result of impaired reflex sensitivity of the muscle stretch receptors which occurs with age and is progressive.

When the FDI is stimulated mechanically by stretching, it responds reflexly. Displacement of the finger results in a double, and sometimes a triple EMG response. (Hammond, 1955 and Crago *et al.*, 1976). The shorter latency response, M1, was found to be significantly smaller in older persons when two groups - young and old - were compared. M2, the longer latency component, was not smaller in the older group. This resulted in a lower M1/M2 ratio in the older subjects.

The possible mechanisms giving rise to the change in this reflex reponse with ageing were investigated.

Changes in muscle spindles

The Ia afferent axons from the primary sensory endings of muscle spindles excite the alpha motor neurones of the muscle in which they lie. The pathways from spindle sensory endings to homonymous alpha motor neurones form the basis of the classical "stretch reflex". The monosynaptic Ia pathway involves synchronous excitation of numerous spindles and summation of monosynaptic volleys at alpha motor neurones. The Ia afferents are

responsible for part of the stretch reflex; according to Boyd (1985) it is a large part.

Mammalian spindles contain three types of intrafusal muscle fibre which are structurally and functionally distinct. There are two types of nuclear bag fibres and one type of nuclear chain fibres (Boyd, 1985). Nuclear bag fibres are so named because of the accumulation of 100 or more nuclei at the spindle "equator" underlying the terminals of the primary sensory ending. The nuclear chain fibres have a single row of nuclei in the equatorial region. The nuclear bag fibres, because of their differing mechanical properties, are called dynamic nuclear bag fibres and static nuclear bag fibres. The principal action of the dynamic bag fibre is to increase greatly the sensitivity of the primary ending to length changes that occur during a change in length i.e., it increases the gain of the system during movement. Many human spindles contain three or four dynamic bag and static bag fibres and up to ten chain fibres making a total of up to 14 in all, but other human spindles contain about 6. Each spindle has one primary sensory ending. This consists of spiral or annular terminations encircling each of the intrafusal fibres of all three types, and all connected to the same group Ia afferent axon.

Swash & Fox (1972) found an increase in spindle capsular thickness in aged muscle which was due to an increase in the amount of collagen in the capsule, laid down in concentric lamellae. Excess collagen was also present in the spindle lumen in aged muscles. The cause of the gradual increase in capsular collagen with increasing age is unknown, although Cooper & Daniel (1963) suggested that it may come from thin fibrous septa, derived from the spindle capsule. These septa normally separate the intrafusal muscle fibres from each other, and are always thicker in the polar regions. In the spindles in the muscles of elderly subjects, these fibrous septa are increased in thickness and are prominent even in the equatorial region (Swash & Fox, 1972).

The intrafusal muscle fibres are normally surrounded by a fine network of elastic tissue which is especially prominent in the polar regions (Cooper & Daniel, 1967). Swash & Fox (1972) found this elastic network to be denser and to consist of more fibres in the muscle spindle in aged muscles. They found the fibres to be slightly coarser, although the distribution of the elastic tissue along the fibres remained the same.

With increasing age Swash & Fox (1972). found a slight, but consistent, decrease in the mean number of intrafusal muscle fibres counted in the spindles studied. In subjects over 60 years the fibres were granular, vacuolated and the normal compact arrangement of the myofibrils had been lost. In more severely abnormal spindles they found the muscle fibres were clumped together in the centre of the spindle lumen and surrounded by fibrous tissue. Sarcoplasmic nuclei were prominent and the normal differentiation of nuclear bag and nuclear chain fibres in the equatorial region was lost.

The properties of the primary endings of the muscle spindle are highly nonlinear - the sensitivity is extremely high for small changes in length, but a transition to a much lower sensitivity occurs when the length change is larger than a fraction of a millimeter (Hasan & Houk, 1975). Nichols & Houk (1976) suggested that muscle stiffness, rather than muscle length, is the regulated property of the stretch reflex. Reflex action was large and the mechanical response was small (due to muscular yielding) with lengthening. It is likely that these changes within the muscle spindle would result in impaired reflex sensitivity to stretch. In isolated spindle recordings in young and old animals Lippold (unpublished communication) found that the sensitivity to stretch of the tenuissimus muscle was greater in kittens than in adult cats.

A change in elasticity within the muscle spindle could result in the reduced M1 response in older people. M2 is not altered by such a change, since there is very little elastic tissue in the skin.

Changes in muscle and joint stiffness

The idea that a stiffening of the joint adjacent to the muscle undergoing stimulation (in this case the FDI) could reduce the reflex response seems a reasonable one to pursue. If a joint in an older subject moved less easily, then there would be less movement in response to a small displacement of the finger, and consequently a lowered activation of the muscle stretch receptors. The results however, show no difference in muscle or joint stiffness within the subjects tested.

Evidence of neuromuscular block

It is possible that with age, neuromuscular block (NMB) might develop and so reduce the number of muscle fibres activated when a "maximal" nerve volley reaches the motor end plates. This might reduce the size of the M1 response and result in a smaller M1/M2 ratio. Further discussion of this aspect will be found in the NMB Discussion section.

Nerve and muscle changes with age

Muscle wasting is frequently observed in the elderly. Many extraneous factors can contribute to neuromuscular changes in the elderly. Some of these include disuse, malnutrition, circulatory impairment and joint stiffness leading to muscle atrophy. Campbell *et al.*, (1973) found a progressive fall in the number of functioning motor units beyond the age of 60, and felt that this decrease was the most important factor contributing to wasting and weakness of ageing muscles. However, their study showed that the severity of the denervating process varied considerably among individuals and that it does not usually commence before the age of 60 years. Campbell *et al.* (1973) were working with the extensor digitorum of human subjects and their results contrasted sharply with those of Gutmann & Hanzlikova (1966). Gutmann & Hanzlikova, working with 30 month old rats, found no loss of motor axons. In these animals, miniature end-plate potentials persisted, although their

frequency of discharge was reduced (Gutmann *et al.*, 1971). These last authors regarded senile muscle atrophy as a specific entity with both pre- and post-synaptic elements.

Effects of facilitation

During a train of afferent nerve impulses the number of motor units contributing to individual reflex responses increases progressively, indicating that the input becomes more and more effective in exciting motor neurones. This process is known as **facilitation**, and it is due to a combination of two factors. First, there is the summation of successive EPSPs in the postsynaptic membrane, each impulse producing a subthreshold depolarization that adds to the remainder of the preceding potential changes. A more important factor, however, is that the amount of transmitter released by each impulse increases during a repetitive series (Katz, 1966). Perhaps, in the older subjects, more individual motor units become blocked and consequently the degree of facilitation that is possible becomes less. This could result in a reduced mean M1 area in the elderly.

Changes in contractile behaviour

As people get older, the contraction time, latency and relaxation time of their reflex responses have been found to get longer, and there is a decrease in the maximal rate of rise of tension in different fast or mixed senescent muscles (in the rat, Gutmann *et al.*, 1971 and in man, Campbell *et al.*, 1973). If this is the case, it may be that the second impulse of a pair is blocked if the interval between them gets too short.

When a subject is asked to maintain a maximum voluntary contraction of the FDI, the force produced gradually falls. This failure to maintain the required force is due to muscle fatigue. The precise mechanisms for this decline in force with time has generated a great deal of research. Merton (1954) considered fatigue an entirely peripheral phenomenon that was located in the biochemical contractile mechanism. This contrasted with the findings of Naess & Storm-Mathisen (1955) who concluded that neuromuscular junction failure was more probable. Krnjević & Miledi (1959) provided evidence for a presynaptic involvement; Thesleff (1959) favoured the neuromuscular junction itself; Paul (1961) produced evidence for changes in the contractile element with fatigue, and Hanson & Persson (1971) the muscle fibre action potential mechanism. Stephens & Taylor (1972) put forward evidence for transmission failure followed by contractile failure.

Present findings showed a loss of force during the time an MVC was maintained, indicating progressive fatigue. The M1 component was usually abolished immediately after the fatiguing contraction, returning within the minute immediately following the fatiguing contraction. Is it possible that the reduced M1 component of the EMG in the older people is due to fatigue? Do the older people suffer muscle fatigue more quickly than the young ones? If so, where in the reflex arc is the fatigue occurring? If the change is in the muscle, is the atrophy resulting from disuse the cause of the fatigue? It was found that the M1 component was abolished in subjects of all ages after the strong voluntary contraction, but if the young subjects were less liable to fatigue than the older subjects during the finger displacement experiments, then this phenomenon would only be apparent in the older group.

Voss (1971) found a reduction in the diameter of the spindles, but no decrease in the number of spindles in the ageing muscle of man has been reported.

During an MVC, presumably the intrafusal fibres become fatigued as well as the extrafusal fibres. This would have the effect of reducing the response of the muscle spindles to a given degree of stretch, because the degree of coupling between extrafusal fibres and the stretch-sensitive mechanism in the equatorial regions of spindles would be reduced.

SECTION 3: NEUROMUSCULAR BLOCK

Neuromuscular block (NMB) of some motor units can occur in the first dorsal interosseous muscle (FDI) under some conditions. In this series of experiments NMB was investigated in a number of ways. Initially, the ulnar nerve at the elbow was electrically stimulated at various frequencies and the responses in the FDI were recorded. In a further series of experiments, the effect produced on the muscle action potential (AP) was looked at when the subject performed a maximum voluntary contraction (MVC).

As a control experiment in the initial M1/M2 series, the ulnar nerve at the elbow was stimulated with two identical electrical stimuli. Motor unit APs were recorded from the FDI. The maximal response was found in each subject and the stimuli given at 2 and 24ms. The procedure was repeated, but the interval between the two stimuli was progressively reduced to see if there was any NMB. One AP acted as a control for the other and no evidence of NMB was seen. Integrated EMG records were also made.

Electrical stimulation of the ulnar nerve at the elbow resulted in neuromuscular block in FDI in every subject if at a high enough frequency. However, the frequency of stimulation at which this block occurred in any one subject varied from 10Hz to 60Hz. The present results show that the NMB was dependent upon the frequency rather than the duration of stimulation. This failure of electrical propagation has been demonstrated in animal and human experiments (Brown & Burns, 1949; Naess & Storm-Mathisen, 1955 and Bigland-Ritchie *et al.*, 1979). Earlier workers have also found that the rate at which NMB develops depends on the stimulus frequency employed. Bigland-Ritchie *et al.*, (1979) found that a rapid reduction of stimulation frequency from 60Hz to 20 Hz during the first 30 seconds of continuous maximal nerve stimulation prevented propagation failure in the adductor pollicis. Krjnević &

Miledi (1958) found rapid failure in response to nerve stimulation at 50Hz but almost none after prolonged periods at 10Hz for the rat diaphragm.

The voltage required to excite axons electrically, increases as their diameter decreases; but according to Henneman (1957) this does not mean that large neurones can be more easily discharged synaptically than small ones. He found that the reverse occurs, and motor neurones may be graded according to the ease with which they can be discharged synaptically; the largest cells require the most intense stimulation. Small tonic motor neurones with small axons are reflexly excited at lower threshold than the larger phasic motor neurones with larger axons (Granit *et al.*, 1957) while weak electrical stimuli to the motor axons, on the other hand, will exicte the larger ones first (Pompeiano & Wand, 1976). The larger a motor neurone the more extensive are the terminal branch points, and since branch points are susceptible to block there will be a greater probability of conduction failure in the large motor neurones. If the recording was from a single motor unit supplied by a large diameter motor axon, perhaps block would occur more often than when recording from small diameter axons.

During sustained isometric maximal voluntary contractions lasting for 1 or 2 minutes the single unit action potential was abolished in some subjects. The fatiguing contraction always resulted in loss of force but this was not always accompanied by a change in the action potential size. In this respect the results agree with earlier work (Merton, 1954; Bigland-Ritchie *et al.*, 1979 and 1982), who concluded that NMB is not a cause of force loss during an MVC of 1 minute duration. However, the action potential was absent immediately after the strong contraction in some subjects. Could this be the result of neuromuscular block of some motor units? Why it happened in some subjects and not others is not clear. Motor fibre size could account for the difference. To investigate this possibility the conduction velocity was roughly measured.

The position of the stimulating electrode at the elbow could excite motor axons of different diameter depending on its exact location. This could result in some units becoming blocked and others remaining unaffected by the MVC. The loss of force was not necessarily accompanied by a reduction of the action potential in the FDI.

In some subjects, visual inspection of the records suggested that more than one unit was present. One motor unit could usually be recognised by the characteristics of each potential profile. Instead of the all or none response of a single unit, the MVC resulted in a reduction in the size of the action potential but not its complete abolition. Some units had blocked and not others. However, so long as the number of units contributing to each action potential stayed the same during the MVC, the change in size suggests that some of the units were no longer contributing to the response, although the size and shape of muscle action potentials does also change with fatigue but not in steps. This step decrease in action potential size was all or nothing and does suggest NMB. Since the units were of the same latency, the NMB in response to the MVC can not have been associated with motor fibre size.

It might be suggested that slight movement of the stimulating electrode from its optimal position occurs during the MVC, and that this results in failure of nerve stimulation to the motor unit. The result would be what appeared to be block of the motor unit in the EMG record. Since the action potential was absent at the end of the MVC and subsequently returned at the same latency and with the same form as the control record taken immediately before the fatiguing contraction this explanation seems seems unlikely. Alternatively, or in addition to this, it is possible that the NMB in some subjects was the result of nerve compression. This is doubtful.

By simultaneously recording the ulnar nerve AP and the muscle AP recorded from the FDI, any interruption of the motor axon potential during

the MVC would result in a change in the nerve AP *pari passu* with the change in the EMG. It was found that NMB of one or more motor units could occur without the nerve AP becoming blocked, although it must be stated that this control was not carried out in all the experiments.

Krnjević & Miledi (1959) produced evidence for the presence of differential conduction at sites of axonal bifurcation. By differential conduction is meant a condition in which only one branch of a bifurcation would block. Most of the branching of motor axons occurs immediately proximal to the point at which the nerve enters the muscle and particularly inside the muscle. If this is the case, the ulnar nerve AP recorded from the forearm would show no signs of transmission failure since it lies proximal to the branch point. Although the majority of bifurcation sites are very close to the muscle, it is advisable to position the nerve recording electrodes some distance from the muscle; Stålberg & Trontelj (1970), in normal subjects, located branching in the tibial nerve as high as 10-15cm above the gastrocnemius muscle.

It has been demonstrated by Grossman *et al.*, (1979a) that propagation of action potentials through a branch point that is geometrically equivalent to an unbranched axon of constant diameter fails at high frequencies. Also that this failure does not necessarily occur at the same time for each branch; conduction into the larger branch is blocked sooner.

The results provide further evidence that NMB does occur in some motor units. When recording from the nerve and the muscle simultaneously it is sometimes necessary to use a voltage which stimulates more than one motor unit so that the nerve AP is large enough to be recorded. Single motor units are recognised by their duration and all-or-nothing behaviour at threshold stimulation.

In agreement with the findings presented here, Grossman *et al.*, (1979a) showed that conduction block at high frequency (50Hz) could be produced *in vivo* by stimulating the axon in the free-moving lobster, and that the axons in the animal fire at frequencies (100-400Hz) sufficient to produce a block of conduction after a few impulses. They showed that the frequency at which NMB can occur is one which can be encountered under normal physiological conditions, and not just under experimental conditions.

Smith (1980a) found in the crayfish leg opener muscle that propagation failed intermittently at branch points during prolonged repetitive stimulation at 50 per second. He showed that depolarization of the axon caused failure to occur first in the small terminal branches and then to spread centrally to larger branches. Later (Smith 1983a) also found conduction failure in the intact animal. He found that failure was related more closely to the frequency of the action potentials than to the duration of stimulation. My experimental results agree with this finding.

However, Smith (1983a) concluded that the occurrence of block could not be predicted solely on the basis of the rate or pattern of excitatory discharge, and that this indicated that some other process may influence the safety factor for conduction at the site of failure. A low safety factor for the propagation of an action potential concerns the presence of conditions under which there is an increased probability of failure of propagation down the motor axon. For example, branch points in the motor nerve are areas where the safety factor for propagation is low due to membrane properties and inhomogeneities of geometry.

Accumulation of extracellular potassium (K^+) has been proposed to underlie the blocking of action potential conduction in peripheral nerves (Grossman *et al.*, 1979b). Parnas & Segev (1979) concluded that any mechanism which will introduce differences in the K^+ concentration around the daughter

branches could provide an explanation for preferential conduction into one branch. However, Smith (1983b) presented evidence that the suggested membrane depolarization and consequent Na^+ inactivation, due to accumulation of extracellular K^+ during repetitive action potentials was not the cause of conduction block. Specifically, he found there was no evidence of a progressive increase in K^+ concentration to some critical level at which conduction block occurred. But he did think that some other K^+ dependent mechanism was probably involved. A rise in external K^+, by reducing the potassium concentration gradient across the nerve membrane, would tend to depolarise rather than hyperpolarise (Liley & North, 1953). From this Liley & North concluded that changes in potassium concentration must influence ACh release by some mechanism other than that concerned with changes in polarisation.

However, Katz & Miledi (1979) found that in the presence of K^+ channel blockers, transmitter release was greatly potentiated and prolonged in time such that the calculated number of quanta far exceeded the number of active zones.

Wedensky inhibition (at high stimulation rates) gives rise to an intense depression of neuromuscular transmission. This type of inhibition can result in postsynaptic as well as presynaptic failure. Nerve fibres can carry impulses at a rather higher frequency than muscle fibres, i.e., the motor nerve has a shorter refractory period than muscle. A nerve impulse arriving at an end-plate while the muscle fibre is still refractory produces only a local end-plate potential, which keeps the muscle membrane depolarized during the refractory period. It further delays the restoration of normal excitability and ionic permeability. Continued high frequency stimulation will maintain the local depolarisation and perpetuate the state of inexcitability. Action potentials will

not be propagated over the sarcolemmal membrane and along the T-tubules of the muscle fibre.

SECTION 4 : REFLEXES IN BICEPS

The monosynaptic reflex in man may be elicited by electrical stimulation of an afferent nerve from a large postural muscle in the leg and recording the EMG from the muscle - this is the Hoffman or H- reflex, and is due to the direct electrical excitation of Ia afferents. In the present work a series of experiments was made using this reflex. If the size of the H-reflex recorded in older subjects was no different from that recorded in younger subjects it would provide supporting evidence for age-related changes in M1 originating in the muscle itself. Unfortunately, the series of experiments did not work. The size of the H-reflex at given voltages of stimulation varied greatly between subjects due, it was concluded, to the anatomical variation in the position of the medial popliteal nerve within the leg. In addition, maximal stimulation can not be used because of the antidromic collision that occurs when both afferent and efferent fibres are active. There was no way of overcoming these variables, and no comparison of inter-subject variations in amplitude could be made. The series was abandoned.

It is generally held that the H-reflex cannot be recorded in arm or small hand muscles because of antidromic collision. However, it is possible to stimulate electrically the ulnar nerve at the wrist and record a reflex response in the biceps muscle. There is no antidromic collison since the muscle is served by a different motor efferent path. No age difference in this reflex response was found.

The latency of the biceps response (around 20-22ms) was correct for a monosynaptic response from stimulated afferents in the ulnar nerve. The response cannot have been from skin afferents since these have a longer latency (Darton *et al.*, 1985).

This result showed that the cause of the age change in the reflex response must lie distal to the ulnar nerve at the wrist, i.e. at the neuromuscular junction, in the muscle itself, or in the section of the motor axon between the wrist and the FDI. I can find no published evidence of age changes in motor efferents which preferentially affect only the most peripheral end of a motor axon.

Changes at the neuromuscular junction are not responsible for the reduced M1 in older subjects since during fatiguing MVCs the M-wave amplitude does not decline (Bigland-Ritchie *et al.*, 1982).

It has been suggested that there are fewer fibres in the muscles of older people and that this results in a smaller response (Edström & Larsson, 1986 and 1987; Gutmann & Hanzlikova, 1966). If this were the case, M1 and M2 would be similarly affected; both would be smaller. The results of the present experiments show the size of M2 is not reduced in the elderly.

SECTION 5 : TREMOR

Tremor is an oscillation; an oscillation is "any motion which is repeated at regular intervals of time". The tremor can normally be detected by the naked eye, and its presence can be established with a suitable recording device. Physiological wrist tremor and finger tremor at 8-12Hz arise from oscillation of activity in the proprioceptive reflex loop (Halliday & Redfearn, 1956, 1958; Lippold, Redfearn & Vučo, 1957 and 1959; Lippold, 1970; Lippold, 1973 and Burne, Lippold & Pryor, 1984). Present findings show no age effect on the amplitude of 8-12Hz tremor in either the wrist or the finger. This suggests that there are no changes in the normal operation of the reflex loop in the older subjects, if it be supposed that the stretch reflex is the basis for the tremor. Alternatively, tremor in the 8-12Hz peak may not be dependent upon the functional normality of the gross stretch reflex.

SECTION 6 : TRAINING IN FDI

A period of training did produce an affect on the EMG of the first dorsal interosseous. These changes tended to be reversed when the training regime was discontinued.

If the reduced M1 component was the result of disuse, which allowed the muscle to atrophy, the effect of training the muscle might be expected to result in a change. Indeed, training might be expected to result in a change even in normally active muscle. This proved to be the case; the stretch reflex response, M1, had a greater amplitude after a two month period of training in a 44 year old subject. The increase in amplitude did not continue when the training regime stopped. Although this was only a pilot experiment, it would seem that whatever the cause of the change in the M1 response that has been found in older people, training can go some way towards reversing it. The amplitude of the reflex response increased in size from quite early on in the training regime. The trend showed a continuing steady increase, but it would seem that continuous exercise would be necessary to maintain the change. Care must be taken when drawing conclusions from this single experiment. For instance, it is not known whether the greater reflex response would have continued to increase in size, would have been maintained or declined despite training, if the experiment had been undertaken for a longer period of time. Would the same improvement occur in all people? And would such improvement be maintained for different lengths of time in subjects of different ages, or decline as quickly in all?

SECTION 7 : COFFEE AND HYPERTENSION

There is considerable volume of data on the effects of coffee on humans. The results are conflicting and it is easy to understand why this is. There are a large number of variables in experimental work of this nature, and the non uniform results are a reflection of this.

The present work was undertaken as a pilot study. Normal subjects were given strong coffee to drink, and their blood pressure was monitored. Variables must be carefully controlled; this is not easy. The determination of the exact quantity of caffeine in the coffee given to the subject is fraught with problems. The caffeine content of different brands of coffee varies; it is important to be consistent. Every care must be taken to give subjects coffee of the same strength, and to give them the same quantity.

Experimental studies of coffee consumption by humans have shown that blood pressure and pulse changes were slight in healthy young volunteers with administration of 3-4mg/kg body weight of caffeine in coffee. Horst (1934) reported a greater blood pressure rise in older men (53-77 years) than young men (21-25 years) after the consumption of coffee. These findings are in agreement with the results presented here. The coffee resulted in very little change in systolic blood pressure in young subjects, but frequently produced a large effect in older subjects.

These preliminary findings lend support to the hypothesis of impaired reflex sensitivity in older people and the involvement of stretch reflexes thoughout the body.

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APPENDIX

ACCELEROMETER DESIGN AND CHARACTERISTICS

General

The basic construction of a piezoelectric accelerometer is shown in Figure 5.1.

The active element consists of a number of piezoelectric discs on which rests a relatively heavy mass. The mass is preloaded by a stiff spring and the whole assembly sealed in a metal housing with a thick base. When the accelerometer is subjected to vibration the mass exerts a variable force on the discs which, due to the piezoelectric effect, develops a variable charge proportional to the force and, therefore, to the acceleration of the mass.

For frequencies much lower than the resonance frequency of the assembly the acceleration of the mass is equal to the acceleration of the whole transducer. Therefore, the charge produced is proportional to the acceleration to which the transducer is subjected.

Design

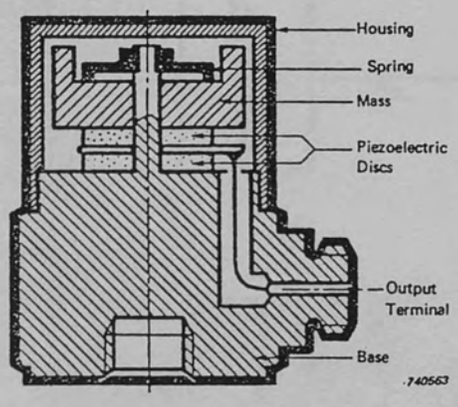
A piezoelectric material is one which develops an electrical charge when subjected to stress. Materials which exhibit this property are intrinsic piezoelectric monocrystals such as quartz and Rochelle salt, and artifically polarized ferroelectric ceramics which are mixtures of different compounds such as barium titanate, lead zirconate and lead metaniobate.

B & K TYPE 4367 - DELTA SHEER DESIGN

Delta Sheer design gives a high sensitivity to mass ratio with relatively high resonance frequency and excellent isolation from base strain and temperature transients. It employs three piezoelectric elements each with their own mass which for reduced sensitivity to extraneous environmental forces are

arranged in the shear mode around a triangular centre post. To maintain good linearity bonding of the piezoelectric elements and their masses is avoided using a high tensile strength preloading ring to clamp them solidly into position.

Figure 5.1 Accelerometer



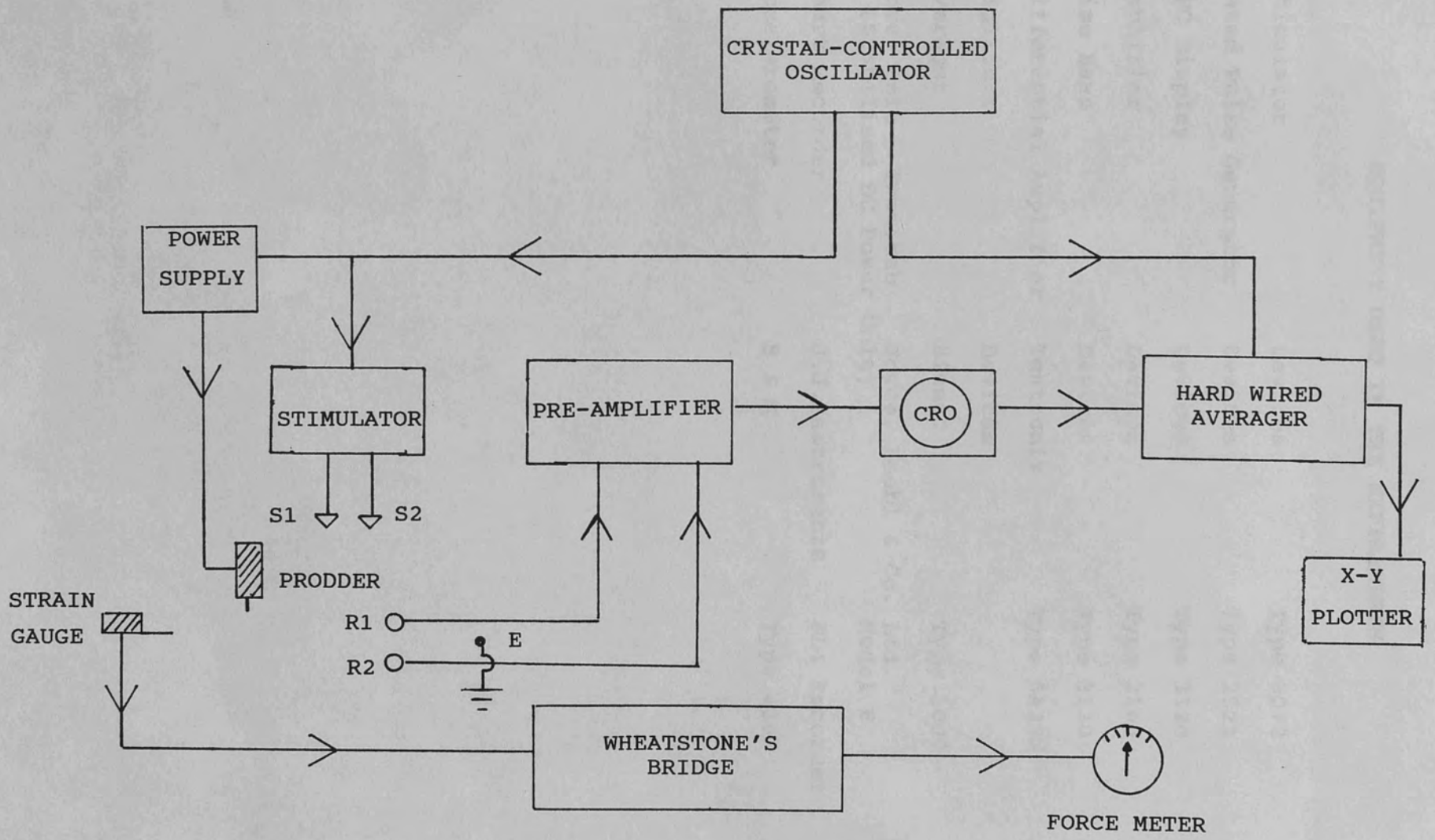


Figure 5.2 Flow diagram showing the equipment used

EQUIPMENT USED IN THE EXPERIMENTS

Stimulator	Devices	Type 3072
Gated Pulse Generator	Devices	Type 2521
CRO Display	Devices	Type 3120
Amplifier	Devices	Type 3160
Time Base	Devices	Type 3130
Differential Amplifier	Tektronix	Type 5A22N
Digitimer	Devices	
Averager	Biomac	Type 1000
Power Unit - Transtab (Stabilised DC Power Unit)	Joyce, Loebl & Co. Ltd.	Model F
Chart Recorder	J.J.Instruments	PL4 Recorder
Accelerometer	B & K	Type 4367

DATA FOR ANOVA - M1/M2 VALUES FOR ALL 16 GROUPS

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
0.44	1.26	0.44	1.35	0.30	0.44	0.44	1.35	0.44							
0.30	0.51	1.26	0.14	0.14	1.26	1.26	0.14	1.26							
0.14	1.35	0.51	2.80	0.15	2.80	0.51	2.80	0.51	0.62	1.26	1.35	0.44	0.51	0.44	1.26
0.01	2.80	0.30	0.72	0.57	0.57	0.30	0.72	1.35	0.64	0.51	0.30	1.26	1.35	0.64	0.51
0.15	0.57	0.57	0.01	0.34	0.62	0.57	0.57	0.30	0.30	0.57	0.14	0.30	0.14	0.15	1.35
0.30	0.62	0.62	0.66	0.74	0.72	0.62	0.79	0.14	0.79	0.62	2.80	0.57	2.80	1.57	0.30
0.30	0.72	0.15	0.64	0.45	0.01	0.01	0.74	2.80	1.57	0.66	0.72	0.62	0.72	0.28	0.14
0.64	0.66	0.57	0.68	0.28	0.66	0.66		0.57		0.44	0.01	0.01	0.66		2.80
0.45	0.64	0.30	1.57		0.64	0.64		0.72		0.68	0.64	0.15	0.64		0.57
0.28	0.68	0.79	0.74		0.68	0.68		0.01		0.15	0.30	0.34	0.68		0.62
	0.57	0.34	0.64		0.30	0.15		0.66		0.57	1.57	0.74	0.57		0.72
	0.79	0.45	0.28		0.79	0.30		0.68		0.79	0.34	0.45	0.30		0.01
	1.57				1.57	1.57		0.15		0.64	0.74		0.79		0.66
	0.74				0.64	0.34		0.57		0.28	0.45		1.57		0.68
						0.64		0.34					0.64		0.57
						0.45		0.74							0.30
						0.28		0.64							0.79
								0.45							0.34
								0.28							0.74
															0.64
															0.45
3.01	13.48	6.30	10.23	2.23	10.44	9.42	7.11	12.61	3.92	7.17	9.36	1.68	10.01	3.08	13.45
0.30	0.96	0.53	0.85	0.56	0.80	0.55	1.02	0.66	0.78	0.60	0.78	0.35	0.83	0.62	0.71
0.18	0.62	0.29	0.76	0.15	0.70	0.38	0.86	0.62	0.47	0.27	0.79	0.28	0.71	0.56	0.60
0.06	0.17	0.08	0.22	0.05	0.19	0.09	0.32	0.15	0.21	0.08	0.23	0.09	0.20	0.25	0.14
10.00	14.00	12.00	12.00	8.00	14.00	17.00	7.00	19.00	5.00	12.00	12.00	10.00	13.00	5.00	19.00
1.196	18.007	4.220	15.009	1.401	15.883	7.532	11.697	15.256	3.973	5.108	14.121	3.469	15.762	3.169	16.060
9.06	181.70...	39.69	104.60	4.97	109.00	88.70	50.50	159.00	15.40	51.40	87.60	2.82	100.00	9.50	181.00

A	M1/M2 OVER 30 YEARS
B	M1/M2 UNDER 30 YEARS
C	HYPERTENSIVE RELATIVES
D	NO HYPERTENSIVE RELATIVES
E	SMOKER
F	NON-SMOKER
G	COFFEE DRINKER
H	NON-COFFEE DRINKER
I	NON-VEGETARIAN
J	VEGETARIAN
K	PLAYS MUSICAL INSTRUMENT
L	DOES NOT PLAY MUSICAL INSTRUMENT
M	SYSTOLIC BLOOD PRESSURE >130mmHg
N	SYSTOLIC BLOOD PRESSURE <130mmHg
O	NO EXERCISE
P	EXERCISE

SUM
MEAN
SD
SE
n
Σx^2
$(\Sigma x)^2$

TOTAL NUMBER OF OBSERVATIONS (n) = 189

$\Sigma x = 123.50$
$\Sigma x^2 = 1195.00$

TABLE 5.1

ANOVA RESULTS FOR THE M1/M2 RATIO

THE TUKEY-SNEDECOR METHOD FOR DETERMINING SIGNIFICANT DIFFERENCES BETWEEN GROUPS AFTER AN ANALYSIS OF VARIANCE

GROUP	MEANS	x - 0.30	x - 0.35	x - 0.53	x - 0.55	x - 0.56	x - 0.60	x - 0.62	x - 0.66	x - 0.71	x - 0.78	x - 0.78	x - 0.80	x - 0.83	x - 0.85	x - 0.96
H	1.02	0.72	0.67	0.49	0.47	0.46	0.42	0.40	0.36	0.31	0.24	0.24	0.22	0.19	0.17	0.06
B	0.96	0.66	0.61	0.43	0.41	0.40	0.36	0.34	0.30	0.25	0.18	0.18	0.16	0.13	0.11	
D	0.85	0.55	0.50	0.35	0.30	0.29	0.25	0.23	0.19	0.14	0.07	0.07	0.05	0.02		
N	0.83	0.53	0.48	0.30	0.28	0.27	0.23	0.21	0.17	0.12	0.05	0.05	0.03			
F	0.80	0.50	0.45	0.27	0.25	0.24	0.20	0.18	0.14	0.09	0.02	0.02				
L	0.78	0.48	0.43	0.25	0.23	0.22	0.18	0.16	0.12	0.07	0.00					
J	0.78	0.48	0.43	0.25	0.23	0.21	0.18	0.16	0.12	0.07						
P	0.71	0.41	0.36	0.18	0.16	0.15	0.11	0.09	0.05							
I	0.66	0.36	0.31	0.13	0.11	0.10	0.06	0.04								
O	0.62	0.32	0.27	0.09	0.07	0.06	0.02									
K	0.60	0.30	0.25	0.07	0.05	0.04										
E	0.56	0.26	0.21	0.03	0.01											
G	0.55	0.25	0.20	0.02												
C	0.53	0.23	0.18													
M	0.35	0.05														
A	0.30															

TABLE 5.2

ANOVA for whole set

$(\Sigma d^2)_T$ GROUP	SUM OF SQUARES $\Sigma x2$	SUM SQUARED $(\Sigma x)^2$	n
A	1.196	9.06	10
B	18.007	181.70	14
C	4.220	39.69	12
D	15.009	104.60	12
E	1.401	4.97	8
F	15.883	109.00	14
G	7.532	88.70	17
H	11.697	50.50	7
I	15.256	159.00	19
J	3.973	15.40	5
K	5.108	51.40	12
L	14.121	87.60	12
M	3.469	2.82	10
N	15.762	100.00	13
O	3.169	9.50	5
P	16.060	181.00	19
	Σ 151.71	Σ1,195.00	

$$(\Sigma d^2)_T = \Sigma x^2 - \frac{(\Sigma x)^2}{n}$$

$$= 152 - \frac{1195}{189}$$

$$= 152 - 6$$

$$= 146$$

$(\Sigma d^2)_{Bet}$

	$\frac{(\Sigma x)^2}{n}$
A	0.90
B	13.00
C	3.30
D	8.70
E	0.60
F	7.80
G	5.20
H	7.20
I	8.40
J	3.10
K	4.30
L	7.30
M	0.30
N	7.70
O	1.90
P	9.50
	Σ 89.20

$$(\Sigma d^2)_{Bet} = 89.2 - \frac{1195}{189}$$

$$= 89.2 - 6$$

$$= 83.2$$

ANOVA for whole set

$(\Sigma d^2)_T = 146$

$(\Sigma d^2)_W = 63$

$(\Sigma d^2)_{Bet} = 83$

F - ratio

$s^2_{Bet} = \frac{83}{16} = 5.19$

$s^2_w = \frac{63}{189} = 0.33$

$F = 15.72$ $\quad df_1 \ n=15$, $df_2 \ n=188$

From table $p<0.0001$

ANOVA TABLE

Source of Variation	df	Sum of squared deviations	Variance Estimates	F
Between groups	15	83	5.19	15.72
Within groups	188	63	0.33	
Total	203	146		

ANOVA for M1/M2 and age and coffee (= Groups A,B and H)

Σx^2	(Σx^2)	n
A = 1.20	9.1	10
B = 18.00	182.0	14
H = 11.70	50.5	7
Σ = 30.9	241.6	31

$\frac{(\Sigma X)^2}{n}$
A = 0.9
B = 13.0
C = 7.2
Σ = 21.1

$$(\Sigma d^2)_T = 30.9 - 7.8$$

$$23.1$$

$$(\Sigma d^2)_{Bet} = 21.1 - \frac{241.6}{31}$$

$$= 21.1 - 7.8$$

$$= 13.3$$

Thus $(\Sigma d_2)_T = 23.1$

$(\Sigma d^2)_W = 9.8$

$(\Sigma d^2)_{Bet} = 13.3$

$$S_{Bet}^2 = \frac{13.3}{3} = 4.4$$

$$S_W^2 = \frac{9.8}{31} = 0.31$$

$$F\text{ - ratio} = \frac{4.4}{0.31} = 14.2$$

$$= 14.36$$

$n_1 = 3$

$n_2 = 31$

From table therefore $p \doteq 0.01$

ANOVA for M1/M2 ratio and age

Σx^2	$(\Sigma x)^2$	n
A = 1.2	9.1	10
B = 18.0	182.0	14
Σ = 19.2	191.1	24

$\frac{(\Sigma X)^2}{n}$
A = 0.9
B = 13.0
Σ = 13.9

$(\Sigma d^2)_T = 19.2 - 6$

$= 13.2$

$(\Sigma d^2)_{Bet} = 13.9 - \frac{191.1}{24}$

$= 13,9 - 7.9$

$= 6.0$

$(\Sigma d^2)_T = 13.2$

$(\Sigma d^2)_W = 7.2$

$(\Sigma d^2)_{Bet} = 6.0$

$$S_{Bet}^2 = \frac{6}{2} = 3.00$$

$$S_W^2 = \frac{7.2}{24} = 0.3$$

F- ratio $= \frac{3.00}{0.30}$

$= 10.0$

$n_1 = 2$

$n_2 = 24$

From table therefore $p<0.001$

Group comparisons

$$S_x = \sqrt{\frac{S_W^2}{n}} = \sqrt{\frac{0.33}{11.8}}$$

$$= 0.167$$

Q = 4.84 (from Q table; df = 16 and 189

D = 4.84 x 0.167

= 0.80

largest difference in means is A - B

0.30 - 0.96

= 0.66

(just not significant at p=0.05 level)

Using LSR

$$LSR = Q\sqrt{\frac{S^2}{n}}$$

= 4.84 x 0.167

= 0.80

(just not significant at p=0.05 level)

BICEPS SERIES : ANALYSIS OF RESULTS

M1/M2 ratio and age

KENDALL'S TAU

For full table of results see Table 3.25 page 150

(# = 18)

$S^+ = 73$

$$n = \frac{(n-1) \times N}{2}$$

$$= \frac{17 \times 18}{2} = 153$$

$s = (2 \times 73) - 153$

$= -7$

$$\tau = \frac{-7}{153}$$

$= -0.046$

$p = 0.05$ when $n = 18$ at τ of $+0.33$

Therefore No significant correlation

M1/M2 SERIES : ANALYSIS OF RESULTS

1. M1 and age

2. M2 and age

REGRESSION ANALYSIS

1.

M1 over 30 years

$\bar{x}$ = 11.00

$\bar{y}$ = 1.125

x^2 = 121

n = 40

Σx^2 = 5640

Σxy = 581.4

$$b = \frac{(xy) - nxy}{(x^2) - nx^2}$$

$$= \frac{581.4 - (40 \times 11 \times 1.125)}{5640 - (40 \times 121)}$$

= 0.108

a = y - bx

=1.125 - (0.108 x 11)

= -0.063

Let x = 10

y = a + bx

= -0.063 +(0.108 x 10)

= 1.017

M1 under 30 years

b = 0.176 a = 1.077

Let x = 10

y = 2.837

2.

M2 over 30 years

b = 0.136 a = 2.464

Let x = 10

y = 3.824

M2 under 30 years

b = 0.185 a = 2.134

Let x = 10

y = 3.984

A Primer in Data Reduction, A.S.C. Ehrenberg.

M1/M2 SERIES : ANALYSIS OF RESULTS

Age and the M1/M2 ratio

WILCOXON RANK SUM TEST

Age : 2 groups

1. over 30 years
2 under 30 years paired observations

Exp #	Age	Values	Ranks
19	60	0.01	1
14	42	0.14	2
23	63	0.15	3
34	52	0.28	4
13	51	0.30	5.5
26	46	0.30	5.5
30	43	0.34	7
8	38	0.44	8
33	49	0.45	9
11	21	0.51	10
24	21	0.57	11.5
16	28	0.57	11.5
17	20	0.62	13
21	20	0.64	14.5
32	59	0.64	14.5
20	21	0.66	16
22	20	0.68	17
18	24	0.72	18
31	25	0.74	19
27	24	0.79	20
10	22	1.26	21
12	21	1.35	22
29	20	1.57	23
15	21	2.80	24

M1/M2

Sum of ranks : over 30 years
(n = 10) = 59.5

Sum of ranks : under 30 years
(n = 14) = 240.5

Number of observations in the 2 groups = 10, 14

Values from Table = 91, 159

There is a statistically significant difference between the two groups ($p < 0.001$).

A Short Textbook of Medical Statistics, Hill, (Sir), A.B. (1977).

M1/M2 SERIES : ANALYSIS OF RESULTS

Systolic blood pressure and the M1/M2 ratio

WILCOXON RANK SUM TEST

Systolic blood pressure : 2 groups

1. SBP <130mmHg
2 SBP >130mmHg

Values	Ranks
0.01	1
0.14	2
0.15	3
0.30	4.5
0.30	4.5
0.34	6
0.44	7
0.45	8
0.51	9
0.57	10.5
0.57	10.5
0.62	12
0.64	13.5
0.64	13.5
0.66	15
0.68	16
0.72	17
0.74	18
0.79	19
1.26	20
1.35	21
1.57	22
2.80	23

Sum of ranks M1/M2 <130mmHg = 186
(n = 13)

Sum of ranks M1/M2 >130mmHg = 90
(n = 10)

Number of observations in the two groups = 10, 13

Values from Table = 79, 161

There is a statistically significant difference between the two groups (p <0.01)

M1/M2 values taken from Table 3.4 page 113.

[*From the Proceedings of the Physiological Society*, 7–8 *April* 1988
Journal of Physiology, **403**, 74*P*, 1988]

The EMG response to stretch in a human hand muscle (M1) diminishes with age

By Maria Corden, O. C. J. Lippold and Helen Loxley. *Department of Human Physiology, Royal Holloway and Bedford New College, University of London, London TW20 0EX*

A brief stretch of muscle held at a constant voluntary tension gives rise to a typical segmented EMG response. The first component, M1, is generally attributed to the monosynaptic stretch reflex whilst the second component, M2, of longer latency, is likely to be due to mechanical stimulation of skin, subcutaneous and other afferents (Darton *et al.* 1985).

Measurement of the area of rectified and summed electrical potentials recorded upon stretching the first dorsal interosseous muscle (FDI), shows marked differences with age of subjects. The component M1 is smaller and has a higher mechanical threshold in older persons. In contrast M2 appears to be unimpaired with age (Fig. 1).

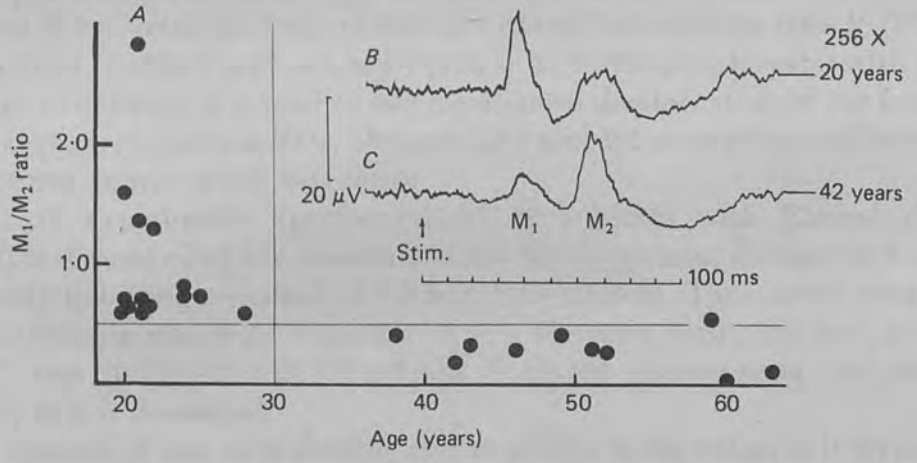


Fig. 1. Graph *A* shows M1/M2 ratio from FDI plotted against age. Inset *B* is a record of the rectified and summed EMG in response to a brief stretch of FDI in a subject aged 20 years, while *C* is the same in a subject aged 42 years. Subject held steady background contraction of 1·1 N throughout the contraction. Prodder set at 7·19 N.

The facts that M2 does not appear to vary with age, that the mechanical properties of the muscle-joint system do not show appreciable differences in older subjects, and that neuromuscular block does not occur in young or old persons during these experiments, indicate that a possible origin of the age-dependent difference lies in the behaviour of muscle spindles.

Ethical Committee approval was obtained for these experiments.

REFERENCE

Darton, K., Lippold, O. C. J., Shahani, M. & Shahani, U. (1985). *J. Neurophysiol.* **53**, 1604–1618.

[*From the Proceedings of the Physiological Society*, 22–23 *September* 1988
Journal of Physiology, **409**, 32*P*, 1989]

Abolition of the short-latency stretch reflex in a human hand muscle by a brief maximal voluntary contraction

By D. M. Corden and O. C. J. Lippold. *Human Physiology, Royal Holloway and Bedford New College, London TW20 0EX*

Neuromuscular function is disrupted by strong voluntary contractions lasting for a minute or longer; the deficits in performance are usually termed fatigue. Reflexes are generally thought of as being relatively resistant to fatigue, but here we report that after two minutes of maximal voluntary contraction (MVC), the short-latency component, M1 of the rectified and averaged electrical response of a muscle to stretch is abolished for up to one minute. In contrast, the effect of fatigue on the size of M2 (which follows M1) is inconsistent and relatively small.

The response M1 is usually regarded as the electrical concomitant of the monosynaptic stretch reflex; M2, the longer-latency component, is likely to be due to the inevitable stimulation of skin and subcutaneous afferents by the stimulus employed to stretch the muscle (Darton *et al.* 1985).

Action potentials were recorded from surface silver disc electrodes 0·9 cm diameter and 2·5 cm apart, over the belly of the first dorsal interosseous muscle (FDI). They were amplified, rectified and averaged (128× at 0·579 ms intervals) with respect to the instant of delivery of a brief (5 ms) mechanical displacement of the forefinger, in the palmar plane, to stretch FDI. The areas M1 and M2 were measured between take-off and return points of the waveform.

Out of 13 experiments (performed on 12 subjects with Ethical Committee approval), 8 showed complete abolition of the M1 component during the 1 min period immediately following cessation of a 2 min MVC of FDI. The control area of M1 for all 13 experiments was $(5{\cdot}3 \pm 0{\cdot}3) \times 10^{-7}$ V s^{-1}. The area during the first minute after the MVC was $(0{\cdot}7 \pm 0{\cdot}2) \times 10^{-7}$ V s^{-1}. In 7 of the experiments the area of M2 increased; in 6 it decreased.

In the absence of any neurological abnormalities in the subjects it seems unlikely that afferent or efferent nerve pathways were affected by the MVC. Thus the abolition of M1 must be due to changes either in the motoneurone pool or in the muscle itself. The tension exerted was reduced by 30–50% of its initial value; moreover, M2 was not systematically altered in size. It is therefore unlikely that the MVC is depressing reflexes through any direct action on the alpha pathway. A possibility is that the MVC is generating fatigue in the intrafusal fibres, which effectively decouples muscle spindles, although as yet we have no supporting evidence.

REFERENCE

Darton, K., Lippold, O. C. J., Shahani, M. & Shahani, U. (1985). *J. Neurophysiol.* **53**, 1604–1618.