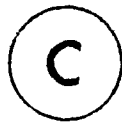


CONTRACTILE PROPERTIES OF NORMAL AND DYSTROPHIC
HUMAN SKELETAL MUSCLES

By



ALAIN YVAN BELANGER, B.Sc., M.Sc.

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CONTRACTILE PROPERTIES
OF HUMAN SKELETAL MUSCLES

TO
MY MOTHER AND FATHER
AND TO
SUSANNE

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AUTHOR: Alain Yvan Bélanger, B.Sc. (Université de Montréal)

M.Sc. (Simon Fraser University)

SUPERVISOR: Professor Alan J. McComas

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ABSTRACT

The aim of this study was to provide a better understanding of muscle function in healthy adult subjects (n=46) and in patients with myotonic muscular dystrophy (MMD; n=25) and limb-girdle muscular dystrophy (LGMD; n=20). Evoked and volitional contractions were examined in two opposing muscle groups in the leg, the ankle plantar-flexors (PF) and dorsi-flexors (DF). The following contractile properties were investigated under isometric conditions: (1) twitch torque, (2) twitch speed, (3) twitch potentiation, (4) voluntary muscle strength, (5) extent of motor unit activation during maximum voluntary effort and (6) muscle fatigue. In both control and dystrophic populations, striking contractile differences were observed between the PF and DF muscle groups. The DF muscles differed from the PF muscles in demonstrating smaller twitches, briefer contraction and half-relaxation times, marked twitch potentiation, more complete motor unit activation, and greater susceptibility to fatigue. Muscle fatigue was found to be caused by peripheral, rather than central failure; it occurred at the level of excitation-contraction coupling and/or the contractile machinery.

Comparisons of muscle contractile properties between patients with muscular dystrophy (MMD and LGMD) and their respective matched controls have disclosed that in any patient at a given stage, the dystrophic process may sometimes spare a muscle group while destroying another, regardless of their functions and fibre-type compositions.

Furthermore, both groups of dystrophic patients showed normal twitch potentiation and muscle fatigue behaviour.

Apart from providing comprehensive information on normal and dystrophic skeletal muscles, this study constitutes a non-invasive and quantitative method for monitoring the time course of human muscular dystrophy and for assessing the benefits of any future therapy.

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"...it is easier to ask clear-cut and quantitative questions in animal work. In human work what one can do to the subject is very obviously restricted and the initial hurdle is to think of questions to ask that will give an answer under the many constraints imposed"

P.A. Merton, 1981.

"...rational therapy (for muscular dystrophy) can just as well be based on an understanding of intermediate steps in the disease process as on discovery of the nature of the fundamental defect"

A.F. Huxley, 1980.

"...one factor of major importance is the failure to use quantitative techniques to assess neuromuscular deficiency. Manual muscle testing and the classic neurology examination are clearly not adequate for evaluation of drug response in man. Subjective evaluation must be replaced by quantitative functional testing and quantitative strength measurements with cable tensiometers and strain-gauges. Even more promising is the application of strength measurements utilized by Edwards et al., which employed muscle stimulation."

T.L. Munsat, 1979.

I. THE PRESENT STUDY

A. Background

In contrast to other types of investigations of human dystrophic muscle, there have been few attempts to analyze the contractile properties of large skeletal muscles. The presenting symptom and the dominant feature of any dystrophic patient remains skeletal muscle weakness. Since the dystrophic muscle presents a variety of anatomical changes which are likely to affect motor performance, non-invasive and quantitative studies of contractile function in-vivo, using both electrical nerve stimulation and voluntary effort, are desirable. In nearly all of the published studies, examinations have been restricted to small distal muscles of the hand and foot leaving partially documented, the contractile behaviour of larger, more proximal muscles which are especially involved in Duchenne, limb-girdle and facioscapulohumeral muscular dystrophy. The above studies have focussed primarily on Duchenne muscular dystrophy, probably because it is the most rapidly progressive and dramatic type of dystrophy. As a result, few studies of muscle contraction have been conducted on other varieties of dystrophy which, although more benign, are actually more common than the Duchenne type; among these other types are the myotonic and limb-girdle dystrophies. The fact that most studies in the latter conditions have been conducted on small numbers of patients and on poorly-matched control subjects further emphasizes the need for more extensive investigation of contractile function in these patients.

B. Aims

The present study examines the contractile properties of two antagonistic muscle groups, the plantar-flexors (PF) and dorsi-flexors (DF) of the ankle. Because of the experimental limitations associated with human investigation, this project relates more to overall contractile function than to the underlying pathophysiological mechanisms of human dystrophy. By making comparisons between the contractile properties of PF and DF muscles of matched healthy subjects and of patients with myotonic muscular dystrophy (MMD) and limb-girdle muscular dystrophy (LGMD), the aim of the present investigation work was to seek answers to the following questions:

in both healthy subjects and dystrophic patients

1. Are twitch properties of TA and PF muscle groups different?
2. Are PF and DF muscle groups equally strong?
3. Can motor units of TA and PF muscles be fully activated during the course of a maximum voluntary isometric effort?
4. Are DF and PF muscle groups equally susceptible to fatigue during sustained maximum voluntary contractions?
5. What are the influences of age and sex on the contractile properties of these two muscle groups?

in both patients with myotonic dystrophy or limb-girdle dystrophy

6. Are DF and PF muscle groups similarly affected by the dystrophic process?
7. Is there preferential involvement by the dystrophic process

of either fast-twitch (type II) or slow-twitch (type I) muscle fibres in either of these two muscle groups?

8. Can patients with MMD or LGMD make full use of their available muscle mass during maximum voluntary effort?
9. Is the tension generated by the dystrophic muscle proportional to its electrical response?
10. What are the isometric fatigue behaviours of dystrophic PF and DF muscle groups?
11. Can patients with MMD and LGMD be distinguished on the basis of their contractile properties?

C. Experimental approaches

The experimental approaches used to answer these questions involved the evoked and volitional testing procedures described below.

1. Maximum isometric twitches (amplitude and time course were measured together with muscle compound action potentials (M-waves)), with the muscle at rest and immediately after five seconds of maximum voluntary contraction. These evoked electro-mechanical responses allowed physiological features such as neuromuscular transmission, muscle fibre impulse propagation, excitation-contraction coupling, contractile machinery, and post-activation potentiation mechanisms to be studied.
2. Maximum voluntary muscle strength was measured with the extent of motor unit activation during such a strong effort. These responses indicated whether or not the whole muscle mass could be fully turned-on during the course of a strong volitional effort. These measurements also permitted an objective assessment of muscle weakness. 3.

Measurement of isometric muscle fatigue and determination of sites of failure following a 60 second sustained maximum voluntary contraction. The monitoring of voluntary muscle strength, motor unit activation, twitch and M-wave amplitudes, before and after fatigue testing, served to identify central (lack of motor unit activation) or peripheral sites of failure (neuromuscular transmission, muscle impulse-propagation, excitation-contraction coupling, and contractile machinery).

D. Significance

This study provides comprehensive information on the contractile properties of two opposing muscle groups in humans, the plantar-flexors (PF) and dorsi-flexors (DF) of the ankle. In normal subjects, a better appreciation of isometric muscle twitch, strength and fatigue behaviour emerge as the relative contribution of various physiological mechanisms, such as motor unit activation, excitation-contraction coupling and contractile machinery, are investigated. Furthermore, the present investigation provides new insights into the nature of muscle weakness in human dystrophy. In view of its physiological basis, the present study complements the many anatomical, biochemical and electromyographic studies of human dystrophic muscles.

Apart from its research interest, this project has considerable practical significance. This type of non-invasive and quantitative contractile assessment, in combination with any other types of muscle investigation, can enable the time course of the dystrophic process to be precisely monitored, and can permit better assessment of therapeutic trials in human muscular dystrophy. As a physiotherapist concerned with

the optimization of muscular function in patients with muscular dystrophy, I feel that studies such as this should serve to establish a better rationale for physical and orthopaedic procedures.

II. REVIEW OF LITERATURE

A. Introduction

The term "dystrophic muscularis progressiva" was first proposed by Erb (1891), a German neurologist, in his attempt to classify various muscle disorders. Some 60 years earlier however, the Scottish surgeon Charles Bell (1830) appeared to have been the first to describe a case of human dystrophy (Ogg, 1971). There is no precise definition of the term 'muscular dystrophy' however, it may be defined as: "...any disease of hereditary nature which leads to progressive degeneration and loss of muscle fibers" (Astrom and Adams, 1979). As stated by Cullen and Mastaglia (1980), a typical dystrophic muscle comprises a mixture of living, dying, necrotic and regenerating muscle fibres present in varying proportions, depending on the stage of the disease and on the type of dystrophy.

This review of literature focusses on studies of contractile function in patients with myotonic dystrophy and limb-girdle dystrophy, and in healthy subjects. The findings in patients with Duchenne muscular dystrophy will also be reviewed because of their possible relevance to the myotonic and limb-girdle types. For each type of dystrophy, three issues are considered: (1) historical and clinical overview, (2) muscle pathology and (3) contractile assessment. For the healthy control subjects, a review of twitch and voluntary contractions is presented for both the ankle plantar-flexor (PF) and dorsi-flexor (DF) muscles. Rather than being exhaustive, this review of literature

attempts to be selective in focussing only on the the most definitive investigations. Since this project deals strictly with the contractile behaviours of dystrophic patients and of healthy subjects, the literature concerned with the controversial question of pathogenesis in human and animal dystrophies will not be addressed.

B. Duchenne muscular dystrophy (DMD)

1. Historical and clinical overview

Duchenne muscular dystrophy is the best known and the most thoroughly investigated of all human dystrophies (for review: Walton, 1974; Adams, 1975; McComas, 1977; Dubowitz, 1978; and Rowland and Layzer, 1979). The British physician Edward Meryon (1852) and the French neurologist Duchenne de Boulogne (1868) first described this disorder. Apart from rare exceptions, only males are affected since the disease is transmitted by a recessive gene on the X-chromosome. The dystrophic children are unusually clumsy in learning to walk and may never succeed in running. By the age of three, they manifest difficulty in rising from the floor (Gowers' sign, 1879). At this stage, obvious weakness and atrophy of some muscles contrast with marked "hypertrophy" of other muscles, such as the calves. Up to the age of eight, there is progressive evolution of weakness and atrophy of the more proximal muscles, while the distal muscles are better preserved. By the age of ten, the child loses his ability to stand and to walk. Thereafter, the inevitable confinement to a wheelchair and the absence of ambulation bring scoliosis and joint contractures. Death usually occurs in the late teens or early twenties, either from bronchopneumonia or from heart

failure. 4

2. Muscle pathology

With the light microscope, Meryon (1852), Duchenne (1868) and Erb (1891) were able to identify some of the major histological changes in dystrophic muscles. These included increased variation in muscle fibre size, centrally placed myonuclei, necrotic fibres, degenerative and regenerative fibres, and infiltration of the muscle by adipose and connective tissues. With the advent of muscle histochemistry, a predominance of type I (slow-twitch) muscle fibres was demonstrated (Dubowitz and Brooke, 1973). More recently, gaps in the muscle plasmalemma have been identified (Mokri and Engel, 1975; Carpenter and Karpati, 1979). As a result, an excessive quantity of extracellular calcium would tend to penetrate the fibre, leading to myofibrillar over-contraction, and possibly to cell necrosis (Wrogemann and Pena, 1976; Brodensteiner and Engel, 1978). Furthermore, ATP depletion in the muscle (Wrogemann and Pena, 1976) or enhancement of calcium-activated proteases (Kan and Pearson, 1977) may lead to muscle weakness and necrosis. Recently, Takamori et al., (1981) compared the contractile and chemosensitive properties of rat diaphragm muscle, treated with the calcium ionophore A23187, with those of human dystrophic muscles. They observed significant discrepancies between the contractile responses of both types of muscle, and concluded that the muscle treated with the calcium ionophore was not entirely similar to the dystrophic muscle. The topic of muscle pathology in Duchenne muscular dystrophy has been comprehensively reviewed by Adams (1975), Dubowitz and Brooke (1973),

Cullen and Fulthorpe (1975) and Rowland and Layzer (1979).

3. Contractile assessment

The first study of contractile behaviour of patients with DMD, using peripheral nerve stimulation, was that of Botelho, Beckett and Bendler in 1960. Their examination was confined to the adductor pollicis muscle, a choice probably influenced by the elegant and careful study of Merton (1954) on voluntary strength and fatigue of this muscle in normal subjects, and by the fact that this distal muscle was better preserved in DMD. Studies of this kind, on this same muscle, were later performed by Roe et al., (1967) and by Desmedt et al., (1968a, 1977b). Other Duchenne dystrophic muscles have been investigated by McComas et al., (first dorsal interosseus, 1968a; extensor digitorum brevis, 1971a), by Buchthal et al., (biceps brachii, 1971) and by Hosking et al., (quadriceps, 1978). Recently, contractile studies of single skinned muscle fibres, obtained from muscle biopsy, have been conducted in patients with DMD (Wood et al., 1978; Takagi and Nonaka, 1981). As anticipated, the results obtained from these studies showed considerable variability from one patient to the next and from one muscle to the other. Nevertheless, three major observations have been disclosed by the above studies: (1) the Duchenne dystrophic process may preferentially affect type II (fast-twitch) muscle fibres, as revealed by the prolonged twitch contraction and half-relaxation times (Botelho et al., 1960; McComas et al., 1968a, 1971a; Desmedt et al., 1968a, 1977b); (2) disorders of excitation-contraction coupling and contractile machinery may be present in DMD, as suggested by the reduced twitch and

tetanic tensions, slower twitch tension development, and by the abnormally pronounced negative staircase and modest positive staircase responses (Desmedt et al., 1968a, 1977b); and (3) single Duchenne dystrophic fibres generate less than normal tension, probably because of structural abnormalities in the organization of myofibrils and possibly because of impaired calcium regulation by the sarcoplasmic reticular system (Wood et al., 1978; Takagi and Nonaka, 1981).

Studies of voluntary contractions in patients with DMD were best conducted by Fowler and Gardner (1967), Ziter et al., (1977), Hosking et al., (1976, 1978) and by Allsop et al., (1981). Despite considerable variability between their results, these studies have revealed four important observations: (1) muscle strength decreases proportionately in proximal muscles of the arm and leg until late in the disease (Fowler and Gardner, 1967); (2) steady loss of strength occurs with age despite the child's growth, weight gain, bracing and loss of ambulation (Ziter et al., 1977); (3) in the early stage of the disease, muscle weakness does not parallel the loss of functional daily muscular activities (Allsop et al., 1981) and (4) isometric strength of muscles such as deltoids, wrist extensors, neck flexors and dorsiflexors of the foot, showed positive correlations for age, weight and height, in patients with DMD (Hosking et al., 1976). To date, no study has yet been conducted with regard to muscle fatigue behaviour of patients with DMD. Studies of muscle performance in human dystrophy have been recently reviewed by Edwards (1980).

C. Myotonic muscular dystrophy (MMD)

1. Historical and clinical overview

The credit for recognizing myotonic muscular dystrophy as a clinical entity is usually given to Steinert (1909) in Germany and to Batten and Gibb (1909) in the United States. However, there is evidence to suggest that the first description of MMD was given earlier by Dana (1888). Myotonic muscular dystrophy has been extensively studied over the past 70 years and current knowledge has recently been reviewed in a monograph by Harper (1979; see also Roses et al., 1979). This disorder differs from the other types of dystrophy in presenting both a widespread involvement of tissues other than skeletal muscles and the phenomenon of myotonia. The latter describes a delayed phase of muscle relaxation following either mechanical excitation or voluntary contraction. Myotonia is associated with high frequency bursts of action potentials initiated in the hyperexcitable muscle membrane (Norris, 1962; McComas and Mrozek, 1968); its ionic defect is, however, not understood (Bryant and Morales-Aguilera, 1971; Lipicky and Bryant, 1973; Adrian and Bryant, 1974; Lipicky, 1979). The most frequent clinical features, apart from the myotonic response, are muscle weakness and atrophy, frontal baldness in males, apathetic faces and, in severely affected cases, mental retardation and dementia (Harper, 1979). An important characteristic of these patients is that weakness is initially manifested not in the proximal muscles, as in other myopathies, but in the distal muscles; there is also early involvement of facial, masticatory and sternocleidomastoid muscles (Fowler and Gardner, 1967; Harper, 1979; Roses et al., 1979). As reported by Harper (1979), an early loss of strength is often seen in the extensor and

flexor muscles of the wrist and fingers, along with the ankle dorsi-flexor (DF) muscles. In the latter case, the weakness may result in foot drop or a stumbling type of locomotion. Although the pattern of inheritance is always by an autosomal dominant gene, the dystrophic muscle changes may occur early or late in life, and they may be mild or severe in nature. Death usually occurs as a result of pulmonary or cardiac dysfunction (Harper, 1979), because of the involvement of respiratory and cardiac muscle by the dystrophic process.

2. Muscle pathology

As early as 1909, Steinert described such microscopic changes as variation of fibre size, fibrosis, and proliferation of myonuclei in muscle specimen taken from patients with myotonic dystrophy. Recent studies of muscle biopsies have disclosed a variety of additional pathological changes of which none, unfortunately, is specific to the disorder (for review: Engel, 1962; Engel and Brooke, 1966; Engel, 1967; Dubowitz and Brooke, 1973; Harper, 1979; Roses et al., 1979). The most characteristic changes reflect preferential atrophy of type I (slow-twitch) muscle fibres and hypertrophy of type II (fast-twitch) fibres, increased numbers of centrally placed myonuclei forming chains inside the fibres, small groups of disorganized myofibrillar materials (sarcoplasmic masses) and ringed fibres. Abnormalities of the tubular and sarcoplasmic reticulum systems are also often present, and may range from swelling to pronounced architectural disorganization (Mussini et al., 1970; Korenyi-Both et al., 1975). Muscle spindles are also affected and may show a remarkable increase of intrafusal fibre splitting (Swash, 1972; Swash and Fox, 1975). At the level of the

neuromuscular junction, abnormally extensive and elongated terminal arborizations are frequently observed (MacDermot, 1961; Engel et al., 1975). Together, the above pathological changes are likely to affect contractile behaviour in patients with myotonic muscular dystrophy.

3. Contractile assessment

To date, there have been only two limited studies of contractile function in patients with MMD. In 1967, Fowler and Gardner measured muscle strength in various muscle groups of only 5 patients, and observed the greatest loss of strength in the handgrip muscles. No measurement was made of ankle PF and DF muscle strength. A few years later, McComas et al., (1971b) conducted a study of twitch function in the extensor hallucis brevis of 17 patients and showed the twitch tension to be reduced and the contraction and half-relaxation times to be prolonged. The prolongation of the two latter measurements was unexpected in the light of a preferential atrophy and impairment of type I (slow-twitch) fibres in myotonic dystrophy (Engel and Brooke, 1966; Dubowitz and Brooke, 1973). McComas et al., (1971b) indicated, however, the need to consider factors such as age and muscle connective tissue in the interpretation of twitch analysis in patients with myotonic dystrophy. To date, there has been no study of muscle fatigue in patients with this disorder.

D. Limb-girdle muscular dystrophy (LGMD)

1. Historical and clinical overview

The term "limb-girdle muscular dystrophy" was first proposed by

Walton and Nattrass (1954) to describe patients with selective dystrophic involvement of upper and lower limb-girdle muscles, the facial and neck muscles being spared. Limb-girdle muscular dystrophy is usually transmitted by an autosomal recessive gene and comprises patients with scapulohumeral weakness (the Erb type, 1884) and with pelvifemoral weakness (the Leyden (1876) and Mobius (1879) type). There have been numerous clinical studies of patients with LGMD and these have been recently reviewed by Bradley (1979). The disease usually appears within the second or third decade. Weakness is first seen in either the scapular or pelvic girdle muscles or both; gradually the weakness spreads to more distal muscles. The involvement of pelvic muscles eventually causes loss of ambulation some ten to twenty years after the onset of the symptoms. Contractures may develop as weakness progresses. In some patients, death may occur in the forties or fifties while other patients may remain ambulant with a normal life expectancy (Bradley, 1979).

2. Muscle pathology

A variety of pathological muscle changes have been identified in limb-girdle dystrophy, but none of them appears to be specific to the disorder (for review: Dubowitz and Brooke, 1973; Bradley, 1979).

Limb-girdle dystrophic muscles are characterized by type I (slow-twitch) fibre predominance, increased fibre size, hypertrophy and splitting of fibres, fibrosis, and moderate amounts of muscle degeneration and regeneration (Dubowitz and Brooke, 1973; Bradley, 1979).

3. Contractile assessment

Studies of contractile properties of patients with limb-girdle dystrophy, using peripheral nerve stimulation, were first conducted by Desmedt (1967) and later by Takamori et al., (1975, 1978) on the adductor pollicis muscle, and by Sica and McComas (1971) on the extensor hallucis brevis muscle. The study of Desmedt (1967) lacked information on the total number of patients investigated and the proportions with limb-girdle as opposed to facioscapulohumeral dystrophy. These authors showed the contraction and half-relaxation times of the maximum isometric twitch to be within normal values. Desmedt postulated, on the basis of abnormal staircase responses, a disorder of electro-mechanical coupling linked to the inability to potentiate calcium release from the sarcoplasmic reticulum. Further studies by Takamori et al., (1975, 1978) supported Desmedt's postulate by showing a variety of abnormalities of twitch, tetanic and staircase responses, which suggested impairment of sarcoplasmic reticulum function. For their part, Sica and McComas (1971) found reduced twitch tension, and prolonged contraction and half-relaxation times of the extensor hallucis brevis. The findings of Sica and McComas (1971), but not that of Desmedt (1967), were in agreement with histological investigations showing the preferential maintenance of type I (slow-twitch) fibres in muscles affected by LGMD (Dubowitz and Brooke, 1973).

Studies of voluntary contractions in patients with LGMD have been conducted by Fowler and Gardner (1967), Dimitrijevic and Gracanin (1968) and by Bradley (1979). These studies have disclosed three major

observations: (1) they have confirmed the predominantly proximal muscle involvement by the limb-girdle dystrophic process (Fowler and Gardner, 1967; Bradley, 1979); (2) they have shown asymmetry in the distribution of weakness between the two sides of the body (Bradley, 1979) and (3) they have shown the tibialis anterior (TA) muscle to be much more affected (weaker) than the gastrocnemius and soleus muscles (Dimitrijevic and Gracanin, 1968; Bradley, 1979). To date, only one study of muscle fatigue has been reported in these patients (Blank et al., 1981). During voluntary isometric contractions of the elbow flexor muscles carried to complete fatigue, Blank and colleagues showed the dystrophic muscles to have the same fatigue responses as the normal muscles, in showing both contractile failure and compensatory motor unit activation.

E. Contractile assessment of ankle plantar-flexor and dorsi-flexor muscles in healthy subjects

1. Twitch studies

The first 'twitch-like' study of human PF muscles, without electrically stimulating the tibial nerve, was conducted in 1951 by Lambert and colleagues at the Mayo Clinic in Rochester. With the subject sitting and his/her foot resting on a hinged platform, the Achilles tendon was tapped and the resulting reflex plantar-flexion contraction of the calf muscles was recorded with a pressure transducer placed underneath the foot-plate. Lambert and colleagues showed twitch measurements to be important aids in the assessment of drug therapy for cases of hypothyroidism (prolonged contraction time) and hyperthyroidism

(shortened contraction time).

The interest in the physiology of slow and fast contracting skeletal muscles, first generated by Ranvier (1873) in the rabbit and pursued further by Denny-Brown (1929) in the cat, led Buller and collaborators (1959) to investigate speed of contraction in human gastrocnemius and soleus muscles. Rather than using an external strain-gauge attached to the limb, Buller et al., (1959) recorded twitches by means of a saline-filled needle inserted into the muscle belly. This needle, which was also used as a stimulating electrode, was connected to a capacitance manometer measuring the pressure changes in the vicinity of the contracting fibres. In contrast to animal results (Close, 1972), which show the soleus to be significantly slower than the gastrocnemius muscles, no significant difference of contraction times could be detected between the soleus and gastrocnemius muscles in humans.

Another approach to this question of speed of contraction in human muscle was that of McComas and Thomas (1968b) who used a piezoelectric bender element. A plastic stylus mounted on the bender indented the skin overlying the muscle belly; the output of the device was connected to the DC amplifier of an oscilloscope. Twitch contraction times were studied in four muscles: the frontalis, first dorsal interosseus, extensor digitorum brevis and lateral gastrocnemius. The mean contraction and half-relaxation times of the lateral gastrocnemius were found to be approximately 120 and 85 ms respectively, values which were larger than those obtained for any of the other muscles examined.

Over the last twelve years, only three twitch studies of ankle plantar-flexor (PF) muscles have been reported in humans (Davies and White, 1981, 1982; Sale et al., 1982). Davies and White (1981) first investigated the effects of dynamic exercises on triceps surae contractile function in young and elderly men, using twitch and tetanic stimulation, as well as voluntary contractions. They showed the triceps surae muscles of healthy male subjects to be weaker after exercise, but not more fatiguable. Then, in a group of elderly healthy men (68-71 years), Davies and White (1982) showed the triceps surae muscles to be weaker, more fatiguable and more slowly contracting in comparison with the triceps surae of younger subjects. Last year, I participated, with Sale, Quinlan, Marsh and McComas, in a study of contractile function of PF muscles in 20 healthy male subjects, using a specially-designed twitch and voluntary torque measuring device mounted with strain-gauges (Sale et al., 1982). In this study, we showed the mean contraction and half-relaxation times to be 112 and 99 ms respectively, and the optimum muscle length for torque generation to correspond to 10 degrees of dorsi-flexion. The most complete study of DF muscles and of the tibialis anterior (TA) muscle in particular, using nerve stimulation, appears to be that of Marsh, Sale, McComas and Quinlan (1981). This latter study was conducted with the same torque-measuring device used by Sale et al., (1982). In 1971 however, Buchthal et al., (1971) recorded twitches from small bundles of fibres belonging to TA muscle in 7 subjects, using a needle inserted into the tendon. With this arrangement, the displacement of the needle, as a result of muscle contraction, was recorded by small sensitive strain-gauges mounted on a

holder fixed to the shaft of the needle. In 90% of the bundles investigated, Buchthal et al., (1971) found the TA twitch contraction times to be approximately 70 ms in duration. In their study of the TA muscle, Marsh et al., (1981) found the contraction and half-relaxation times to be approximately 80 and 83 ms respectively, and the optimum muscle length for torque generation to correspond to 20 degrees of plantar-flexion.

2. Post-activation potentiation and motor unit activation

Much is known about the phenomenon of post-tetanic potentiation (PTP) of twitch tension in animals (Sandow, 1964; Standaert, 1964; Close, 1972) and in humans (Botelho and Cander, 1953; Desmedt and Hainaut, 1968; Rosenfalck, 1974). The above authorities have proposed an explanation based on the 'active state' of the muscle fibres. This term described the period following excitation in which myosin and actin filaments interact; it reflects the intensity and time course of the muscle tension generating mechanism, in the absence of the series-elastic component (Hill, 1949, 1953; Bahler et al., 1967). Since the potentiated twitch was faster than the control one, the authors (cited above) concluded that the potentiation depended on an increase in the intensity of the 'active state', rather than in its duration.

The issue of motor unit activation during voluntary muscle contraction has been studied for many years and has been recently reviewed (Buchthal and Schmalbruch, 1980; Burke, 1981; Desmedt, 1981). It has been recognized, since the pioneering study of Adrian and Bronk (1929), that the recruitment and firing rate of motor units are the two

mechanisms by which the central nervous system regulates muscle tension. The question as to whether an individual can fully activate all of his/her motor units (complete recruitment and optimum firing rate) during the course of a 'maximal' voluntary effort remains a controversial matter (Merton, 1954; Ikai et al., 1965; Edwards et al., 1975). Furthermore, there is a lack of knowledge on the issue of post-activation potentiation of twitch tension following voluntary contractions.

3. Muscle strength and fatigue


The importance of muscle strength was well recognized in ancient times and was seen as an expression of outstanding physical achievement (warriors and athletes) and of a sign of general health. The modern era concerning muscle strength development and measurement began with the Second World War, when the need arose for physical rehabilitation of hundreds of thousands of injured soldiers and civilians. An important contribution of the aircraft industry to the field of physical rehabilitation was the adaptation, by Clarke and colleagues (1948, 1950), of the cable tensiometer for the measurement of human muscle strength. Today a wide variety of pressure transducers, tensiometers, strain-gauges and hydraulic systems are available for muscle testing in research and clinical settings (for review: Darcus, 1953; Beasley, 1961; Tornvall, 1963; Hislop and Perrine, 1967; Marsh et al., 1981). Manual muscle testing, despite its subjective component, remains today the most widely used method of strength assessment. This is probably because it requires only a pair of good hands and discriminative judgement, and

because it can be applied to most muscle groups in the body (Daniels and Worthingham, 1972; Medical Research Council, 1976; Nicholas et al., 1978; Brooke et al., 1981).

Much more is known about the contractile behaviour of human plantar-flexor muscles (for example, Lippold, 1952; Herman and Bragin, 1967; Murray et al., 1976; Falkel, 1978; Fugl-Meyer et al., 1979, 1980; Fugl-Meyer, 1981; Davies and White, 1981, 1982; Sale, Quinlan, Marsh, McComas and Belanger, 1982) than about the dorsi-flexor muscles (Buchthal et al., 1971; Desmedt and Godaux, 1977; Fugl-Meyer, 1981; Marsh et al., 1981). The two studies by the McMaster group (Marsh et al., 1981; Sale et al., 1982), together with the other studies cited above, have disclosed the following general observations: (1) PF muscles are stronger than DF muscles (Marsh et al., 1981; Fugl-Meyer, 1981; Sale et al., 1982), (2) males are stronger than females throughout the adult years (Fugl-Meyer et al., 1980), (3) the soleus-gastrocnemii complex is the major contributor to ankle plantar-flexion torque (Herman and Bragin, 1967; Murray et al., 1976; Sale et al., 1982) while the TA muscle is the main dorsi-flexor (Marsh et al., 1981), (4) PF and TA optimum muscle lengths correspond approximately to 10 degrees of dorsi-flexion (Sale et al., 1982) and to 20 degrees of plantar-flexion respectively (Marsh et al., 1981), and (5) age and weight are two of the major variables affecting strength of PF muscle group (Falkel, 1978).

A common experience of everyday life is fatigue of voluntary muscle contractions. To date, there is still no consensus as to the underlying mechanisms involved and as to the major sites where fatigue takes place. There have been numerous studies of muscle fatigue in

humans, most of which were concerned with either the adductor pollicis muscle (Merton, 1954; Edwards et al., 1977; Bigland-Ritchie et al., 1979; Jones et al., 1979) and the quadriceps muscle (Edwards et al., 1977; Bigland-Ritchie et al., 1978; Tesh, 1980; for a recent review, see Porter and Whelan, 1981). In contrast, there has been no study of muscle fatigue in both PF and DF muscles in which the loss of voluntary force over time was recorded. Instead, the susceptibility to fatigue of the soleus and gastrocnemius muscles was investigated electromyographically (Ochs et al., 1977). Following a series of fatiguing dynamic exercises, Ochs and collaborators showed the EMG response of soleus to be better preserved than that of gastrocnemius thereby suggesting the greater capacity of soleus to resist fatigue. However, this study would not have detected fatigue resulting from failure of excitation-contraction coupling or of the contractile machinery. Studies of fatigue in soleus and gastrocnemius muscles have also been conducted at the level of single motor units (Stephens and Usherwood, 1977; Garnett et al., 1978). These two studies have shown slow-twitch type motor units to be more resistant to fatigue than those of the fast-twitch type.

The fatigue behaviour displayed by any muscle or group of muscles is bound to be dependent on the type and duration of the fatiguing exercise. The present study is concerned with the fatigue responses of PF and DF muscles following 60 seconds of maximum sustained isometric contraction. Studies of the quadriceps muscle, following such a testing procedure, have shown fatigue to be partially due to a reduced central drive (lack of motor unit activation), because voluntary  on

was seen to decline more than the muscle tension achieved by stimulating the muscle at 50Hz. No evidence for neuromuscular failure, tested by surface EMG recordings, were seen in the quadriceps muscle during the fatiguing exercise (Edwards et al., 1977; Bigland-Ritchie et al., 1978). Similar studies, conducted on the adductor pollicis muscle, revealed that isometric fatigue was associated with a progressive reduction in the firing rate of motor units (Edwards et al., 1977; Bigland-Ritchie et al., 1979; Jones et al., 1979). Such a reduction in the firing rate was seen by the above authors as being beneficial to the muscle, in that a fatiguing muscle could generate greater tension when stimulated at low frequencies than at higher frequencies. This finding is in keeping with the finding of Marsden et al., (1971) who showed the frequency of discharge of motor units in the adductor pollicis muscle to be approximately 100 Hz at the onset of contraction with a subsequent decline to lower values (20-30 Hz).

III. SUBJECTS AND METHODS

A. Healthy subjects and dystrophic patients

Experiments were first conducted on 46 healthy subjects aged 19-65 years, none of whom had clinical evidence of neurological disease or of lumbosacral root lesions (Table 1). The majority of control subjects enjoyed a sedentary way of life and only a few engaged in physical recreation or undertook manual work in local factories. University students, housewives, laboratory technicians and blue collar workers constituted this control group. Twenty five patients with myotonic dystrophy, aged 19-63 years, and twenty patients with limb-girdle dystrophy, aged 19-68 years, were then investigated (see Results; Tables 3 and 5). Most of these patients originated from the Hamilton area. Every effort was made to get in touch with all of the patients known to the McMaster University muscular dystrophy clinic. A letter was first sent to each patient explaining the nature of this project and the techniques to be used. A few weeks later, I telephoned each patient and inquired if he or she was prepared to participate in the present study. None of the patients declined this opportunity to have their skeletal muscles investigated; most were eager to come and, after testing was completed, inquired about a repeat. Each patient had been diagnosed by at least one specialist on the basis of family history, clinical examination, serum CPK and LDH analyses, comprehensive electromyographical (EMG) examination and, in some instances, by muscle biopsy. Of these aspects, the family history, clinical examination and

<u>PARAMETERS</u>		<u>CONTROL SUBJECTS</u>		
		MALE	FEMALE	
n		31	15	
AGE	(M)	34.3	36.9	NS
	(SD)	13.3	10.4	
HEIGHT	(M)	176.5	165.5	S
	(SD)	6.5	6.1	
WEIGHT	(M)	74.3	62.8	S
	(SD)	8.5	13.4	

TABLE 1. Physical characteristics of healthy subjects. Age (yr), height (cm) and weight (kg) values are represented with their respective means (M) and standard deviations (+/- SD). Males are seen to be significantly taller and heavier than the females. Significance was assessed at the 5% level, using independent t-tests. (S, significant; NS, not significant)

EMG examination carried the most weight in determining the final diagnosis. All patients were ambulant except for four patients with LGMD who required the use of a wheelchair. Nine patients (3 with MMD and 6 with LGMD) exhibited a restriction in passive dorsi-flexion of the ankle joint, due to Achilles contractures. The cooperation of the patients throughout the testing sessions was excellent. Only two patients, both affected with MMD, showed mental retardation, as revealed by their social behaviour and by the fact that they were accompanied and instructed by a close member of the family. Mental impairment in these patients could have affected their volitional performance during the experiments. To compensate for such a situation, my verbal and manual instructions were re-emphasized, to ensure that the simple motor tasks were clearly understood. Drawn from the population of 46 controls were two groups of 25 and 20 subjects, who served as controls for the myotonic and limb-girdle patients respectively. Subjects in each control group were matched for age, sex, weight and height to their dystrophic counterpart (see Results; Tables 3 and 5). The advantage of closely matching the controls to the dystrophic patients for such variables is that any abnormalities of contractile function, observed in either dystrophic group, cannot be accounted for by discrepancies in age, sex, weight and height. All patients and subjects volunteered for the experiments, signed consent forms and were paid. This project carried the approval of the Ethics Committee of McMaster University.

B. Muscle groups investigated

Experiments were conducted on the ankle plantar-flexor (PF) and

dorsi-flexor (DF) muscles of the lower leg. The choice of these two muscle groups was influenced by my previous work on the PF muscles (Sale et al., 1982) and by my familiarity with a study of the DF muscles (Marsh et al., 1981). These leg muscles provide several technical and physiological advantages. As regards technique, each muscle group is easily identifiable and presents no difficulty in stimulating and recording. As to the physiological aspect, there is no confusion as to the functional role played by each of these muscle groups; they are almost completely devoted to ankle plantar-flexion and dorsi-flexion movements. They also possess the advantages of being antagonist to each other and of mediating both postural and locomotion functions. The PF muscle group comprises the triceps surae complex (soleus, medial and lateral gastrocnemii) together with the tibialis posterior, plantaris, peroneus longus, peroneus brevis and the long flexors of the toes (Gray, 1973). The tibialis anterior (TA), which is studied in detail in this report, together with the extensor hallucis longus, extensor digitorum longus and peroneus tertius muscle, constitute the DF muscle group (Gray, 1973). Studies of fibre type composition of human soleus-gastrocnemii and TA muscles, performed on both post-mortem and freshly biopsied tissues, have shown type I (slow-twitch) muscle fibres to be most prevalent in the soleus (SOL) muscle, while both the gastrocnemii (G) and TA muscles were seen to possess similar fibre-type compositions (Edstrom and Nystrom, 1969; Johnson et al., 1973; Gollnick et al., 1974a; Edgerton et al., 1975; Elder, 1979).

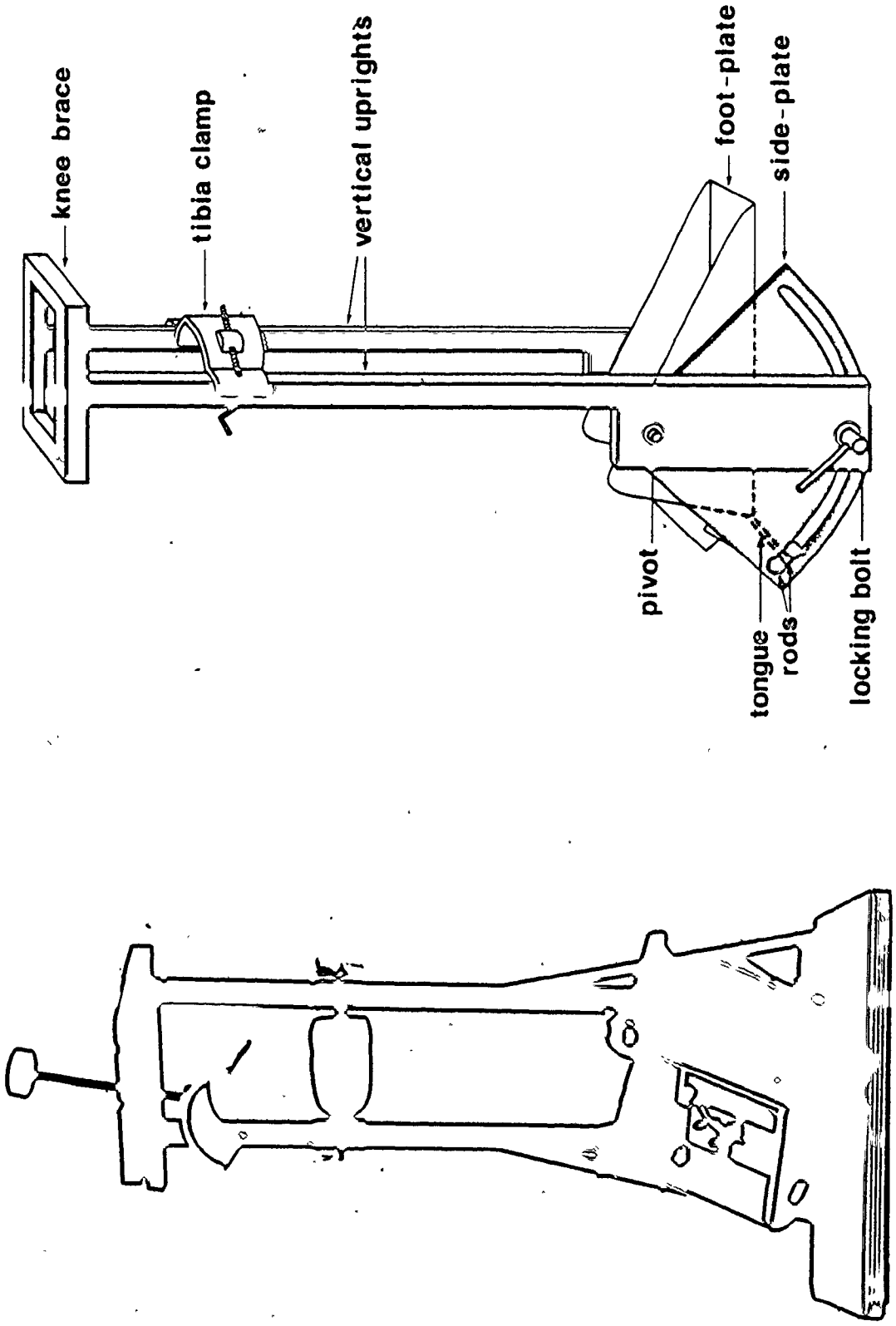
C. Techniques of investigation

1. Torque measurement

With the individual sitting and with his/her knee kept at a right angle, the leg was placed inside a specially designed torque-measuring device (Fig. 1). This device consisted of two vertical steel pillars, two side-plates and a thin steel foot-plate; the latter was free to rotate about an axis which passed through the ankle joint. A short metal tongue projected from the rear of the foot-plate and abuted against either the lower horizontal rod (during dorsi-flexion torque) or upper horizontal rod (during plantar-flexion torque), both of these rods being fixed to the two side-plates. Sensitive strain-gauges (Micro-Measurement Inc.) mounted on either side of the metal tongue detected any bending resulting from evoked or voluntary dorsi-flexion or plantar-flexion movements of the ankle joint. The side-plates and foot-plate could move together so as to adjust the position of the ankle joint prior to testing muscle function. The resonant frequency of this apparatus was 120 Hz unloaded and 80 Hz with the foot in position. Signals from the strain-gauges were fed to a bridge amplifier and displayed on the cathode-ray oscilloscope. The foot was attached to the foot-plate with Velcro straps. The knee was prevented from moving upwards during plantar-flexion by an adjustable metal clamp placed on the top of the knee. Measurements of torque, i.e. force about the axis of rotation, were made in Newton-metres (N.m). Previous studies by Marsh et al., (1981) and by Sale, Quinlan, Marsh, McComas and Belanger (1982) have found the optimum muscle length to correspond to 20 degrees of plantar-flexion for the DF muscles, and to 10 degrees of dorsi-flexion for the PF muscles, the reference position being

Figure 1:

Specially designed leg-holder and ankle torque-measuring device. The strain gauges are mounted on either side of the metal tongue. See text for full description.



perpendicularity between the sole of the foot and the medial border of the tibia (0 degree). Because of the effect of lever arm on torque measurement, one might argue that the optimal joint angle did not correspond to the optimal muscle length for the PF and DF muscles. In the case of PF muscles, we showed (Sale et al., 1982), using radiographic examination of the ankle joint, that the length of the lever arm changed significantly between full dorsi-flexion and full plantar-flexion, being longer in the fully plantar-flexed position (Appendix I). On the basis of mechanical advantage, therefore, one should have expected to measure maximum PF torque values with the ankle almost completely plantar-flexed, since the effect of the lever arm was maximal. This was not the case, however, since maximum evoked and voluntary PF torques were obtained with the ankle positioned between 10 and 20 degrees of dorsi-flexion. Thus, the development of maximum PF torque in the presence of a shorter lever arm (dorsi-flexion) strongly indicated that optimum joint angle did indeed corresponded to optimum muscle length. In the case of the DF muscles, long tendons of which are kept at a constant distance from the axis of rotation of the ankle throughout joint movements, the lever arm would not be expected to influence torque development. Thus, the optimal joint angle for DF muscles was seen as a true reflection of muscle length effects (Marsh et al., 1981). Contractile function was tested with the ankle joint at 20 degrees of plantar-flexion (for DF muscles) and at 10 degrees of plantar-flexion (for PF muscles), except for nine dystrophic patients. The latter patients, because of Achilles tendon contractures, were tested for plantar-flexion at 0 degrees. Throughout the experiments,

the leg was warmed by an infra-red lamp such that the skin over the tested muscles remained between 34 and 38 degrees Celsius.

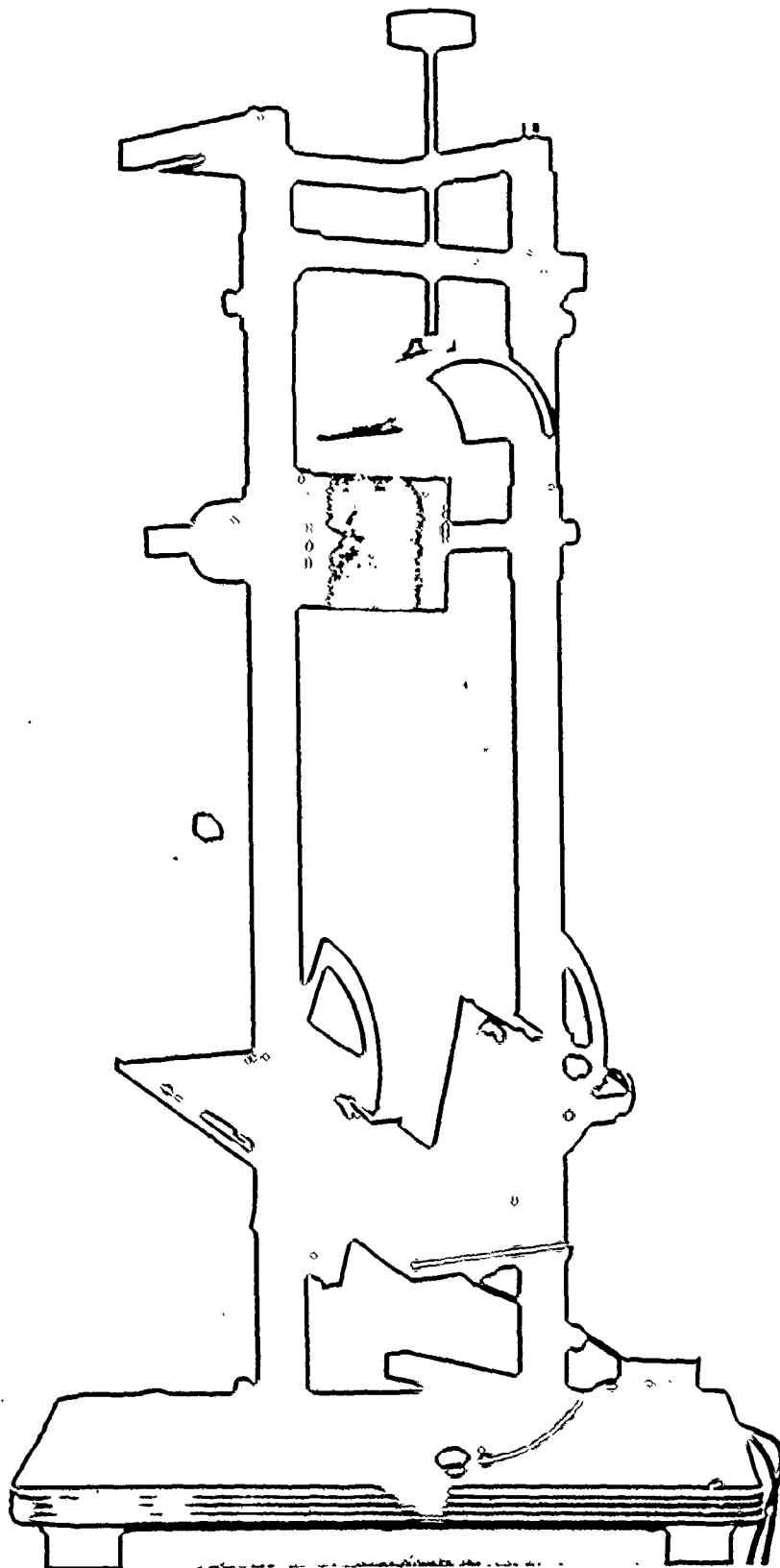
Testing of the most severely affected patients was carried out with another specially designed ankle torque-measuring device (Fig. 2). This device differed from the first apparatus in being more sensitive to applied torques and was therefore more suitable for those patients with very small twitch responses. The apparatus was not sufficiently robust to accommodate the maximum voluntary contractions of healthy subjects, however. As in the first apparatus described, the position of the ankle joint could be adjusted prior to contraction but the mechanism was different. A steel pin was inserted into the appropriate locking hole in each of the two side-axes. The strain-gauges in this device were attached to two aluminum side-arms connected to the locking system. Repeated calibrations of each torque-measuring device, throughout the period of the study showed less than 5% deviation from linearity over the entire range of torque values encountered in these experiments (0-250 N.m). Calibrations were made by measuring the DC voltage changes resulting from hanging known weights from the foot-plate.

2. Stimulating and recording systems

To minimize discomfort, only surface stimulating and recording techniques were employed. Lead plates, covered with saline-impregnated cloth, served as stimulating electrodes. To excite PF muscles, stimuli were applied to the tibial nerve in the popliteal fossa using a 3 x 2 cm electrode as cathode. To excite DF muscles, stimuli were applied to the TA muscle, using a 3 x 2 cm cathode placed on the muscle belly at the level of the motor point. In each instance the anodal electrode, 18 x

Figure 2:

Specially designed leg-holder and ankle torque-measuring device, used to examine severely affected patients. See text for full description.



14 cm, was placed under the thigh. Stimuli were rectangular voltage pulses, 50-200 microseconds in duration, delivered from a stimulator (Devices Ltd.; model 3072), which was itself triggered by a digital timing device (Devices Ltd.; Digitimer model 3290). In most experiments, muscle compound action potentials (M-waves) were recorded from the TA and PF muscles using pairs of chlorided silver cup electrodes, 7 mm in diameter, filled with conducting cream and attached to the skin. For the TA muscle, the stigmatic and reference electrodes were placed over the lower part of the muscle belly and the adjacent region of the tibia respectively. For PF muscles, the stigmatic electrode was placed in the midline over the soleus muscle belly, approximately 3 cm below the gastrocnemii; the reference electrode was fastened over the heel. After preamplification, the torques and evoked muscle action potentials were displayed on two variable-persistence storage oscilloscopes (Hewlett-Packard, type 141B). The major pieces of equipment used in this study and their arrangement are presented in Appendix II.

D. Protocol of investigation

This present project utilized the following testing programme, illustrated in Figure 3 (see Results), except for the section on motor unit activation (see Results, Figures 9 and 10).

1. Twitch and electrical properties

With the leg muscles at rest for about 5 minutes, a single maximal electrical stimulus was first delivered to the appropriate motor nerve fibres. Measurements were then made of (1) the peak twitch torque

(PT), (2) the contraction and half-relaxation times (CT and $1/2$ RT) and the peak-to-peak amplitude of the evoked muscle compound action potentials (M-wave). In two subjects, the relationship between twitch torque and M-wave was investigated by progressively increasing the stimulus intensity until maximum values were obtained. The almost linear relationship between these two parameters indicated that the amplitude of the muscle compound action potentials was a satisfactory index of excitable muscle mass (Appendix III). No evidence of 'back' responses could be detected in the motor nerve terminals of either TA or PF muscles using the double pulse stimulating technique described by Brown and Matthews (1960). The PT:M-wave ratio was then calculated. These above values constituted the "resting" twitch properties. A maximal voluntary contraction (MVC) was then performed for approximately 5 seconds and immediately after completion a second maximum shock was delivered to assess whether or not post-activation potentiation (PAP) of the twitch had occurred. The 'potentiated' values of twitch torque, twitch contraction and half-relaxation times and of M-wave were then determined.

2. Muscle strength and motor unit activation

Measurements of maximal isometric voluntary strength (MVC) during a series of 4 contractions, each lasting about 3 seconds, were made and the mean of the two largest values calculated (see Results, Fig. 3b). To test whether or not these contractions were maximal, I used the twitch interpolation technique first suggested by Denny-Brown (1928) and then employed by Merton (1954) on the adductor pollicis muscle. The rationale behind this technique is that if any motor units

had not been fully activated (recruited and firing at their optimum frequencies) , then the same units should give a detectable twitch-like response superimposed on the top of the voluntary torque recording, following supramaximal nerve stimulation (see Results, Fig. 10 b,c and e,f). To validate this technique, I simulated in three healthy male subjects conditions of 'incomplete PF motor unit recruitment' and of 'sub-optimal PF motor unit discharges' by interpolating a single maximal shock during tetanic muscle stimulation (see Results, Fig. 9). In the first type of experiment, submaximal stimulation of PF muscles at 20 Hz was used to simulate weak voluntary contraction. A maximal stimulus was then delivered, coincident with one of the shocks in the tetanic train, so as to excite the entire population of motor units, including the previously inactive ones. The experiment was then repeated with progressively stronger shocks being delivered at the same tetanic frequency. Finally the tetanic stimulus was made maximal thereby activating all the motor units (see Results, Fig. 9, Left). The second type of experiment was designed to see if a momentary increase in tension could result when a single maximal stimulus was interposed between two of the shocks within a tetanic train of maximal stimuli (see Results, Fig.9, right). In this condition, maximal pulses were delivered in tetanic trains at rates ranging from 8 to 35 Hz. During voluntary contraction, the extent of motor unit activation was expressed as a percentage of the difference between the control twitch and the smallest interpolated twitch value. Increased resolution of the superimposed interpolated twitch response was achieved by using a transiently unclamped amplifier (see Results, Fig.10 b and e).

3. Muscle fatigue

Prior to fatigue experiments, which consisted of a sustained maximal voluntary contraction lasting 60 seconds (see results, Fig. 3c), measurements of twitch PT and M-wave were made (control values). Periodic checks (every 20 seconds) for full motor unit activation, using the twitch interpolation technique described above, were made during the fatiguing effort. The amount of motor unit activation (MUA), just prior to the end of contraction, served as an indicator of central fatigue. Immediately after the end of the fatiguing contraction, the twitch torque and M-wave amplitude were recorded (fatigue values). After one minute of rest, another set of twitch, M-wave and MVC measurements were recorded (recovery values). Comparisons between values of twitch torque, M-wave, motor unit activation and maximum voluntary torque in the 'control', 'fatigue' and 'recovery' conditions were then made.

E. Data analysis, statistical procedures and reproducibility of measurements

All measurements were determined manually from photographs of oscilloscope displays. Statistical values such as mean, standard deviation and standard error of the mean were calculated. I assessed the significance between means with both the Student t-test and the analysis of variance (ANOVA). The ANOVA analysis was followed by the Newman-Keuls' test of significance. Corrections for the level of significance were made in cases of non-homogeneity of variance according to Snedecor and Cochran (1974). Correlation analyses were performed

with the Pearson coefficient of correlation. The significance level for each comparison of means was fixed at 5%. Statistical textbooks by Snedecor and Cochran (1974), Bruning and Kintz (1977), Colton (1977) and Runyon and Haber (1977) served as references. I also consulted Dr. Harry Shannon, biostatistician at the McMaster Health Centre, who approved the above statistical approach. A test-retest method was used to assess the reproducibility of each contractile measurement (Thorstensson, 1976; Sale, 1979). Calculation of method error values and of coefficients of variation were performed. All the contractile measurements taken in the present study were reproducible within 10 % error (Appendix IV).

IV. RESULTS

The present study is concerned with four major components of muscle function: 1) twitch properties, 2) voluntary muscle strength, 3) motor unit activation and 4) muscle fatigue. Each component comprises the results obtained from; (a) the control population (n=46), (b) the patients with myotonic dystrophy (n=25) and (c) the patients with limb-girdle dystrophy (n=20). The influence of age and sex of the individuals on the above contractile functions is also reported.

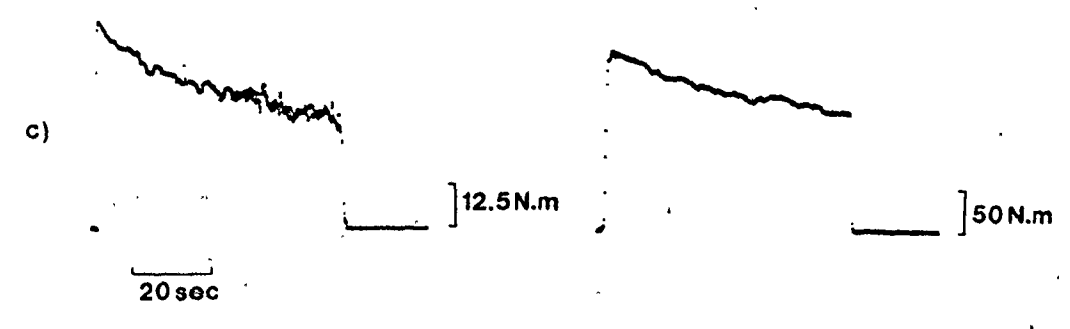
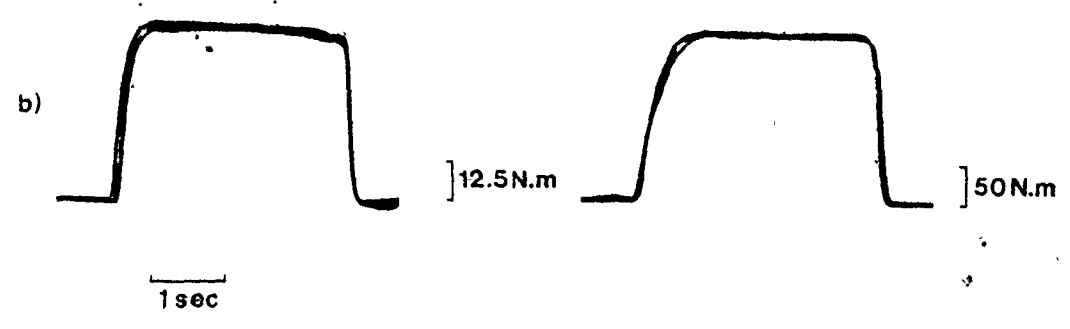
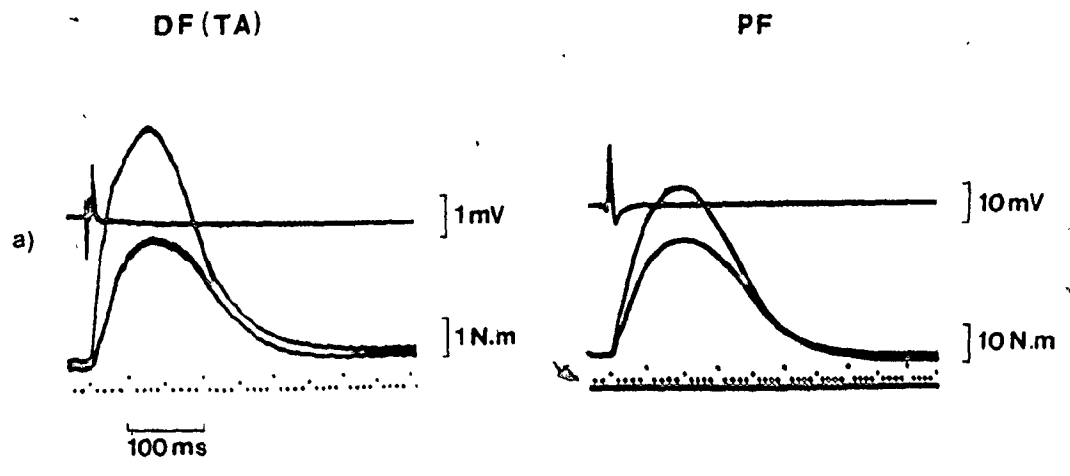
A. Twitch properties

1. Control subjects

Figure 3a shows typical twitch responses recorded from a 32 year old male subject. The smallest response in each pair of records is the twitch following a single maximal stimulus, delivered after the subject had rested his foot in the torque-measuring device for at least 5 minutes. The tibialis anterior (TA) twitch is significantly different from the plantar-flexor (PF) twitch in that in the former, the peak torque and M-wave are smaller and the contraction and half-relaxation times shorter (Table 2). After the 'resting' twitch was recorded, the subjects were instructed to make a maximum voluntary contraction for 5 seconds and then to relax. A second twitch was elicited within 1 second after the onset of relaxation (Fig. 3a). The larger response in each pair of records is the potentiated twitch (PAP); the two M-waves are seen to be superimposed. In every subject tested in this way (21 men and 15 women), the second TA twitch was greater than the first (range,

Figure 3:

Contractile properties of DF/TA and PF muscles contrasted in a 32 year old male subject. (a) Maximum isometric twitches. The smaller of each pair of responses is the control (resting) twitch and the larger is the potentiated one; superimposed M-waves shown on top traces. DF twitches were obtained from the TA muscle only. (b) Three seconds of maximum voluntary effort. (c) 60 seconds of maximum voluntary effort constituting the fatigue test.



	PT	CT	1/2RT	M-w	PAP	MVC	MVC/PT	PT/M-w	MUA
	N.m	ms	ms	mV	%	N.m	-	N.m/mV	%
<u>PLANTAR-FLEXORS (PF)</u>									
(M)	18.5	126.5	119.6	15.5	20.9	139.4	7.6	1.4	93.4
(SD)	4.1	19.3	18.5	5.6	25.3	31.3	1.8	.78	8.4
<u>DORSI-FLEXORS (DF)</u>									
(M)	2.1	81.2	94.7	2.1	144	41.5	14.7	1.06	100
(SD)	1.82	11.3	21.8	1.3	30	11.5	11.2	.86	(1)
<u>Signif.</u>	S	S	S	S	S	S	S	NS	-

TABLE 2.

Summary of contractile properties of PF and DF muscles obtained from male and female control subjects. Mean (M) and standard deviations (+/-SD) are represented. Values of twitch peak torque (PT), contraction time (CT), half relaxation time (1/2 RT), muscle compound action potential (M-w), twitch post-activation potentiation (PAP), maximum voluntary torque (MVC), and motor unit activation (MUA) are shown. Significance was assessed at the 5% level, using independent t-test. (S, significant; NS, not significant)

6% to 470%, mean value 144 ± 30 %). The potentiation of the twitch was accompanied by a speeding-up of the responses, such that the mean CT and $1/2$ RT decreased to 78.9 and 76.9ms respectively, compared with the resting values of 86.2 and 93.8ms. In the PF muscles, the potentiation was always smaller than that in the TA muscle (Figs. 3 and 17a), the mean value being 20.9%. In 9 subjects there was no increase in the PF twitch and in one there was actually a decrease. The CT and $1/2$ RT were also shorter during potentiation in PF muscles, the mean CT decreasing from 130.5ms to 118.8ms. In neither the TA or PF muscles was there a significant alteration in the M-wave during the potentiating event. The various differences of twitch contractile behaviour between these two muscle groups are illustrated in Figures 3a and 17a as well as in Table 2.

2. Patients with myotonic dystrophy

Figure 4 illustrates the typical twitch and M-wave responses from the PF and TA muscles of a 45 year old patient and his matched control. In none of the patients was there evidence of myotonic after-discharges, which could have influenced the twitch values. Furthermore, controls were perfectly matched for those important physical variables; thus, no statistical difference was found between the control subjects and the myotonic patients for age, weight and height (Table 3). Valid comparisons could therefore be made between dystrophic and control contractile responses. As anticipated, both TA and PF twitch torques were significantly smaller in the dystrophic patients than in the control subjects, but the range of values in the dystrophic population was much greater (Table 4). As shown in Figure 5,

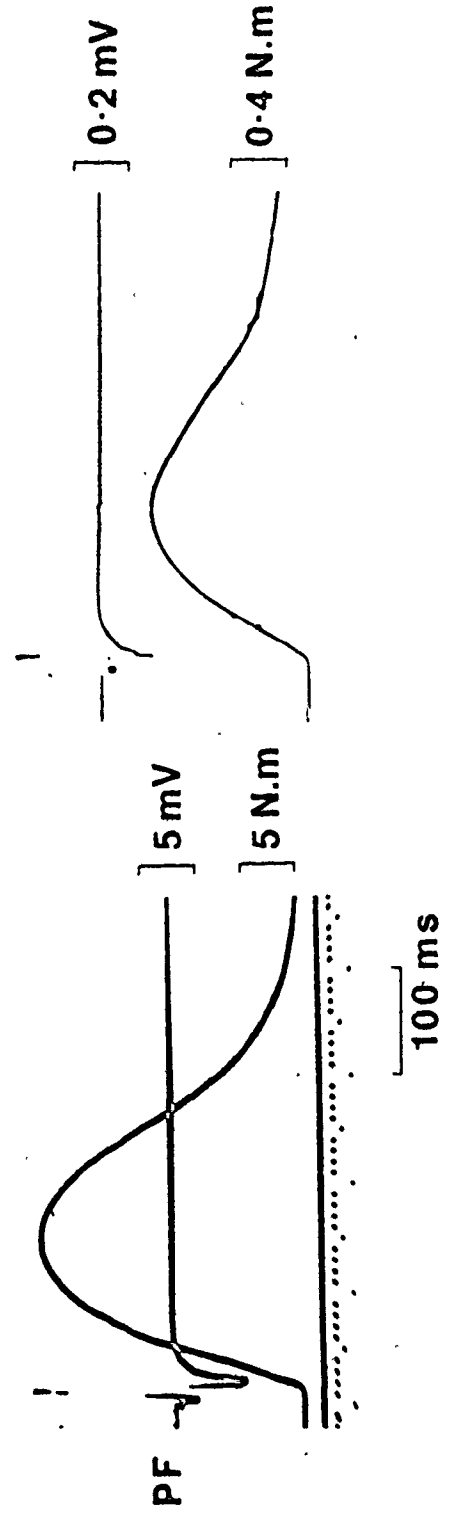
Figure 4:

Twitch and M-wave responses obtained from PF and TA muscles of a 45 year-old male patient and his matched control. Note in the dystrophic patient the significantly reduced twitch peak torque and M-wave, as well as the absence of myotonic after-discharge responses.

DYSTROPHIC



NORMAL



SEX	<u>CONTROLS</u>			<u>MYOTONIC DYSTROPHY</u>		
	M	F	M+F	M	F	M+F
n	15	10	25	15	10	25
AGE	(M) 39	36	37.8	38.9	35.7	37.6
	(SD) 13.2	10.8	12.1	13.6	12.9	13.1
HEIGHT	(M) 176.2	167.5	172.4	174.2	161.2	168.7
	(SD) 5.8	5.2	7.8	8.8	7.6	10.5
WEIGHT	(M) 75.5	57.3	68.2	72.7	53.4	64.7
	(SD) 7.6	6.6	11.6	12.9	10.1	15.1

TABLE 3. Physical characteristics of patients with myotonic dystrophy and their matched controls. Age (yr), height (cm) and weight (kg) values are given with their respective means (M) and standard deviations (+/-SD). There were no statistical differences between the dystrophic patients and their controls for each of these variables. Significance was assessed at the 5% level, using independent t-tests.

TABLE 4.

Summary of contractile properties of PF and DF muscles, obtained from patients with myotonic dystrophy (MMD) and from their matched control subjects (C). Means (M) and standard deviations (+/-SD) are represented. Values of twitch peak torque (PT), contraction time (CT), half relaxation time (1/2 RT), muscle compound action potential (M-w), twitch post-activation potentiation (PAP), maximum voluntary contraction (MVC) and motor unit activation (MUA) are shown. Significance was assessed at the 5% level, using independent t-tests. (S, significant; NS, not significant).

	PT	CT	1/2RT	M-w	PAP	MVC	MVC/PT	PT/M-w	MUA
	N.m	ms	ms	mV	%	N.m	-	N.m/mV	%
<u>PLANTAR-FLEXORS (PF)</u>									
<u>C</u> (M)	18.2	134.1	120.6	14.7	17	132.1	7.5	1.47	94.3
(SD)	4.5	16.1	19.7	5.3	21	30.2	1.9	.92	8.9
<u>MMD</u> (M)	10.2	112	113.6	8.6	11	73.6	9.9	1.72	83.9
(SD)	6.9	15.5	28.4	6.1	26	49.1	6.9	1.87	22.4
<u>Signif.</u>	S	S	NS	S	NS	S	NS	NS	S
<u>DORSI-FLEXORS (DF)</u>									
<u>C</u> (M)	1.8	84.8	102.8	1.89	130	40.8	13.8	1.09	100
(SD)	1.4	10.2	24.1	1.12	82	11.1	7.9	.92	-
<u>MMD</u> (M)	.65	76.2	92.3	.74	90	22.2	15.8	1.2	100
(SD)	.66	10.8	17.9	.71	58	15.3	10.3	.86	-
<u>Signif.</u>	S	S	NS	S	NS	S	NS	NS	NS

the twitch torque values of the myotonic group were within the corresponding control ranges for approximately one-third of the PF muscles and two-thirds of the TA muscles. At the other extreme, there were 8 patients in whom it was impossible to record twitches from TA muscles. Furthermore, twitches were significantly faster in dystrophic PF and TA muscles than in controls; no significant difference was seen in the values of twitch half-relaxation times (Table 4). There was a significant positive correlation between twitch torque and contraction time in the PF muscles of patients with myotonic dystrophy ($r=0.50$).

In order to assess the efficacy of muscle impulse activity in eliciting contractile responses in dystrophic muscles, M-wave amplitudes were compared with the twitch torques (Fig. 6). In both the TA and PF muscles of dystrophic patients, significant correlations between the two variables could be demonstrated ($r= 0.73$ and 0.72 , respectively). Nevertheless, there were five dystrophic TA muscles in which the M-waves were not associated with detectable contractions. Similarly, there was one dystrophic male patient in whom the PF muscles generated a large M-wave (19mV) with very little twitch torque. Also, two female patients had normal-sized PF M-waves (7, 10mV) associated with small twitches (Fig. 6). Despite these striking instances, the twitch torque:M-wave ratios were not statistically different for TA and PF muscles in dystrophic patients compared with control values (Table 4).

After the 'resting' twitch had been recorded, post-activation potentiation (PAP) was assessed by measuring the twitch at the end of 5 seconds of maximal voluntary contraction. No difference of PAP was observed between the dystrophic patients and control subjects, the TA muscle showing approximately 8 times more potentiation than that seen in

Figure 5:

Twitch torque as a function of contraction time for PF and TA muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote the control values while filled symbols identify results from patients with myotonic dystrophy. Arrows indicate TA twitch torques greater than 3 N.m. Apart from the increased scatter of values in the myotonic group, note the absence of twitches in the TA muscles of 8 patients (6 males and 2 females) as well as the trend to reduced twitch torques and shorter contraction times in the remainder.

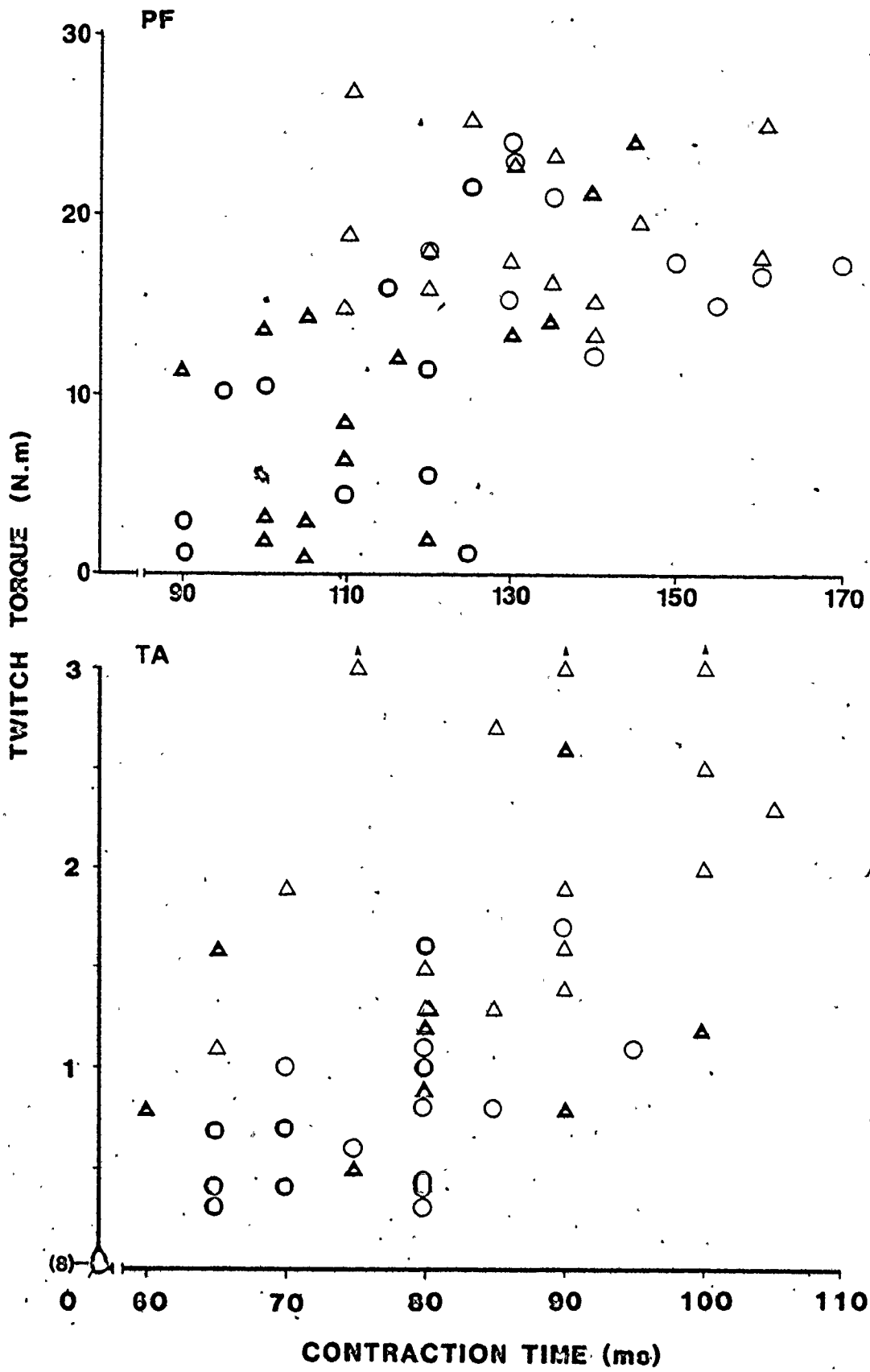
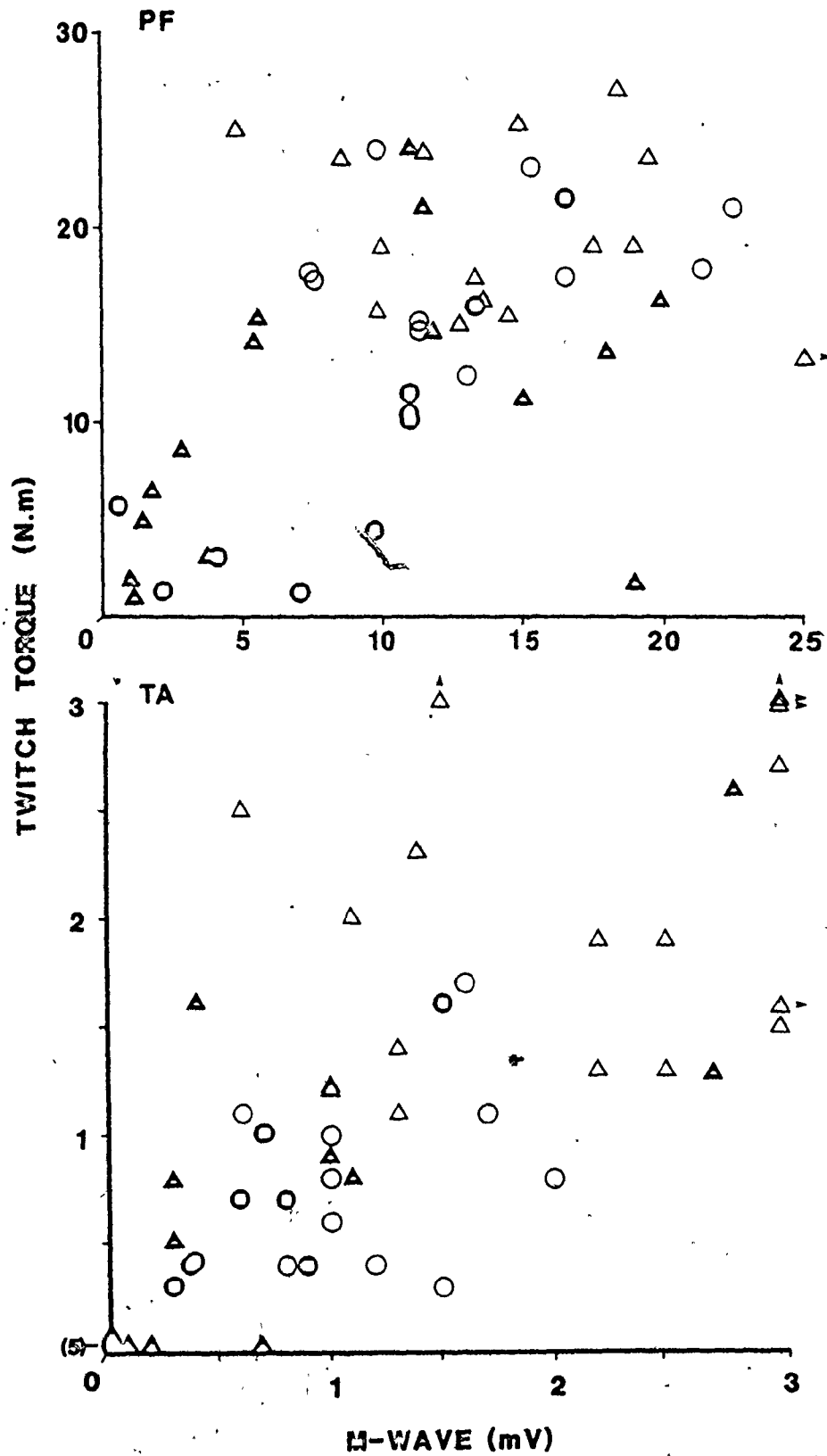


Figure 6:

Twitch torque as a function of muscle compound action potential amplitudes (M-waves) for PF and TA muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote control values while filled symbols identify results from patients with myotonic dystrophy. Arrows indicate values beyond limits of axis. Note the greater variability of results in the myotonic group. Of interest is the absence of TA twitches and M-waves in 5 patients, and the absence of TA twitches in a further 3 patients in whom M-waves were present.



PF muscles (Table 4). As with the control group, the potentiated TA and PF twitches in patients with myotonic dystrophy showed briefer contraction and half-relaxation times, suggesting that the twitch potentiation resulted from an increase in the intensity of the active state process rather than in its duration.

3. Patients with limb-girdle dystrophy

Table 5 shows the control subjects to be closely matched to the limb-girdle patients in physical attributes, as no statistical difference was found between age, weight and height values. For the TA muscles, normal values of twitch contraction and half-relaxation times, post-activation potentiation and M-wave were found. In contrast, twitch torque was significantly reduced (Table 6). Twitch torque and M-wave values of PF muscles were also significantly reduced in the dystrophic patients. As in Figure 7, it could be seen that one third of the dystrophic PF twitch torques were within the control range while in 9 patients, no TA twitch response could be detected. It appeared as if the TA muscle was either barely touched, or else severely affected, by the limb-girdle dystrophic process. It also suggested that, in contrast to the PF muscles, the TA muscles failed more rapidly, i.e., they changed from a state of normal function to one of minimal contractile activity in a short period of time. In contrast, in only one patient was the PF twitch undetectable, while in another male patient, the PF twitch was extremely small (Fig.7). In the dystrophic PF and TA muscles, the CT and 1/2 RT times were not significantly different from control values (see Table 6 and Figure 7).

As with the myotonic patients, the efficacy of muscle impulse

SEX	<u>CONTROLS</u>			<u>LIMB-GIRDLE DYSTROPHY</u>		
	M	F	M+F	M	F	M+F
n	13	7	20	13	7	20
AGE	(M) 47.5	43.3	46.1	45.7	47.1	46.2
	(SD) 12.4	10.7	11.7	14.7	14.2	14.2
HEIGHT	(M) 173.4	167.3	170.2	171.2	163.6	168.9
	(SD) 6.5	3.9	7.2	7.1	5.7	7.5
WEIGHT	(M) 77.7	60.1	71.6	73.8	66.8	71.6
	(SD) 9.3	7.0	11.9	14.1	7.4	12.6

TABLE 5. Physical characteristics of patients with limb-girdle dystrophy and their matched controls. Age (yr), height (cm) and weight (kg) values are given with their respective means (M) and standard deviations (+/-SD). There were no statistical differences between the dystrophic patients and their controls, for each of these variables. Significance was assessed at the 5% level, using independent t-tests.

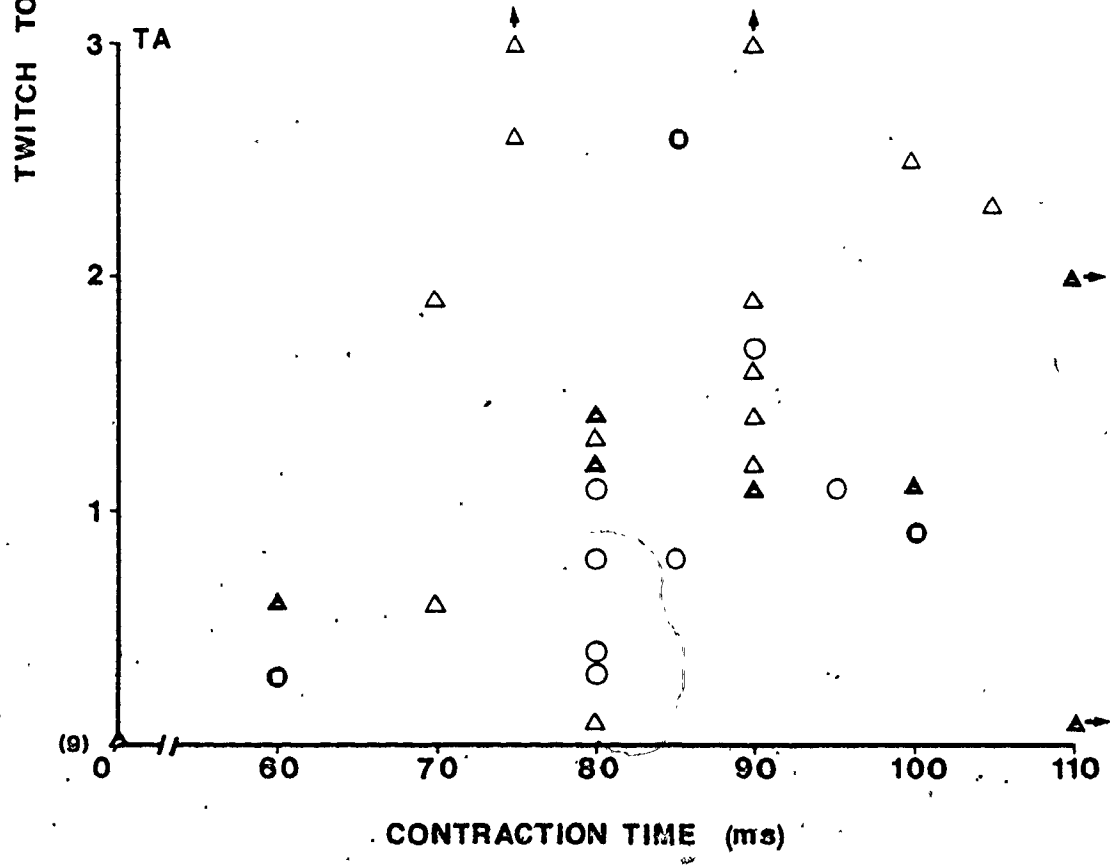
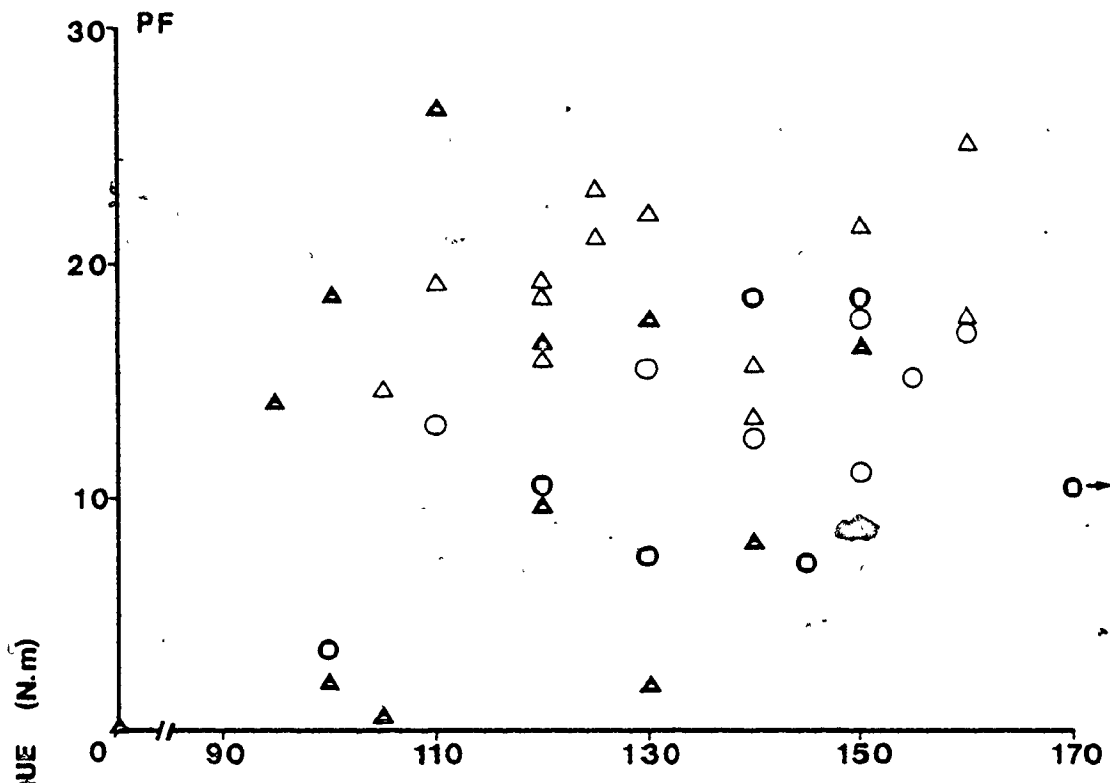
TABLE 6.

Summary of contractile properties of PF and DF muscles, obtained from patients with limb-girdle dystrophy (LGMD) and their matched control subjects (C). Mean values (M) of twitch peak torque (PT), contraction time (CT), half relaxation time (1/2 RT), muscle compound action potential (M-w), twitch post-activation potentiation (PAP), maximum voluntary torque (MVC), and motor unit activation (MUA) are shown. Significance was assessed at the 5% level, using independent t-tests. (S, significant; NS, not significant).

	PT	CT	1/2RT	M-w	PAP	MVC	MVC/PT	PT/M-w	MUA
	N.m	ms	ms	mV	%	N.m	-	N.m/mV	%
<u>PLANTAR-FLEXORS (PF)</u>									
<u>C</u> (M)	17.4	135	122	13.5	17	129.5	7.5	1.56	94.6
(SD)	3.7	17.9	21.8	5.1	17	38.3	1.5	.99	7.5
<u>LGMD</u> (M)	11.2	124.2	125.7	8.8	40	67.3	8.1	1.46	92.8
(SD)	7.3	22.1	27.2	5.4	58	56.2	4.6	.99	10.5
<u>Signif.</u>	S	NS	NS	S	NS	S	NS	NS	NS
<u>DORSI-FLEXORS (DF)</u>									
<u>C</u> (M)	1.93	84.7	95	2.0	140	39.3	13.1	1.07	100
(SD)	1.99	9.6	23.3	1.3	30	11.8	7.5	.97	-
<u>LGMD</u> (M)	.58	88	96.5	1.4	100	19.8	17.1	.49	100
(SD)	.77	20.5	29.5	1.5	52	14.4	11.3	.33	-
<u>Signif.</u>	S	NS	NS	NS	NS	S	NS	NS	-

Figure 7:

Twitch torque as a function of contraction time for PF and TA muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote the control values while filled symbols identify results from patients with limb-girdle dystrophy. Arrows indicate values exceeding limits of axes. Note the absent PF twitch in one patient and the absent TA twitches in nine patients with LGMD.



CONTRACTION TIME (ms)

activity in eliciting contractile response was assessed by comparing the M-wave amplitudes and the twitch torques (Fig. 8). In both the dystrophic PF and TA muscles, significantly positive correlations were obtained ($r=0.59$ and 0.45 , respectively). For the PF muscles, one patient showed a small M-wave (2.5 mV) but no detectable twitch torque. For the TA muscles, twitches and M-waves were not detectable in 8 patients, while in another patient a small M-wave (1.5 MV) was not associated with any twitch torque. Despite such cases, however, the PT:M-w ratios were not significantly different from the normal values in the dystrophic TA and PF muscles (Table 6). No difference was observed between the post-activation potentiation of dystrophic and control muscles, the TA muscle displaying the greatest potentiation in both populations (Table 6). In keeping with the control results, the potentiated TA and PF twitches of patients with LGMD showed shorter CT and $1/2$ RT values. This observation pointed to an increase in the intensity of the active state process rather than in its duration as a cause for potentiation.

B. Motor unit activation and muscle strength

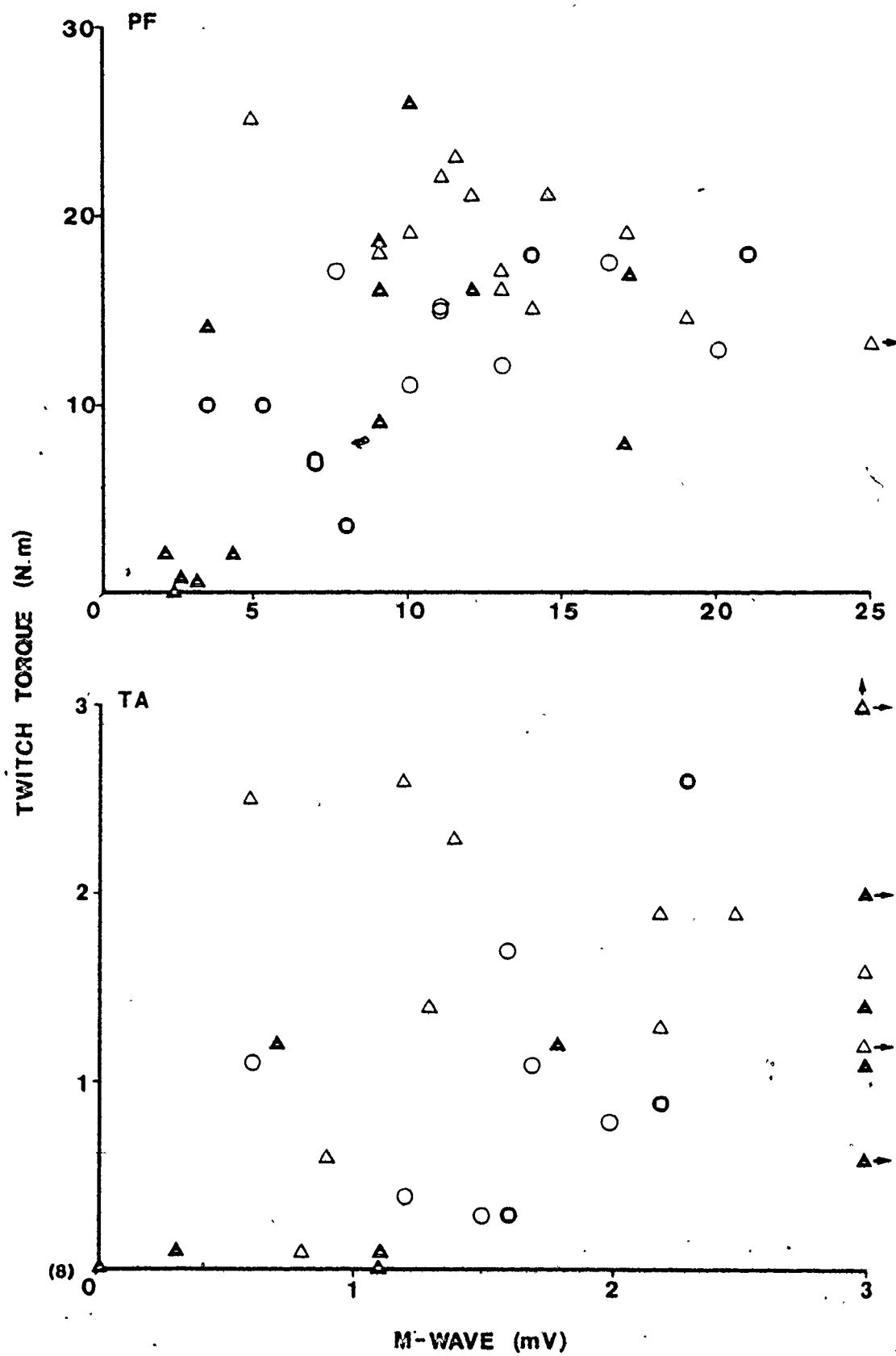
1. Control subjects

1.1. Validation of the twitch interpolation technique

The extent of motor unit activation during maximal voluntary effort was assessed using the twitch interpolation technique. To validate this technique, conditions of 'incomplete PF motor unit recruitment' and of 'suboptimal PF motor unit discharge' were simulated by experiments in three healthy male subjects. In Figure 9 (left panel), the response of the additional motor units can be seen as a

Figure 8:

Twitch torque as a function of the muscle compound action potential amplitudes (M-wave) in PF and TA muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote control values while filled symbols identify results from patients with limb-girdle dystrophy. Arrows indicate values exceeding limits of axes. Note the considerable scatter of results from dystrophic TA muscles and the absence of TA twitches and M-waves in 8 patients.



twitch superimposed on the tetanic torque recording (second trace from bottom). The experiment was then repeated with progressively stronger shocks being delivered at the same tetanic frequency. As more motor units were activated, the tetanic torque became greater. However, because fewer quiescent units were available for stimulation by the interpolated shock, the superimposed twitch was smaller than before. Finally when the tetanic stimulus was maximal and activating all the motor units, the extra stimulus was unable to evoke any additional torque, as would have been expected (left, top trace).

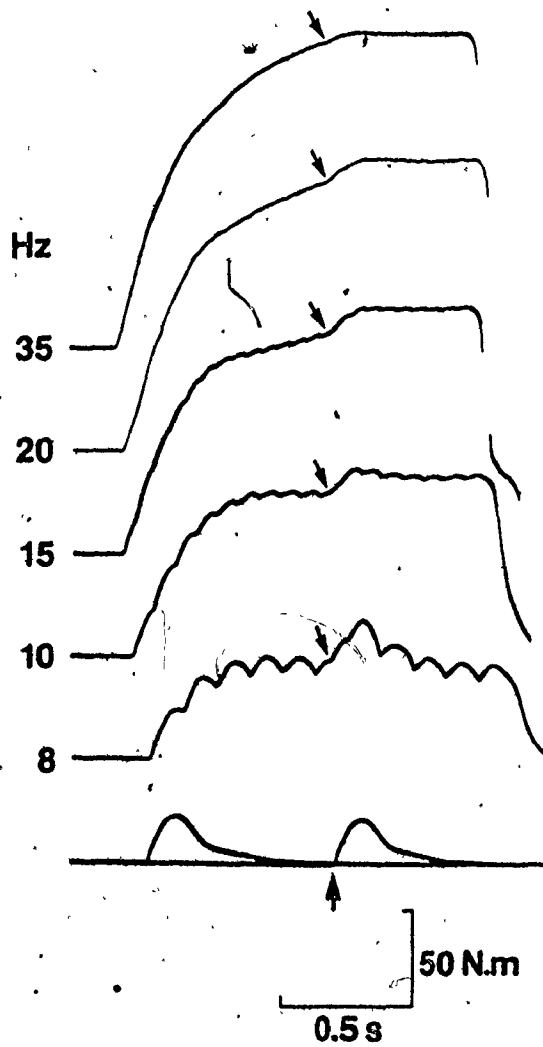
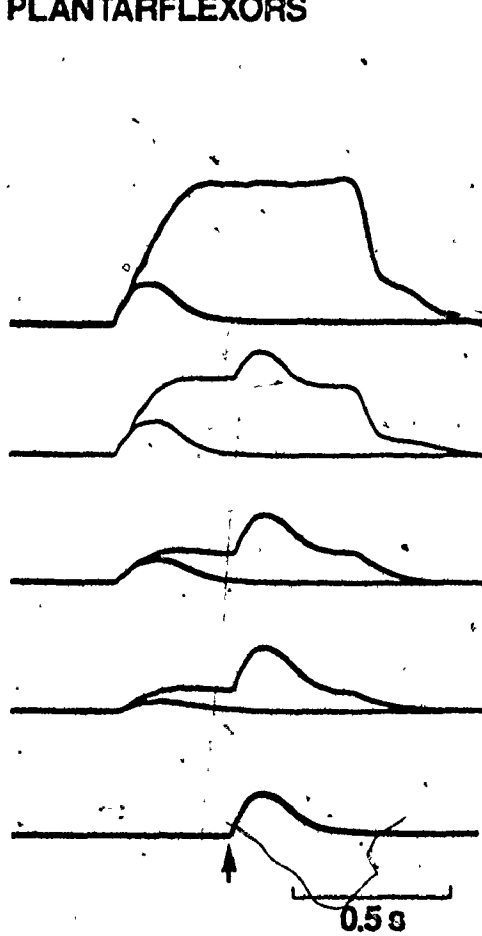
The second type of experiment was designed to see if a momentary increase in torque could result when a single maximal stimulus was interposed between two of the shocks within a tetanic train of maximal stimuli. Figure 9 (right panel) shows substantial increments of torque at tetanic stimulating frequencies between 8 and 15 Hz. Although the increments became less, one was still visible at the highest frequency employed (35 Hz). The results of this experiment indicated that a single stimulus would elicit additional torque if all the motor units were participating in a contraction but discharging at less than the frequency required for maximal torque.

In theory, then, there would be more than one interpretation of an experiment in which extra torque resulted from a stimulus delivered during voluntary contraction. Either some motor units had not been recruited (incomplete recruitment) or else some units were discharging at a submaximal frequency (suboptimal frequency). There could, of course, be units fulfilling either condition within the same population. On the basis of the differences in the form of the incremental responses, it might be thought possible to distinguish between

Figure 9:

Left: Effect of single maximal interpolated shocks (arrow, bottom trace) on plantar-flexor torque developed during 0.8 second train of 20 Hz stimulation. Strength of tetanic stimulation increased from below upward: responses to stimuli of similar intensity, delivered alone, appear as twitches in lowermost of each pair of records. Solitary twitch in uppermost panel, being maximal, is equivalent in all aspects to twitch in lowermost panel. When tetanic stimuli were of maximal intensity, no increment was superimposed on tetanic tension recording (top trace). Note that interpolated shocks were made to coincide with one of the stimuli in tetanic trains. Right: Effect of single maximal shocks interposed between 2 successive stimuli during tetanic stimulation of maximal intensity and variable frequency (numbers at left of traces). Interpolated responses shown by arrows. A small increment can just be distinguished in top record, made during 35 Hz stimulation. Twitch responses to 2 maximal shocks are shown in bottom trace. Torque calibration applies to the right² panel only, as approximately half the amplification was used for traces in the left panel.

PLANTARFLEXORS



incomplete recruitment and suboptimal frequency conditions. Thus, whereas in Figure 9 (left) the additional stimulus evoked a twitch-like response, in Figure 9 (right) a prolonged increment resulted. The latter was best seen during stimulation at 10 and 15 Hz, and strongly resembled the "catch-like" effect observed in single motor units of the cat (Burke, Rudomin and Zazac, 1976). Unfortunately, this distinction could not be made during submaximal voluntary contractions, for although twitch-like increments were found, these could also have resulted from the effect of the silent period (SP) in the electromyogram (seen after a single shock in the PF muscle; Figure 10b) on a response that would otherwise have been "catch-like". In view of the difficulty in distinguishing between incomplete recruitment and suboptimal frequency conditions, I have preferred to interpret submaximal voluntary contraction in terms of reduced activation of motor units without specifying which of the two mechanisms might be predominant.

1.2. Twitch interpolation technique applied to PF and TA muscles

The effect of the interpolated stimuli was observed in all of the 46 subjects, of which 17 males were studied during a series of progressively stronger contractions. Figure 10 shows the effect of interpolated shocks on the PF and TA muscles of a 26 year-old control subject. In agreement with theory, a large twitch was apparent during the weakest of the contractions, and the response diminished as the voluntary contraction became greater (Fig. 10c,f). During the strongest PF contraction (Fig. 10c, top trace), increments were just visible but could be recognized more readily in the recordings made at higher gain, using a transiently unclamped amplifier (Fig. 10b). In 52% of the male

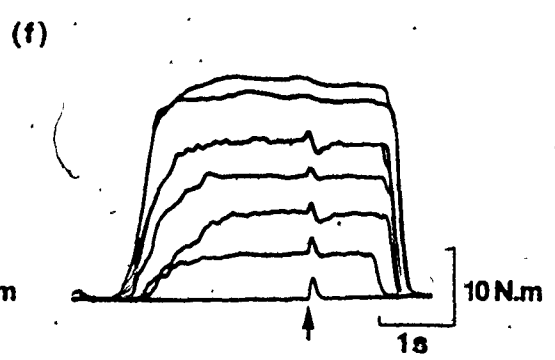
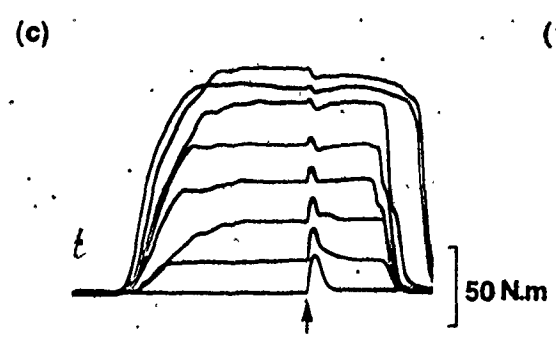
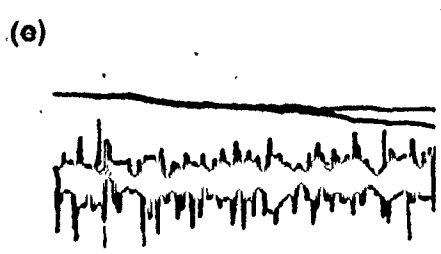
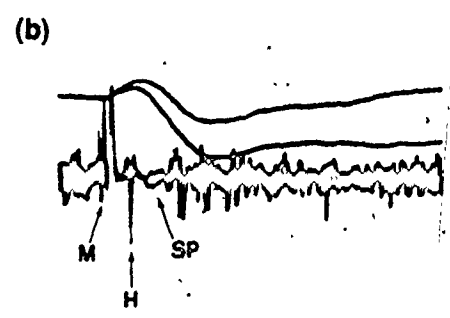
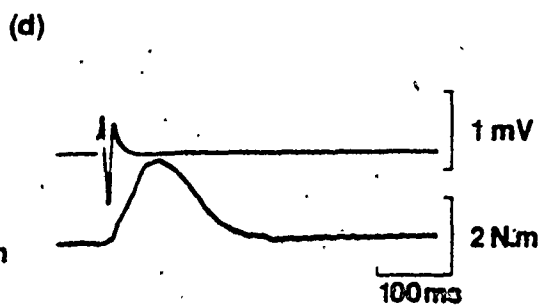
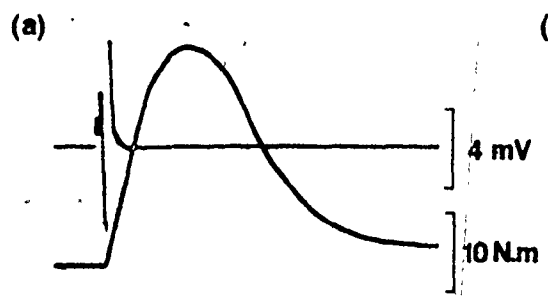
Figure 10:

Effects of interpolated shocks on recording of voluntary torque in DF/TA and PF muscles. a,d: Twitch responses to shocks of maximal intensity. c,f: Responses to shocks of same intensity delivered during successive, increasingly forceful contractions. Even during extreme effort, small superimposed twitch-like responses can be seen in PF recordings following the interpolated stimuli (c, top 2 traces); same responses are seen at higher amplification in b, together with electromyogram. Note the silent period (SP) following the M-wave (M) and H-reflex (H) responses of PF muscles. In contrast to PF, no interpolated TA twitches were observed during maximal voluntary dorsi-flexion (e, and top 2 traces in f).

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PLANTARFLEXORS

TA/DORSIFLEXORS



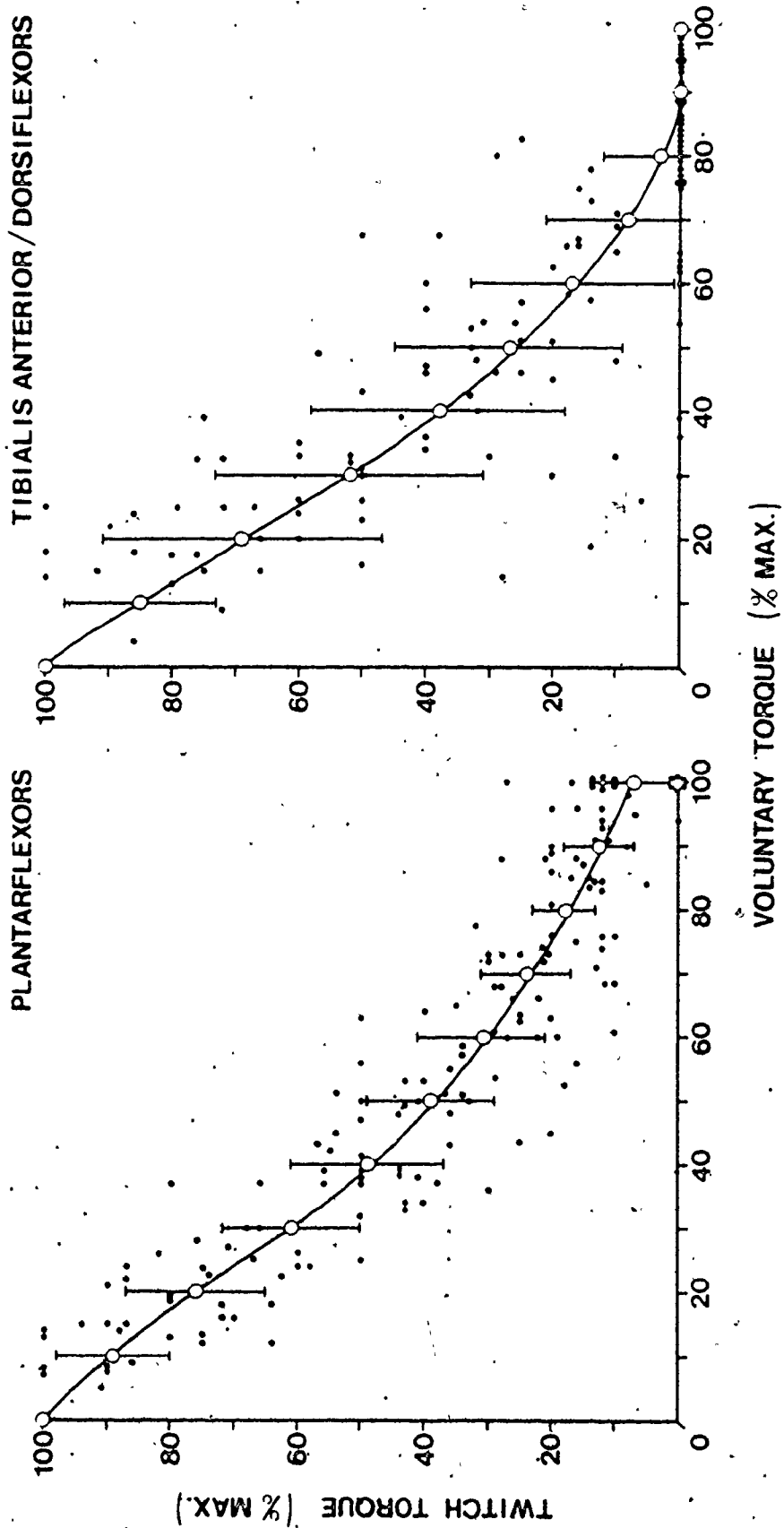
and 62% of the female subjects, similar results, indicative of incomplete activation of PF motor units, were observed.

Stimuli were also applied to the TA muscle during different strengths of voluntary dorsi-flexion (Fig. 10f). In most subjects, the results obtained with the TA muscle differed from those of the PF muscle in that the increment of the interpolated twitch torque became undetectable before maximal voluntary torque had been achieved, thus indicating full motor unit activation (Fig. 10f, top 2 traces). The latter finding was confirmed by the enlarged recordings (Fig. 10e) obtained through the unclamped amplifier. The results obtained with the TA muscle also differed from those of the PF muscles in that they showed more variability from one subject to another, and hence larger standard deviations (Fig. 11). Among the 46 subjects, there was only one subject (female) in whom full activation of TA muscle could not be obtained. Figure 11 shows the pooled results for the 17 male subjects. Similar data points were observed for the female subjects, although fewer levels of voluntary force production were studied. For each male subject, a curve was fitted to the experimental points by eye, and values of increment were then read off, corresponding to voluntary contractions of 10-100% maximal amplitude. These values were then averaged and used to plot the composite curves for the population of subjects. As some of the subjects did not achieve full activation of their PF motor units, the curve fell short of the abscissa by 7%. On the basis of the study by Merton (1954), a linear relationship was anticipated for both PF and TA curves in Figure 11. The inverted S shape actually found was probably caused by four factors: 1) during a weak contraction, the reduction in the series-elastic component would tend to make the

Figure 11:

Amplitudes of interpolated twitches superimposed on recordings of voluntary torque of PF and DF muscles of 17 male subjects.

Determination of mean and standard deviation values as described in the text.



interpolated twitch larger than at rest; 2) during a stronger contraction, the silent period (SP) after the interpolated stimulus would transiently depress voluntary torque thus interfering with the later part of the twitch; 3) the peroneus longus and brevis muscles, not affected by the interpolated stimulus, could have made a greater relative contribution to strong plantar-flexion than to weak plantar-flexion; 4) the extensor hallucis longus, extensor digitorum longus and peroneus tertius muscles, also not affected by the interpolated shock, would have contributed more to strong rather than to weak, dorsi-flexion of the ankle.

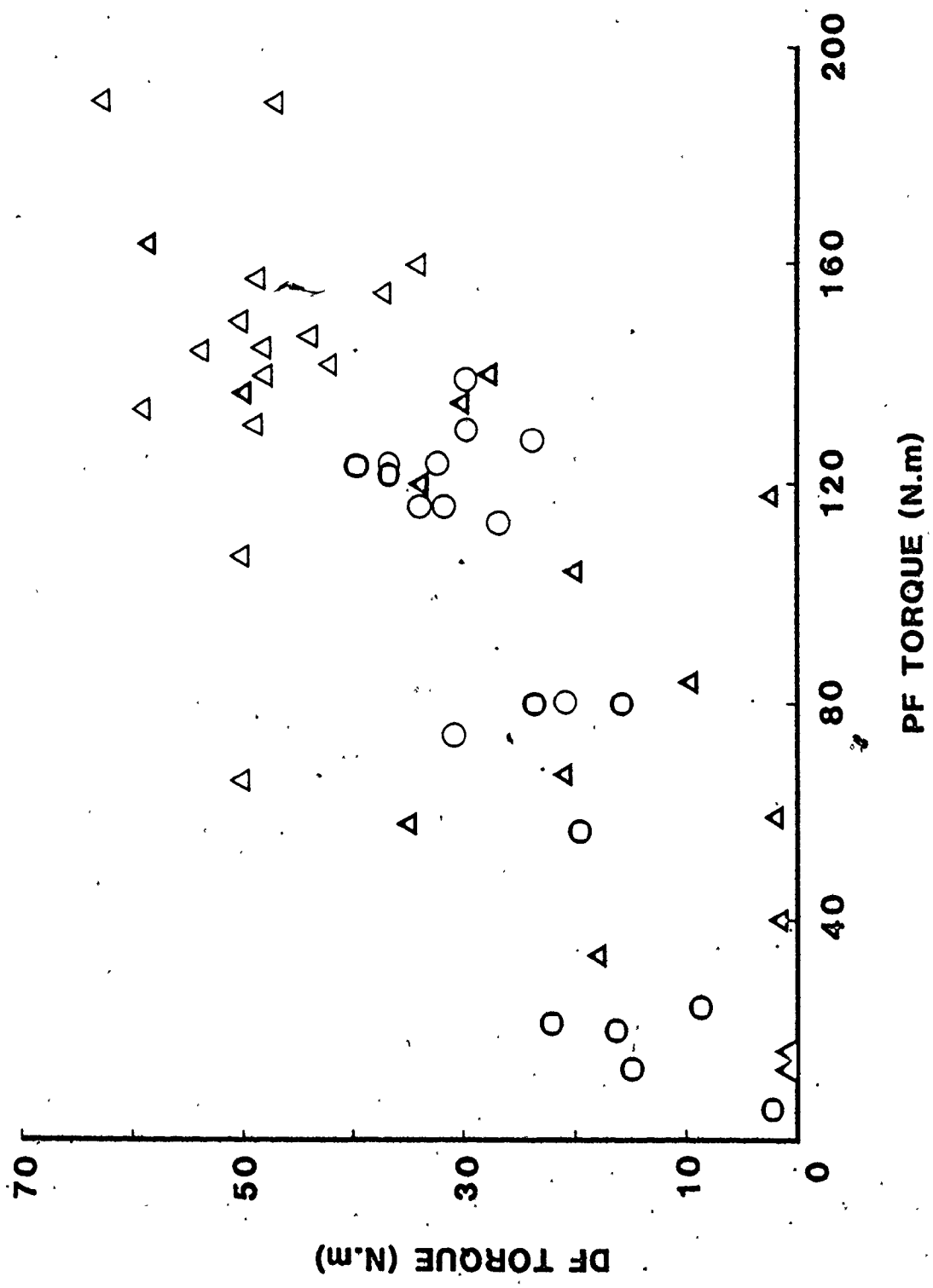
As far as isometric muscle strength was concerned, each subject was instructed to make a maximum isometric plantar-flexion or dorsi-flexion contraction lasting about 4 seconds. Each attempted contraction was repeated 2 or 3 times and the average value was calculated for the two largest responses. From Figure 3b and Table 2, it can be seen that PF torque was approximately three times greater than that for DF muscles. A single maximal electric shock was interpolated during each contraction to ascertain if motor unit activation (MUA) was complete; while this was always the case with the TA muscles (except for one subject), it was not always true for the PF muscles (Table 2).

2. Patients with myotonic dystrophy

Figure 12 shows the voluntary torque values of DF and PF muscles plotted against each other. The results for normal subjects fell into two clusters reflecting the greater muscle strength of males. In the dystrophic population there was a much greater range of observations, with some patients still possessing normal values and others having very

Figure 12:

Maximum voluntary DF torque as a function of PF torque in patients with myotonic dystrophy (filled symbols) and in their matched control subjects (open symbols). Values for males and females are shown as triangles and circles respectively. Note the considerable disproportion between PF and DF torque in some male patients. Among the control subjects, men are shown to be stronger than women, and as expected, the patients with MMD were weaker than their matched controls.



little torque. In two cases, there was complete paralysis of dorsi-flexion. Among the dystrophic patients, the loss of strength in one muscle group was often not proportional to the weakness in the other. The most extreme example was a 39 year old man in whom dorsi-flexion strength was only 5% of the control mean value whereas his plantar-flexion strength was 90% of the control mean (Fig. 12). There was a significant positive correlation between the PF and DF voluntary torques in the control subjects ($r=0.43$) but not in the dystrophic patients. As anticipated, maximum voluntary strength was significantly reduced in both the PF and DF muscles of patients with MMD (Table 4), the patients being approximately half as strong as their matched control subjects.

There was a tendency for DF muscles to show the greatest relative impairment of voluntary torque in the male patients, and for PF voluntary torque, in the female patients (Fig. 12); however, this impression may have been the result of the size of the sample. I also observed that six of eight patients in whom twitches of the TA muscle were absent, could develop measurable dorsi-flexion torque during maximal voluntary effort. I believe that the latter was achieved mostly, or entirely, through use of the long extensors of the toes. As a result, no significant correlation could be found between the TA twitch and voluntary DF torques in the myotonic patients ($r= -0.04$), although such a correlation was present for the same muscles in the controls ($r= 0.60$). For the PF muscles, significant correlations were seen between twitch and voluntary torque values in both dystrophic patients ($r=0.79$) and matched-controls ($r=0.42$).

During maximal isometric strength testing, the twitch interpolation technique was used to establish whether or not patients with MMD were making full use of their surviving motor units. The dystrophic patients resembled controls in fully activating their TA muscles, but they showed a significantly reduced PF motor unit activation (Table 4). Full PF motor unit activation was achieved in only 28% (n=7) of patients as opposed to 48% (n=12) of controls. During the course of the testing session, I noticed in some patients a progressively increasing ability to generate voluntary torque over repeated trials. Figure 13 shows the results obtained in a 20 year -old male patient who required 5 attempts before his PF torque became maximal. That this increase in strength was not artefactual, but resulted from better motor unit activation, was revealed by the progressively decreasing interpolated twitches (Fig.13).

3. Patients with limb-girdle dystrophy

Figure 14 shows the PF and DF voluntary torques plotted against each other. As expected, the limb-girdle patients were weaker than their matched controls, for both the PF and DF muscles (Table 6). Nevertheless, approximately one third of the patients had normal torque values. An important observation was that the two muscle groups could be affected differently in each patient; for example, one patient showed relatively strong PF muscles (55 N.m) but weak DF muscles (2 N.m). Another patient presented with weaker PF than DF muscles while in another patient, no DF torque could be recorded although 15 N.m of torque was generated by the PF muscles. Despite these instances, there

Figure 13:

Evidence for increased plantar-flexors (PF) muscle strength as a result of better motor unit activation in a 20 year-old male myotonic patient (see legend). There was no further increase of voluntary muscle strength following the fifth trial.

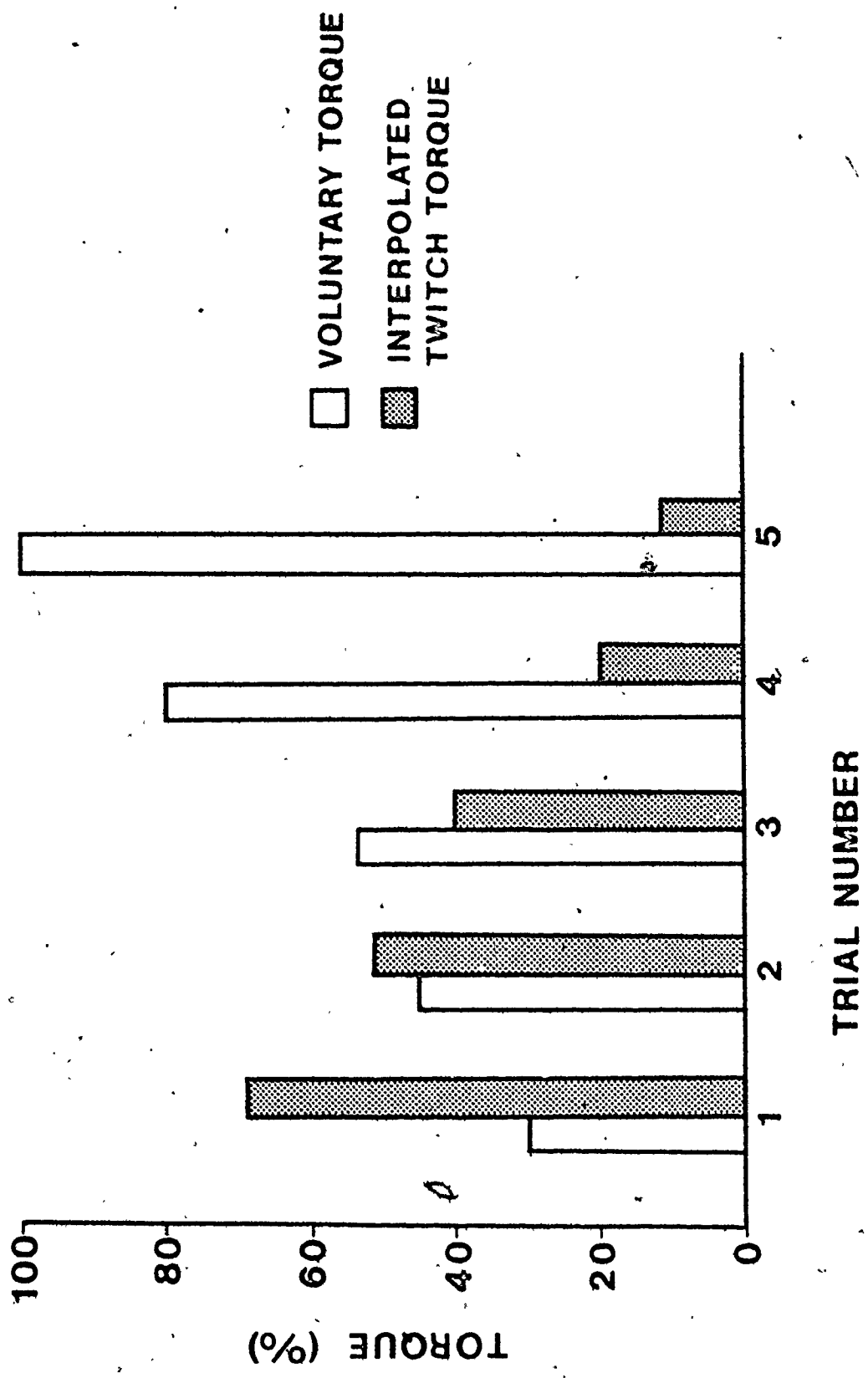
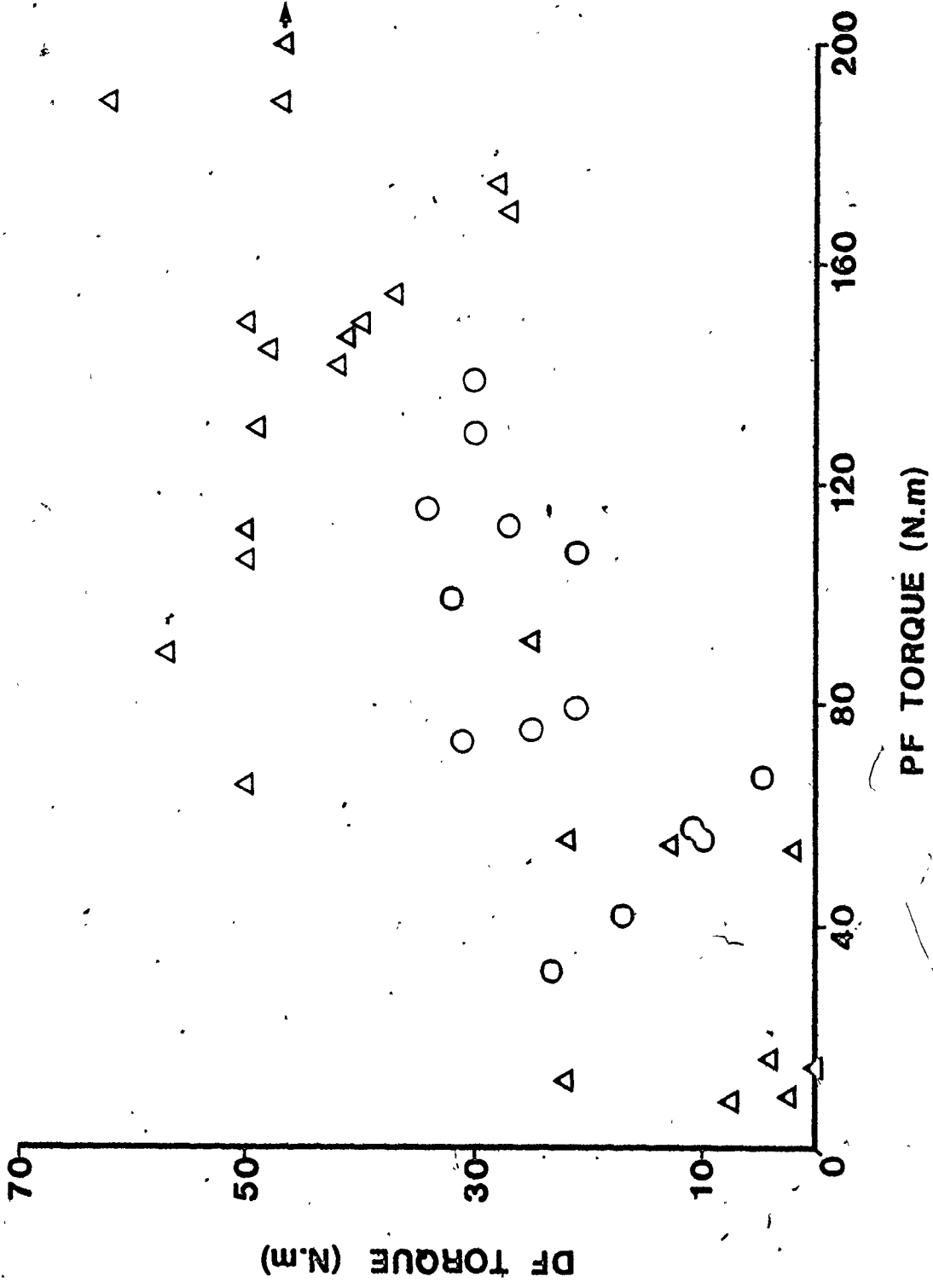


Figure 14:

Maximum voluntary DF torque as a function of PF torque of patients with limb-girdle dystrophy (filled symbols) and their matched control subjects (open symbols). Values for males and females are shown as triangles and circles respectively. As expected, patients with LGMD were weaker than the control subjects. Note the considerable variability of muscle strength between male dystrophic patients.



was a significant correlation between PF and DF muscles in the patients ($r=0.76$) but not in controls ($r=0.21$). Of interest was the fact that the highest PF voluntary torque generated during the course of this study was by a 34 year-old male patient with LGMD (235 N.m). The voluntary dorsi-flexor torques generated by patients with absent TA twitches were ascribed to residual activity in the long extensors of the toes. As a result, no correlation was found between the TA twitches and the DF voluntary torques in this group of patients with LGMD ($r=0.45$), while a significant correlation was observed for the control subjects ($r=0.60$). For the PF muscles, both the dystrophic patients ($r=0.81$) and the control subjects ($r=0.76$) showed significant correlations between twitch and voluntary torque values.

There was no significant difference in the ability to fully activate PF and TA motor units during maximum voluntary effort between patients with LGMD and their matched-controls (Table 6). While TA muscles were fully activated by both patients and controls, only 25% of the patients and 50% of the controls could fully activate their PF motor units.

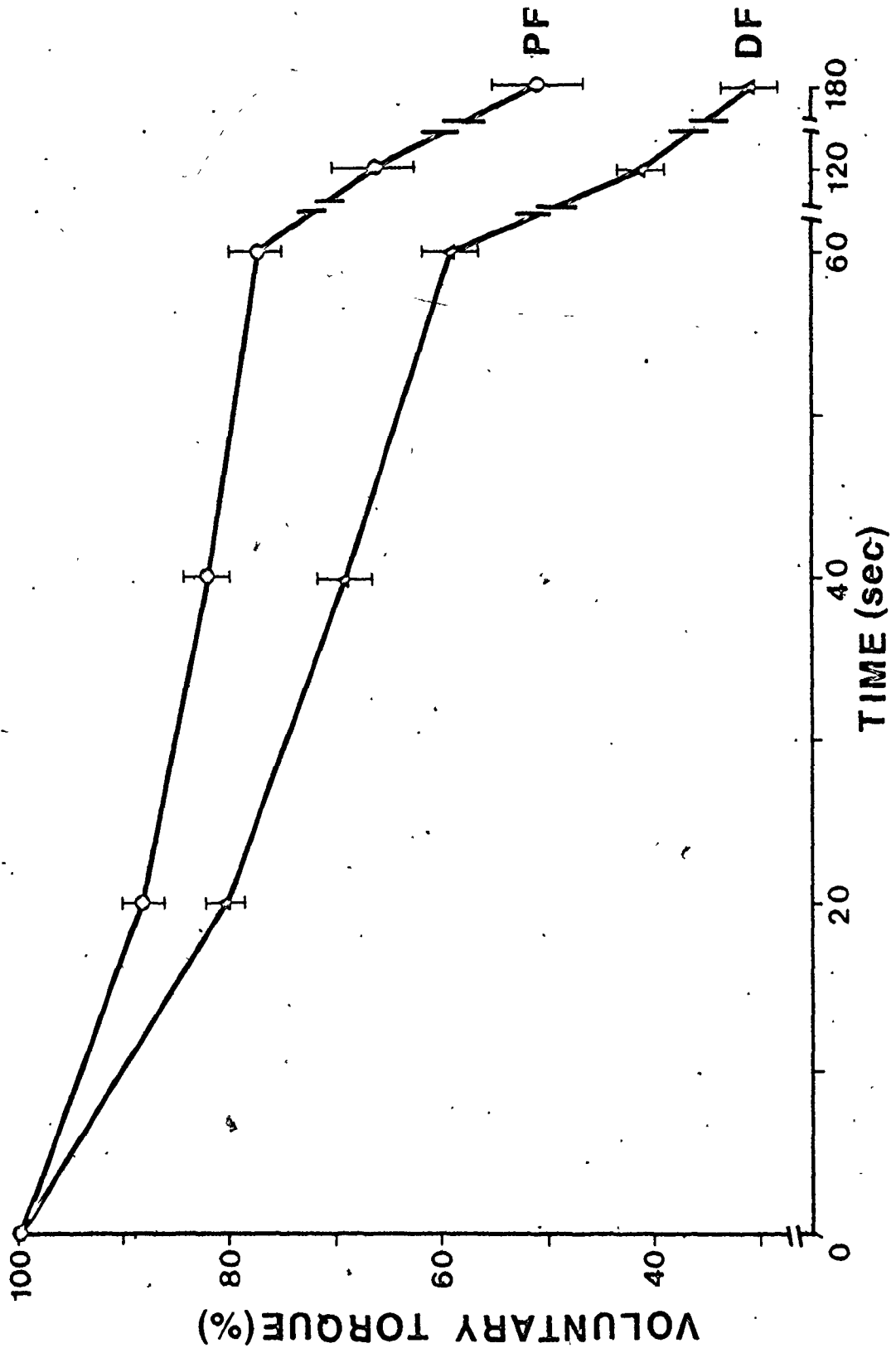
C. Muscle fatigue

1. Control subjects

The susceptibility of the DF and PF muscles to isometric fatigue was determined by requesting subjects to perform maximal voluntary contractions lasting either 1 or 3 minutes (see Fig. 3c); measurements of torque were made at 20 second intervals. The mean torque values for the two muscle groups at each interval are shown in Figure 15. It can be seen that throughout the contraction, fatigue was more pronounced in

Figure 15:

Decline of maximum voluntary torque of DF and PF muscles: values shown are means and standard errors of the mean. The fatigue behaviour of PF and DF muscle groups was examined following 60 seconds (n=21), and 180 seconds (n=9) of maximum voluntary contractions. Note the greater susceptibility of DF muscles to fatigue.

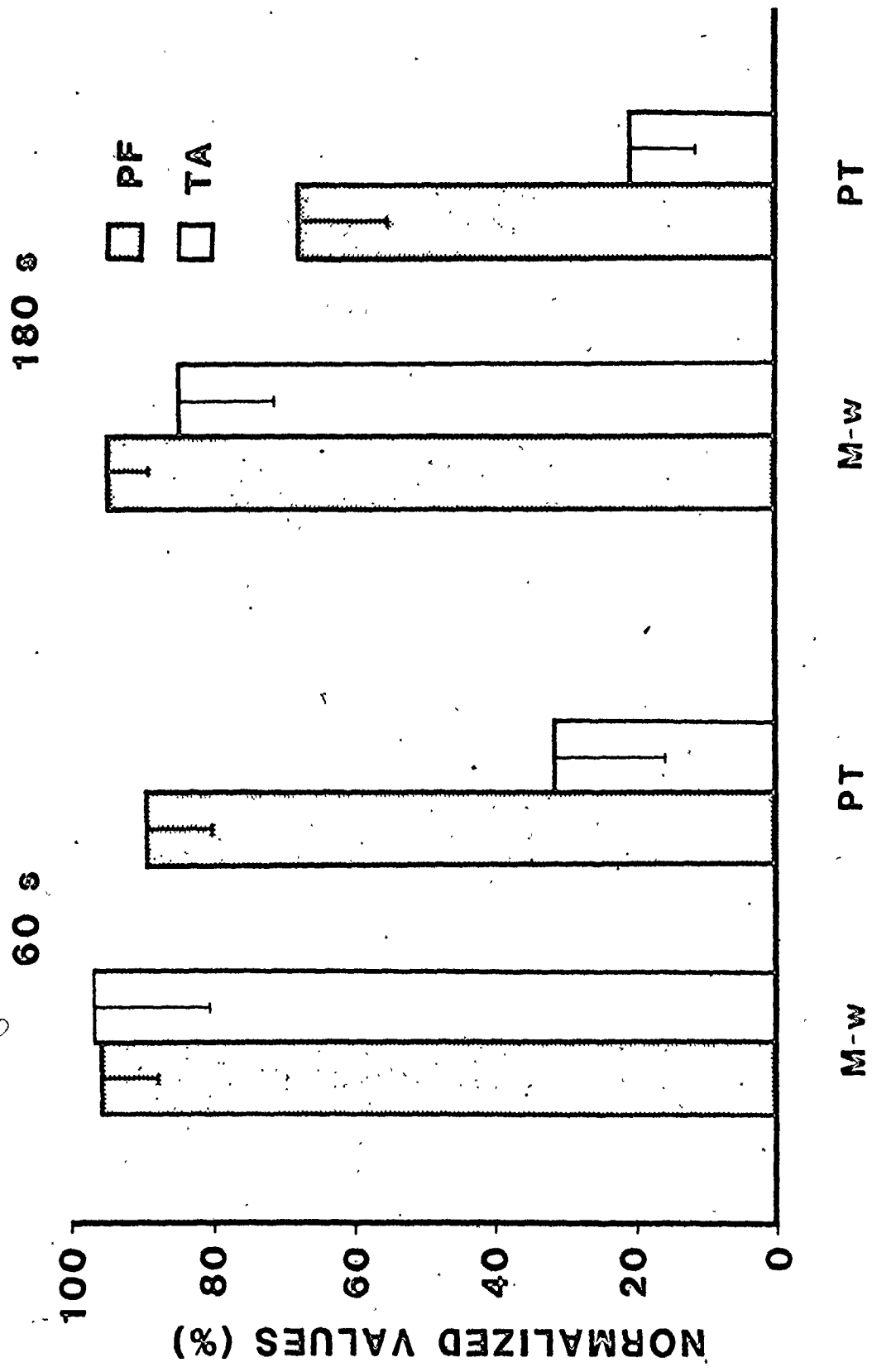


the DF than PF muscles. By the end of 60 seconds, the mean voluntary torque had declined to 60% of the initial value in the DF muscles and to 78% of the normal value in the PF muscles. By the end of 180 seconds, the mean voluntary torques had declined further to 32% (DF) and 50% (PF). In order to investigate further the mechanisms of fatigue, interpolated stimuli were used to detect any impairment of motor unit activation in a group of 21 control subjects. In the case of the TA muscles, motor unit activation (MUA) was complete throughout the one minute contraction in all but one of the 21 subjects; this finding indicated that the site of fatigue was peripheral in TA muscles. The extent of motor unit activation of the remaining DF muscles could not be determined by the interpolated technique. For PF muscles, there appeared to be a small central component, since twitches could be superimposed on the recordings of voluntary torque in 17 subjects. The mean amplitude of the interpolated twitch was 6% of the initial value.

To explore the peripheral components of fatigue lasting one minute, a single maximal stimulus was given immediately after the voluntary contraction had ended and measurements were made of the M-wave and twitch torque. In both PF and TA muscles, small reductions in M-wave amplitude were observed (3.7% and 2.6% respectively) but the most striking change was in the twitch amplitude of the TA muscles (Fig. 16; 60s). The mean twitch torque, expressed as the ratio between the twitch obtained immediately after the fatigue run and the control twitch, fell to 32.8% in the TA muscles and to 89.8% in the PF muscles. The discrepancy between the behaviour of the TA twitch torque and maximal DF torque was still evident 1 minute later, the maximum voluntary torque having recovered to 96% of the initial value while the twitch torque had

Figure 16:

The effect of isometric fatiguing contractions, lasting either 60 or 180 seconds, on muscle compound action potentials (M-w) and twitch torques (PT) of PF muscles (stripped columns) and TA muscle (open columns). After 60 second contractions (60s), marked disproportionality existed between the M-waves and twitches of the TA muscles, the latter twitches being very significantly reduced. After 180 second contractions (180s), the TA twitches were further reduced, while fatigue of the PF muscles became apparent, as shown by the reduced twitch torque.

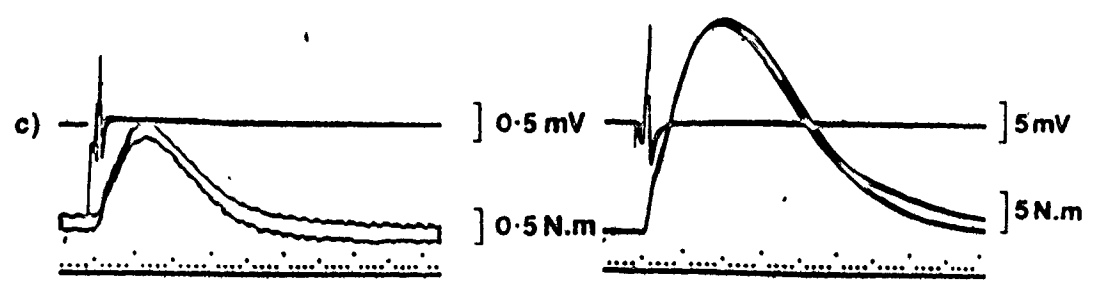
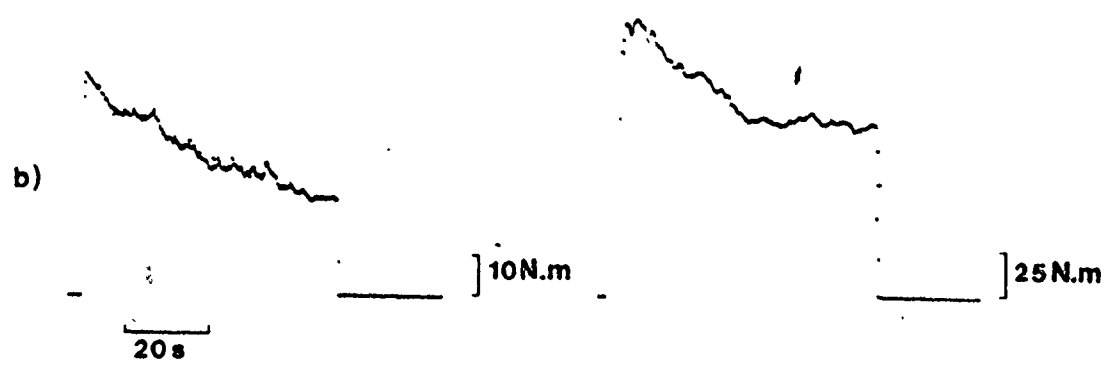
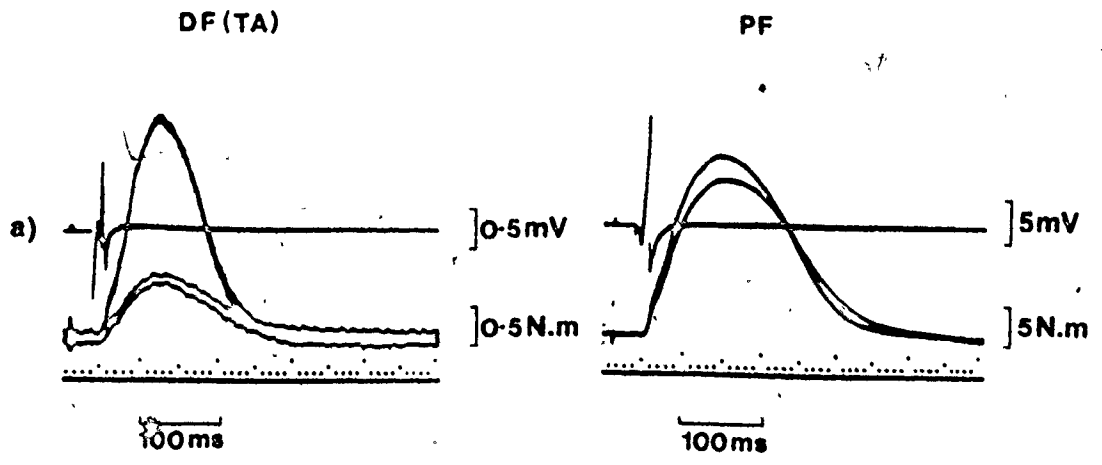


only risen to 66.5%. In contrast, the twitch torque of the PF muscles recovered to 94.4% of the initial torque. As with DF muscles, recovery of maximum PF voluntary torque was nearly completed (94.8%). A similar analysis was made of fatigue which followed three minutes of maximum voluntary effort on a group of 9 male subjects. As shown in Figure 15, the mean voluntary torque declined to 30% of the initial value in DF and to 50% in PF muscles. At the end of the 3 minutes, full motor unit activation was retained in the TA muscle (except for one subject) whereas for PF muscles it had fallen to 80%. As shown in Figure 16 (180s), the twitch torque declined to 20% for TA and to 67% for PF muscles, while the amplitudes of the M-waves were seen to decrease by 15% and 5% respectively in the TA and PF muscles. No analysis was made of recovery from this particular length of fatigue.

To substantiate the above results, further experiments were conducted on a group of 5 subjects in whom circulation of the leg was occluded by an arterial pressure cuff. It is known that PF muscles become ischemic when developing forces greater than 30% of maximal, since the intramuscular pressure exceeds the systolic blood pressure (Barcroft and Millen, 1939). Although the application of an arterial occlusion cuff would not have been expected to change the metabolic milieu of maximally contracting fibres, the persistence of ischemia at the end of contraction had the advantage of delaying recovery and allowing the peripheral component of fatigue to be analysed further. In each subject, 'control' and 'potentiated' twitches were elicited before the fatigue run (Fig. 17a). Maximal voluntary PF and DF contractions were then performed for 1 minute during arterial occlusion (Fig. 17b). Within 5 seconds of the end of the effort, while the cuff was still

Figure 17:

Contractile properties of DF and PF muscles contrasted in a 26 year old male subject. a) Maximum isometric twitches. The smaller of each pair of responses is the control (resting) twitch and the larger is the potentiated one; superimposed M-waves shown on top traces. DF twitches were obtained from the TA (tibialis anterior) muscle only. b) 60 seconds of maximum voluntary effort. c) Maximum isometric twitches at end of (b), obtained with, and without, brief preceding 'potentiating' contraction; responses displayed as in (a). In this subject, responses (b) and (c) were observed during ischemia; however, similar recordings were also obtained without employing arterial occlusion.



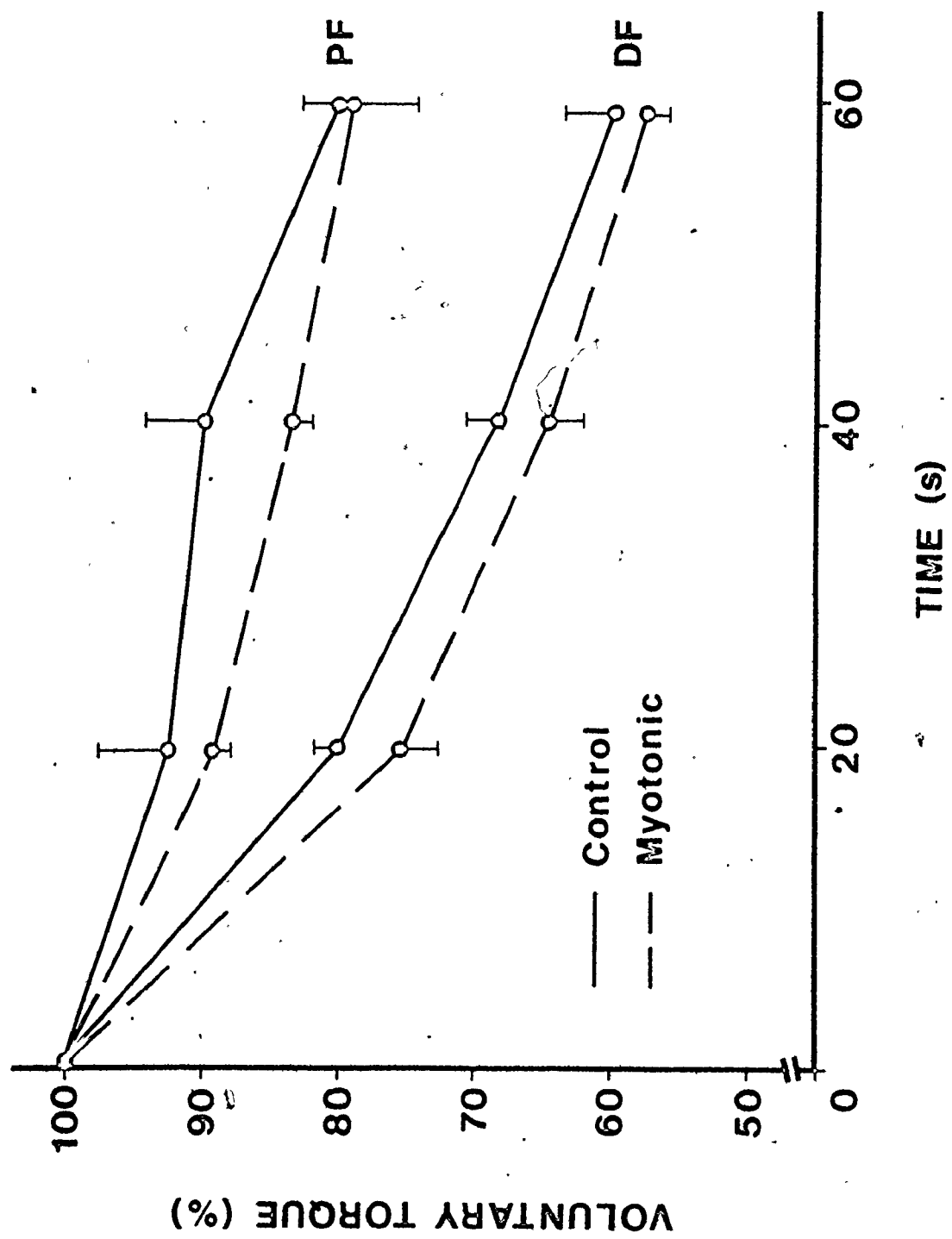
inflated, a single maximal stimulus was delivered to the previously active muscle and the twitch recorded (Fig 17c). A second twitch was then elicited immediately after 5 seconds of maximal effort to ascertain if additional potentiation could occur. From Fig. 17a,c it can be seen that, in the case of the TA muscle, there was a striking reduction in the size of the potentiated twitch after ischemic exercise. This finding contrasted with that obtained for PF muscles, in which the potentiated twitch was slightly larger immediately after exercise. Similar post-ischemic responses were observed in all five subjects. It was significant that the M-wave amplitudes were not measurably affected by the ischemic exercise in either the TA and PF muscles. In the TA muscle, the preservation of the M-wave in association with a drastically reduced twitch, pointed to a disorder of excitation-contraction coupling or of the contractile machinery as being the sites of fatigue (Merton, 1954; Edwards et al., 1977).

2. Patients with myotonic dystrophy

The susceptibility of dystrophic muscles to fatigue was tested by measuring the decline in isometric torque during 60 seconds of maximal voluntary dorsi-flexion and plantar-flexion. At the end of each 20 second epoch, the mean torque for the dystrophic muscles, expressed as a percentage of the initial value, was not significantly different from the mean value obtained for the control subjects (Fig. 18). In both the control subjects and dystrophic patients, a maximal stimulus was interpolated towards the conclusion of voluntary contraction to establish whether any decline in torque was due to failing motor unit activation. In none of the TA muscles could superimposed twitches be

Figure 18:

Decline of maximum voluntary torque of DF and PF muscles of patients with myotonic dystrophy and their matched control subjects. Means and standard errors of the mean are shown. No significant difference was found between the results for dystrophic patients and controls. In patients with myotonic dystrophy and in control subjects, DF muscles showed a greater susceptibility to isometric fatigue than PF muscles.



detected while, if one was present for the PF group, it was no larger than that present during short intense effort. While these observations clearly indicated that the site of fatigue was peripheral, they did not distinguish between a failure of muscle fibre excitation, on the one hand, and of excitation-contraction coupling or of the contractile machinery, on the other. For this reason a single maximal stimulus was delivered within two seconds of the end of the fatiguing contraction and the amplitude of the M-wave was compared with that of the twitch torque (Fig. 19). It was found that, in both the control and the dystrophic populations, M-waves of TA muscles were not measurably different from those recorded in the resting state. In contrast, the mean TA twitch torques were reduced from the initial values by 62% and 40% for the control subjects and dystrophic patients respectively. These results showed that fatigue in dystrophic TA muscles resembled that seen in healthy muscles and resulted from failure in some step beyond the excitation of the muscle fibres. In the PF muscles, which showed less fatigue than the TA muscle, the results were in the same direction though less striking (Fig. 19). The recovery of TA and PF twitches and voluntary torques followed similar time courses in the normal and dystrophic populations.

3. Patients with limb-girdle dystrophy

The susceptibility to muscle fatigue in the patients with limb-girdle dystrophy was similar to that observed in the myotonic dystrophy population. In Figure 20, the DF muscles are seen to be less resistant to fatigue than the PF muscles. No statistically significant difference was observed between the dystrophic patients and controls

Figure 19:

The effect of a 60 second maximum voluntary contraction on muscle compound action potentials (M-w) and on twitch torques (PT) of PF and TA muscles of controls and myotonic patients. Note the insignificant changes in the amplitudes of the M-wave in both muscle groups, as opposed to the marked decrease of twitch torques, especially in the TA muscle.

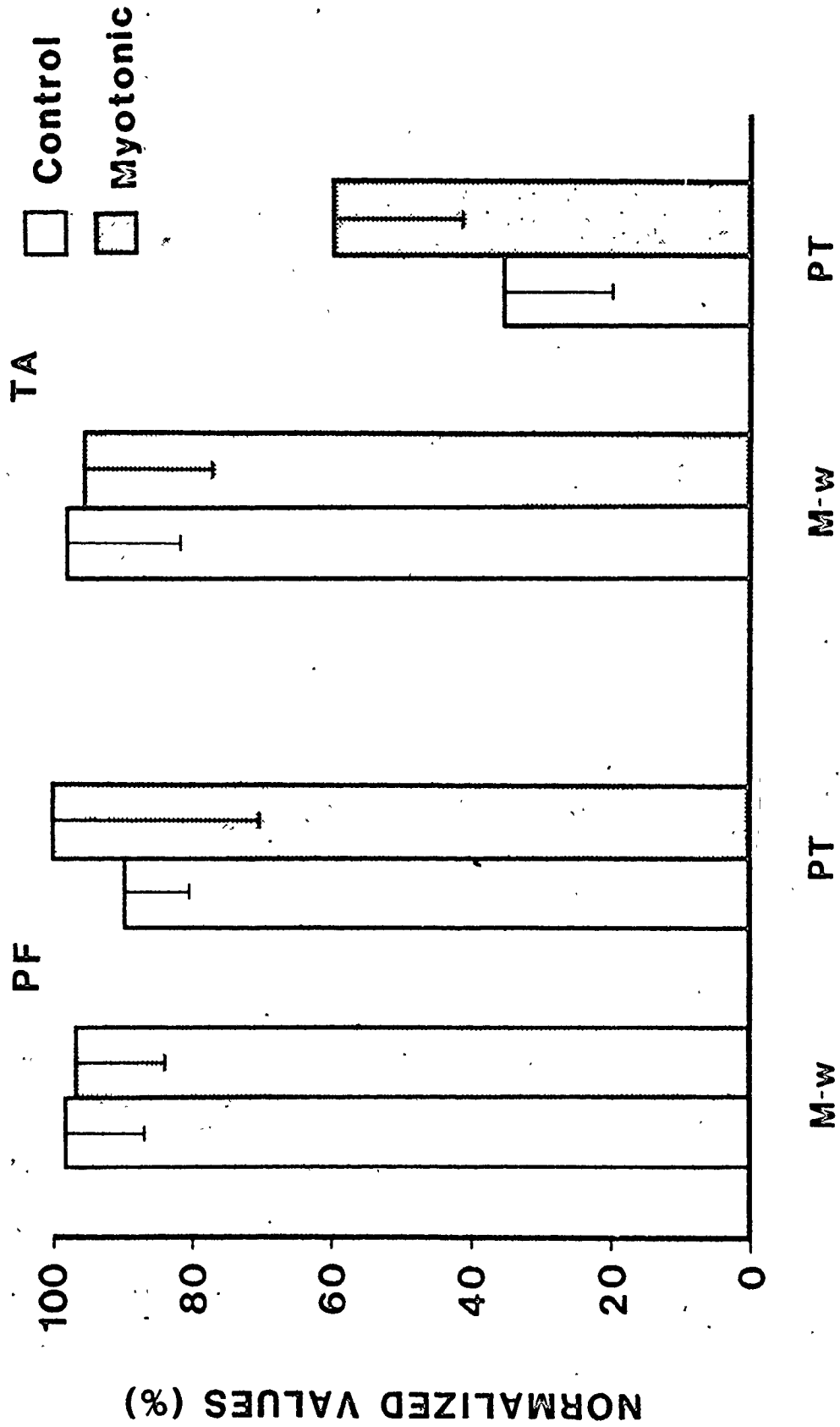
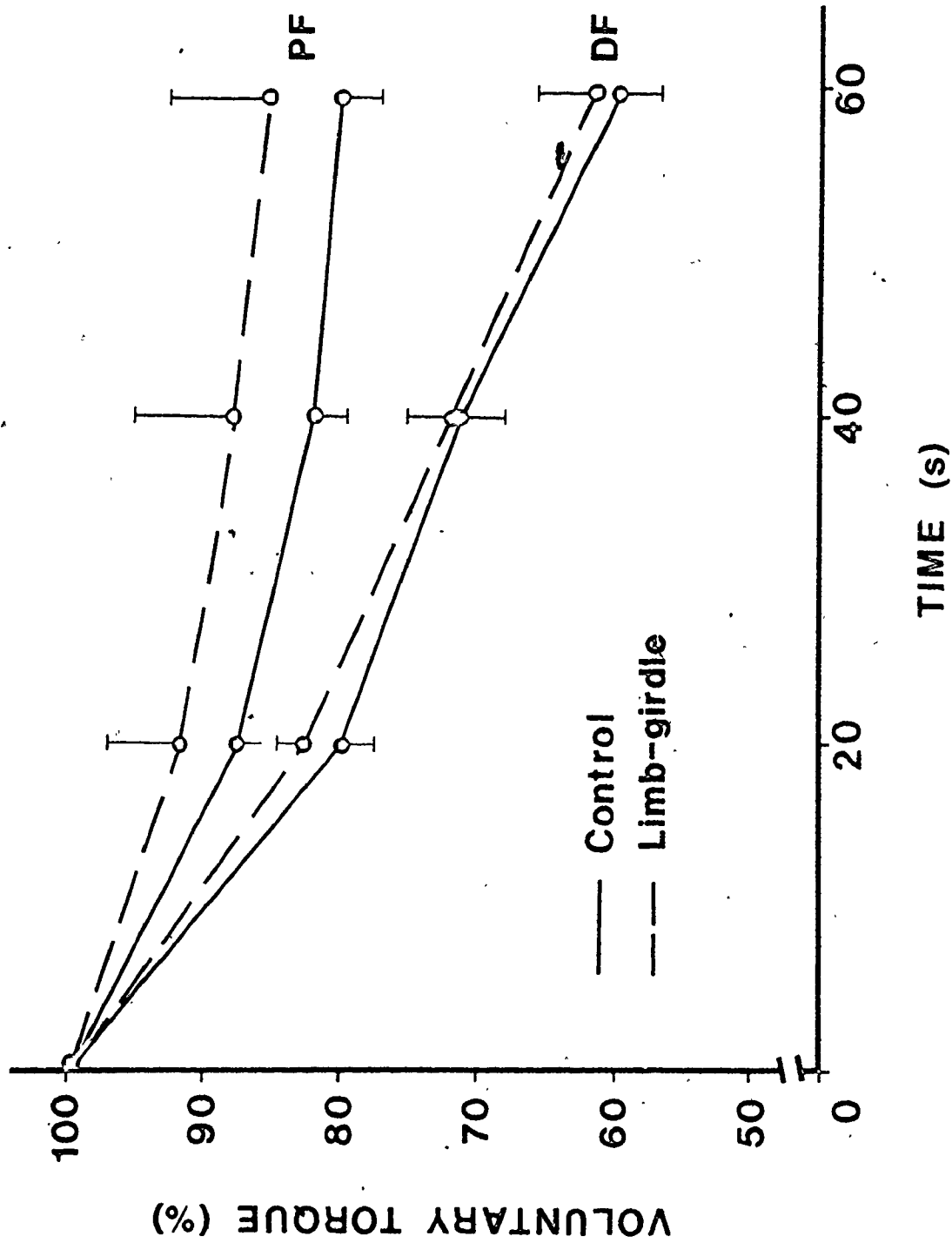


Figure 20:

Decline of maximum voluntary torque in DF and PF muscles of patients with limb-girdle dystrophy and matched control subjects. Mean values are shown with their standard errors of the mean. No difference was seen in the fatigue behaviour, as measured by the amplitude and the rate of decline of voluntary tension, between the dystrophic patients and the matched control subjects. As with the control subjects, the DF muscles showed less resistance to isometric fatigue.



when the mean torque values were measured at 20 second intervals and expressed as percentages of the respective initial values. The postulate that the origin of fatigue was peripheral, rather than in the central nervous system, was supported by the fact that no additional reduction of motor unit activation (MUA) was observed in the dystrophic PF and TA muscles during the fatiguing effort. To distinguish between a failure of muscle action potential propagation and of excitation-contraction coupling or contractile machinery, the M-wave and twitch torque amplitudes were compared before and after the fatigue test. As shown in Figure 21, there was no appreciable reduction of the M-waves in either muscle group during fatigue. In contrast, there were very marked decreases in the mean TA twitch torques, which declined to 40% and 55% of the initial values for the controls and dystrophic patients respectively. As with the matched controls, the PF twitches were only slightly reduced after the fatiguing exercise. As already noted in controls and patients with myotonic dystrophy, isometric muscle fatigue in patients with limb-girdle dystrophy appears to take place at some step beyond muscle impulse propagation. The time course of recovery from fatigue in patients with limb-girdle dystrophy was similar to that observed in the matched control subjects.

D. Influence of age and sex on contractile function

1. Control subjects

In the present study, the youngest subject was 19 years of age and the oldest, 65 years. Throughout this age span there was no significant change in the strength of the PF and DF muscles, as measured by maximal twitch and voluntary torques (Figs. 22,23). For the PF

Figure 21:

The effect of 60 second of maximum voluntary isometric contraction on the M-waves and twitch torques (PT) of PF and TA muscles, of both controls and limb-girdle dystrophy patients. In both the PF and TA muscles, note the insignificant changes in the M-wave amplitudes, as opposed to the marked reductions in twitch torque, especially in the TA muscles.

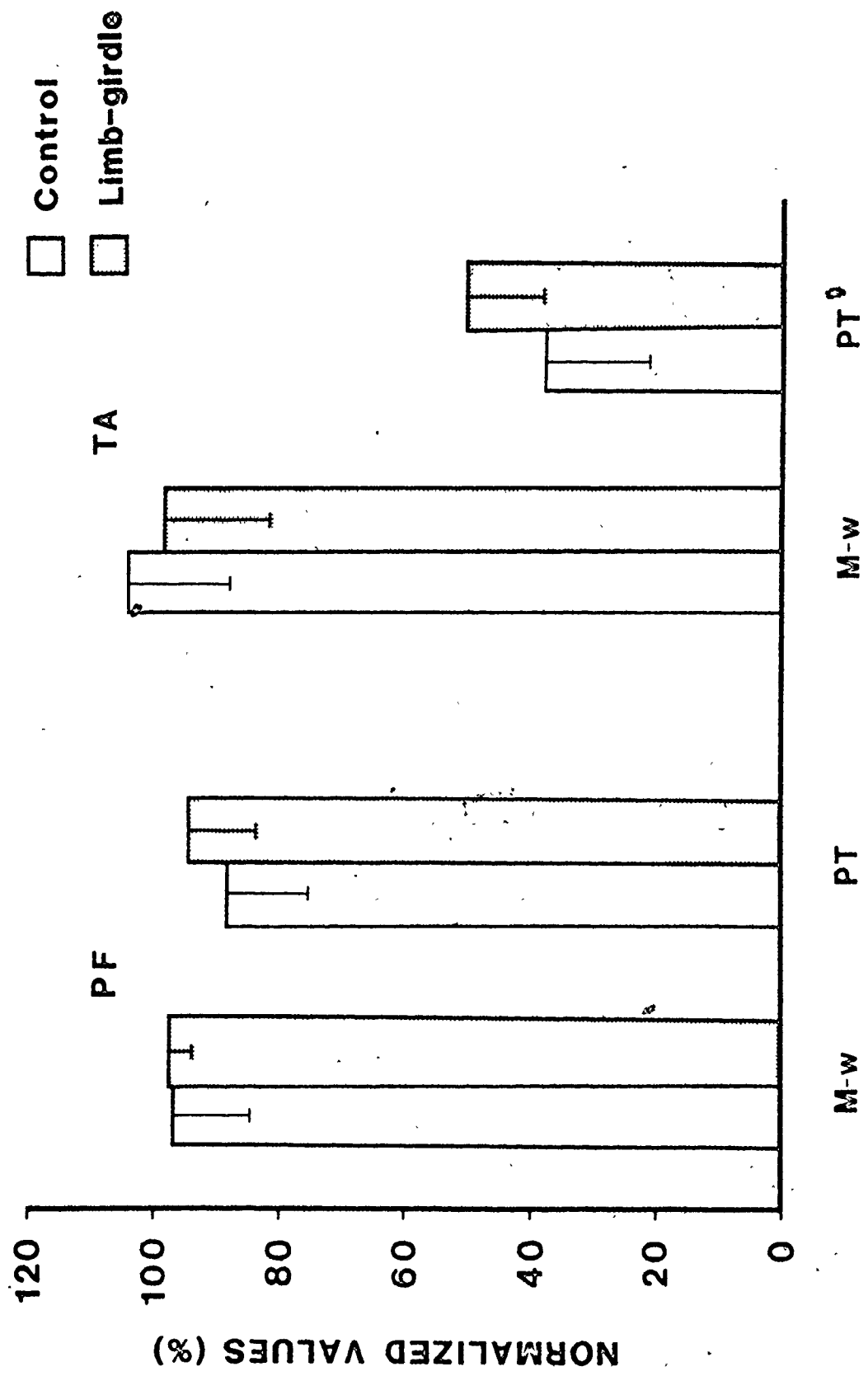


Figure 22:

Twitch torque as a function of age for TA (open symbols) and PF muscles (filled symbols). Values for males, and females shown as triangles and circles respectively. Note the difference between the two muscle groups, and the relatively smaller TA twitches in females.

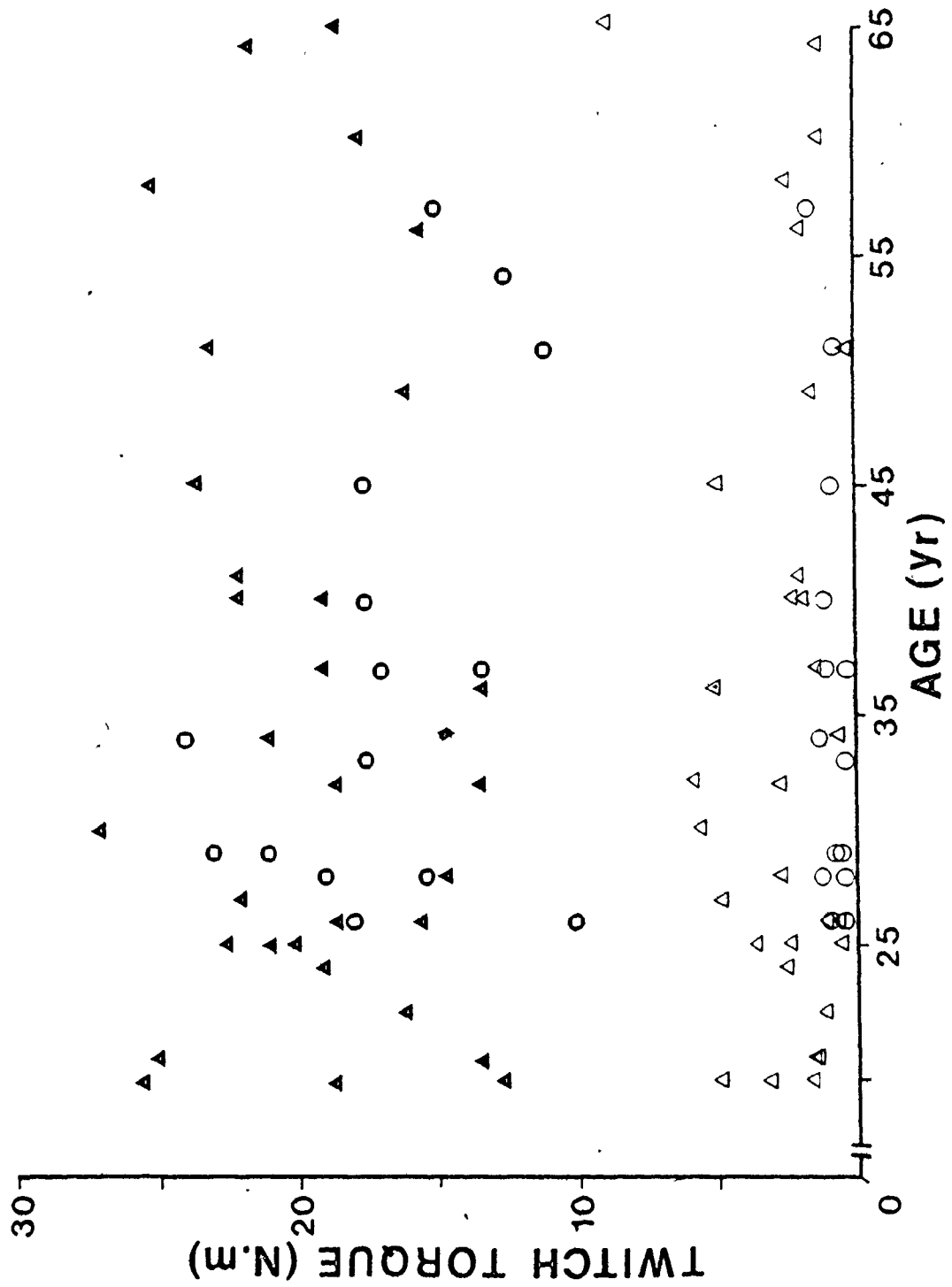
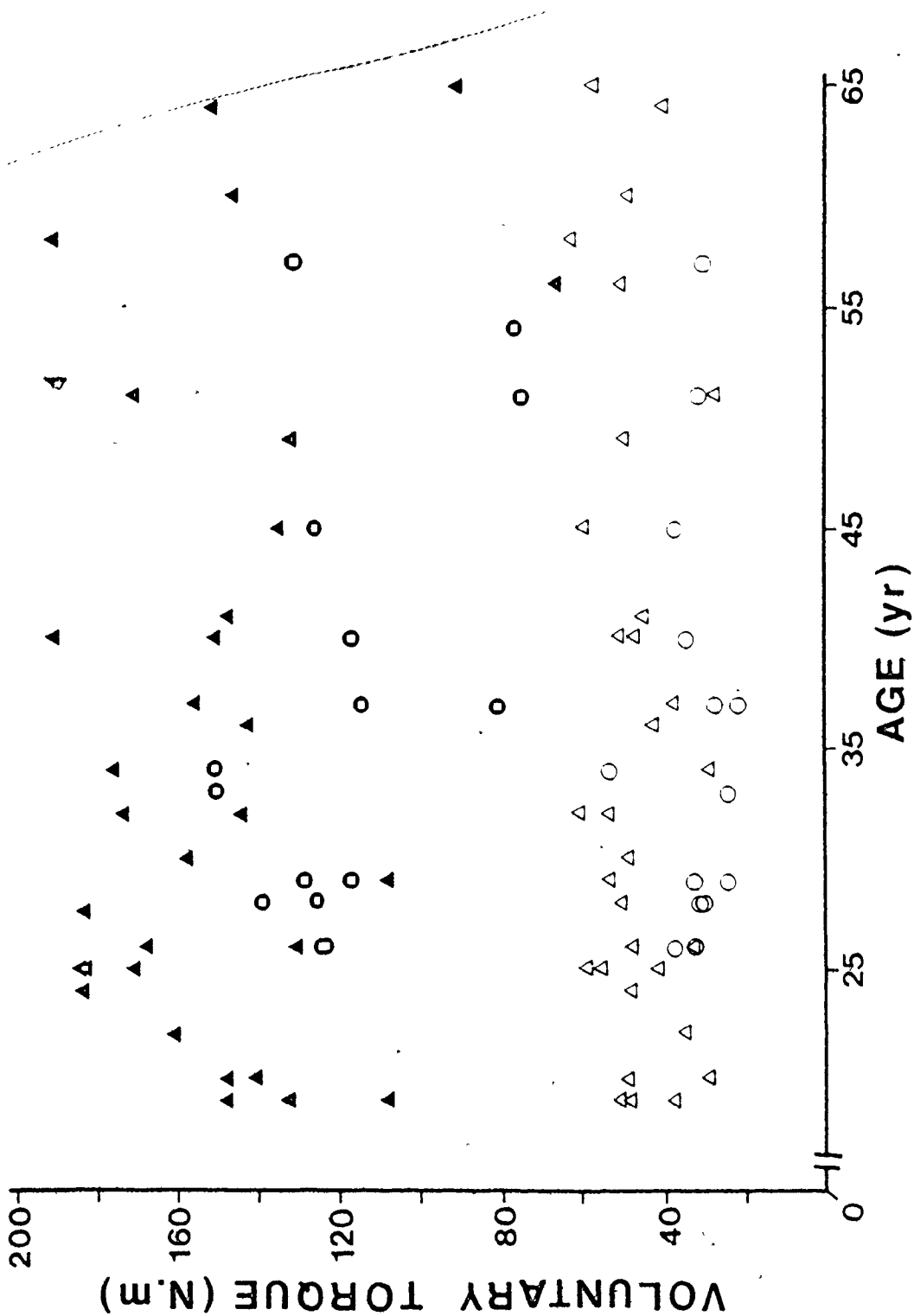


Figure 23:

Maximum voluntary torque as a function of age for DF and PF muscles (filled symbols). Values for males and females shown as triangles and circles respectively. Note larger values for PF and DF voluntary torque in males.



muscles, the correlation coefficients between PT and age and between MVC and age were -0.02 and -0.27 respectively, while for the PF muscles, values of 0.08 and 0.06 were found. In both muscle groups, however, there was a significant tendency for the twitch speeds (CT) to decrease with age (Fig. 24; $r=0.62$ for PF muscles and 0.44 for DF muscles). In the PF muscles, the slowing of CT appeared to take place after the age of 40 years, while in the TA the slowing occurred before this age. As far as the relationship between M-wave and age is concerned, a significant negative correlation was obtained for the PF muscle ($r=-0.50$) while the DF muscles showed no relationship ($r=-0.01$).

In keeping with common belief, men were stronger than women at all ages, both in terms of maximal twitch torque and voluntary torque (Figs. 22, 23 and Table 7). The differences were not the same for the two muscle groups however, for whereas the mean maximum voluntary PF torque was only 27% greater in men than in women, there was a 52% difference in DF torque. The disparity in mean twitch torques was even more marked, being 15% for PF muscles and 217% for TA muscles. The surprisingly small twitch torques of TA muscles in female subjects were responsible for the much higher mean voluntary torque:twitch torque ratio in women than in men, the respective values being 18.8 and 11.6 (Table 7). The mechanism responsible for the relatively small TA twitches in female subjects was investigated by measuring the joint position: voluntary torque (i.e. length:tension) relationship for TA and PF muscles in 7 young female subjects. In Figure 25, the results have been compared with those obtained from male subjects in other studies by the McMaster group (Marsh *et al.*, 1981; Sale *et al.*, 1982). In the case of the TA muscles, the optimal joint position for voluntary torque

Figure 24:

Twitch contraction time as a function of age for TA (open symbols) and PF muscles (filled symbols). Values for males and females shown as triangles and circles respectively. Note difference between the two muscle groups and the tendency for PF twitches to become slower with age.

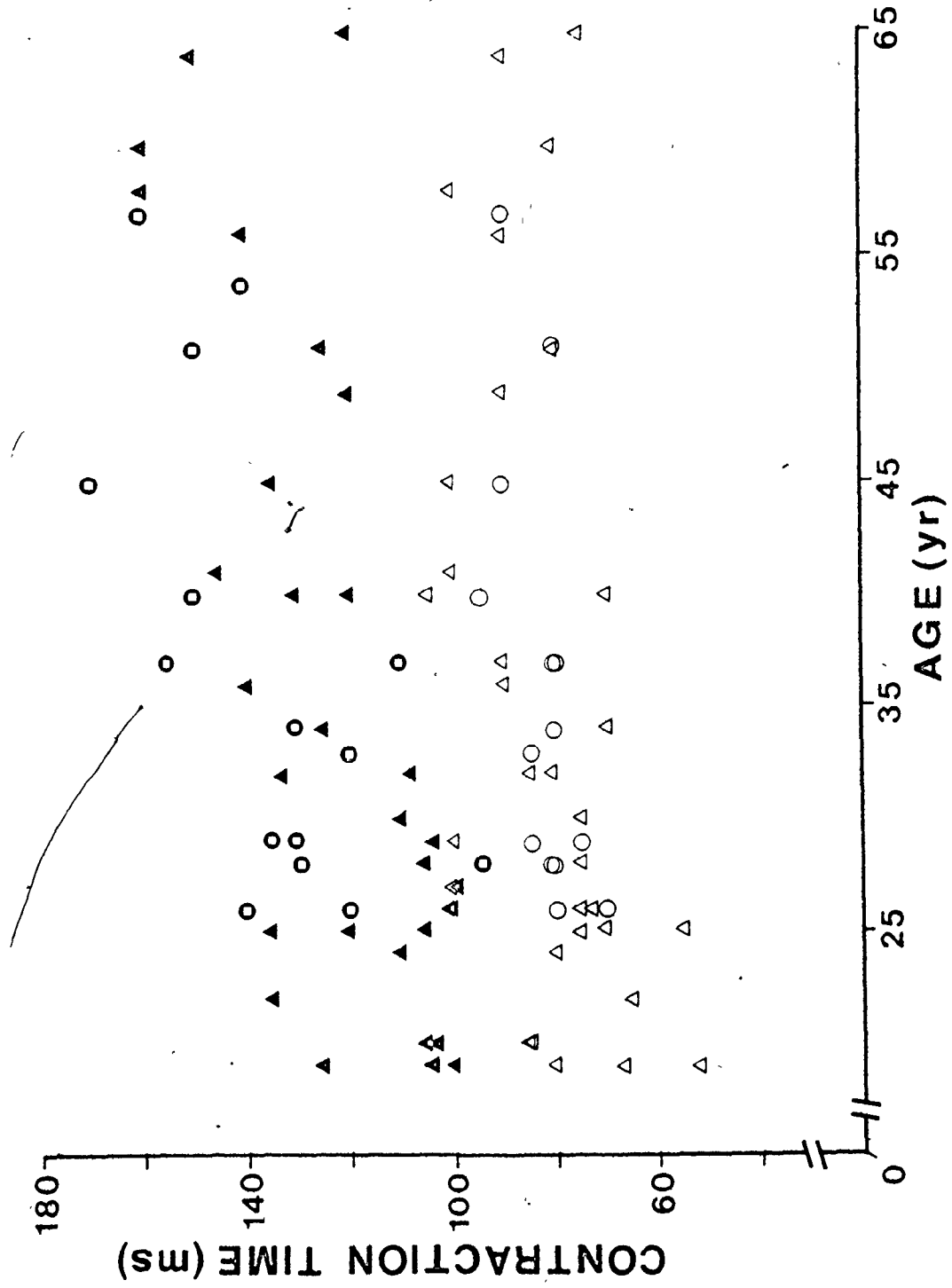


Figure 25:

Effect of ankle joint position on maximum voluntary torque, developed by 25 male (M) and 7 female (F) subjects, in PF and DF muscles (upper and lower halves of figure respectively). Values shown are means and standard errors of the mean. Note the difference in optimum joint position for TA muscles between males and females subjects.

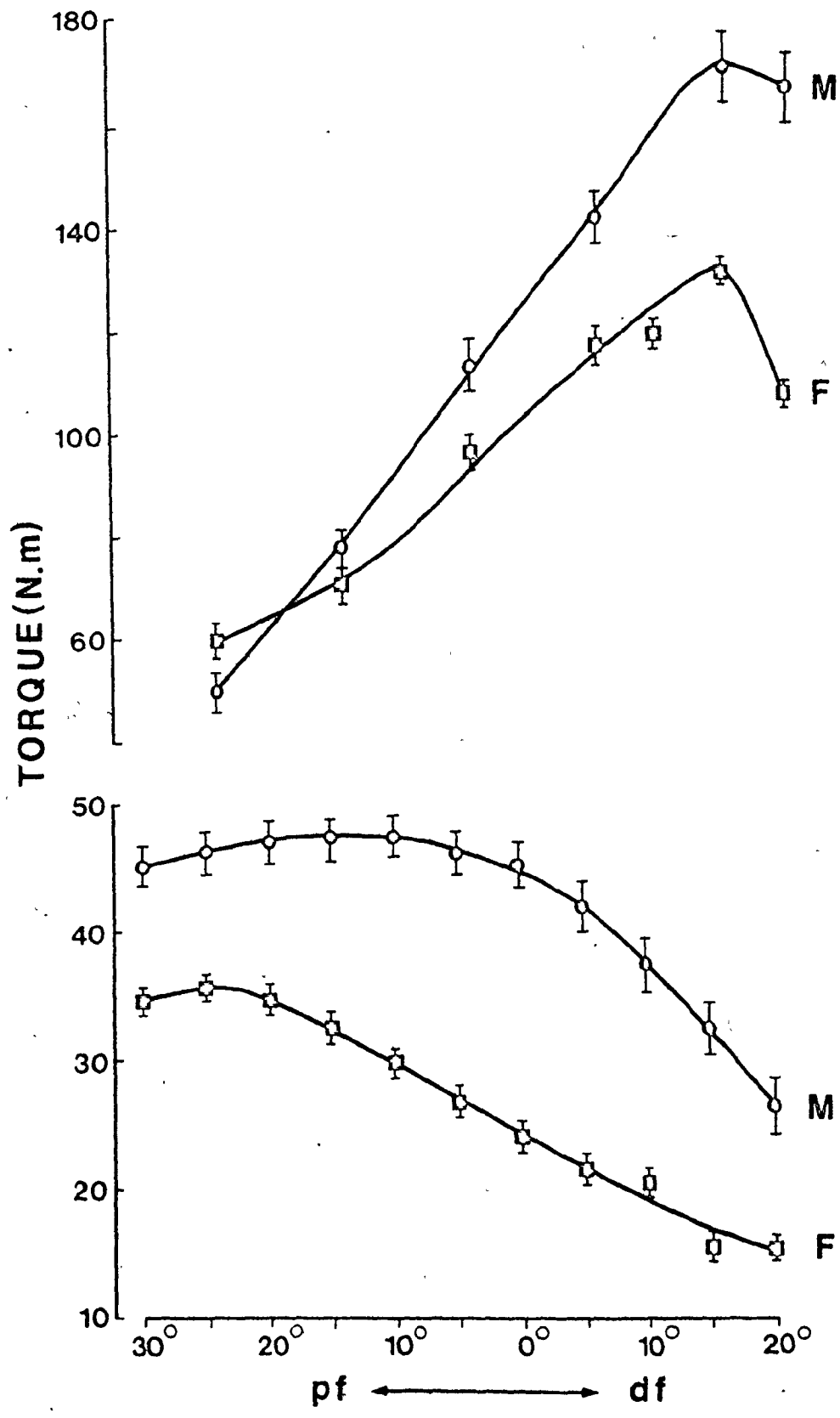


TABLE 7.

Summary of contractile properties of PF and DF muscles between male (M) and female (F) control subjects. Means (M) and standard deviations (+/-SD) are depicted. Values of twitch peak torque (PT), contraction time (CT), half-relaxation time (1/2 RT), muscle compound action potential (M-w), twitch post-activation potentiation (PAP), maximum voluntary torque (MVC), and motor unit activation (MUA) are shown. Significance was assessed at the 5% level, using independent t-tests. (S, significant; NS, not significant)

		PT	CT	1/2RT	M-w	PAP	MVC	MVC/PT	PT/M-w	MUA
		N.m	ms	ms	mV	%	N.m	-	N.m/mV	%
<u>PLANTAR-FLEXORS (PF)</u>										
<u>M</u>	(M)	19.1	122	115	16	23	149.8	7.9	1.48	92.3
	(SD)	4.0	18	19.6	5.8	23	29.3	1.9	.86	9.6
<u>F</u>	(M)	16.6	136	129	14.6	21	117.8	7.2	1.28	95.7
	(SD)	4.1	20	11	4.9	23	24	1.7	.58	4.4
<u>Signif.</u>		S	S	S	NS	NS	S	NS	NS	NS
<u>DORSI-FLEXORS (DF)</u>										
<u>M</u>	(M)	2.7	80.8	93.6	2.4	135	47.4	11.6	1.25	100
	(SD)	2.3	13	25.1	1.3	13	9.5	8.9	.94	-
<u>F</u>	(M)	.85	82.1	97.8	1.6	156	31.2	18.1	.66	100
	(SD)	.4	6.4	13.8	.9	86	.96	8.4	.42	-
<u>Signif.</u>		S	NS	NS	S	NS	S	S	S	-

development was found to differ between the sexes, being 25 degrees of plantar-flexion in women and 10 degrees of plantar-flexion in men; thus, the optimal muscle length was greater in women than in men (Fig. 25). No obvious difference was found in the joint positions for maximal torque development by the PF muscles in male and female subjects. The M-waves, which reflected the excitable muscle mass, were found to be significantly smaller in TA muscles of female subjects, whereas they were similar for males and females in PF muscles (Table 7). These findings caused the mean PT:M-w ratio for TA muscles to be significantly smaller in females than males. An additional observation was that the twitch was significantly slower, both in CT and 1/2 RT, in the PF muscles of females compared to the values for males (Table 7). In contrast, only a small difference was found between the twitch speeds of the TA muscles in both sexes.

2. Patients with myotonic dystrophy

In contrast to the control group, there was no significant difference between the contractile properties observed in male and female patients ($p > .05$). As expected, male patients were significantly taller and heavier than the female patients, although not stronger as measured by PT and MVC. The only significant correlations with age were for PT ($r = 0.65$) in the TA muscle and for the M-wave ($r = -0.51$) in the PF muscles. These results may have reflected an increase in the TA tendon stiffness and a decrease of PF muscle mass, leading to weakness with age.

3. Patients with limb-girdle dystrophy

Only one significant difference in contractile properties could be found between male and female patients with LGMD; this was the longer mean twitch contraction time for PF muscles in the female group. In this group of dystrophic patients, only the M-waves of the TA muscle were seen to diminish significantly with age ($r=0.51$). For the PF muscles, values of twitch torque ($r=-0.47$), M-waves ($r=-0.51$) and maximum voluntary torque ($r=-0.47$) were seen to significantly decrease with age.

E. Comparison of contractile properties between the control groups and the patients with MMD and LGMD

Table 8 summarizes the differences seen in the anthropometric and contractile properties of control subjects and of patients with MMD and LGMD. No significant difference was seen for age, weight and height between the controls and the patients. Comparison between contractile properties of control subjects and patients with MMD showed the M-wave and the maximum voluntary torque values to be significantly reduced in both dystrophic PF and DF muscles. Values of twitch torque for PF and DF muscles, as well as twitch contraction times for PF muscles, were significantly different in patients with MMD. Further comparison between the contractile properties of patients with LGMD and control subjects showed twitch torque and maximum voluntary torque values to be significantly reduced in both the dystrophic PF and DF muscles. Finally, comparison between patients with MMD and LGMD revealed only two significant differences in their contractile responses; in the myotonic group the mean contraction time of PF muscles was briefer and the mean M-waves amplitude was smaller.

TABLE 8.

Summary of anthropometric and contractile differences observed between the PF and DF muscles. Among all the contractile properties gathered in the present study, only values of twitch torque (PT), contraction time (CT), half-relaxation time (1/2 RT), muscle compound action potential (M-wave) and maximum voluntary torque (MVC) showed significant differences.

Statistical significance between mean values was assessed by an analysis of variance followed by Newman Keul's tests. Significance was given at the 5% level. (S, significant; NS, not significant).

df: degree of freedom

F : calculated statistical F-value

C1: control group for the patients with MMD

C2: control group for the patients with LGMD

ANALYSIS OF VARIANCE

	<u>df</u>	<u>F</u>	<u>Newman-Keul's</u>		
			C1+C2:MMD	C1+C2:LGMD	MMD:LGMD
AGE	73	2.4	NS	NS	NS
HEIGHT	71	0.86	NS	NS	NS
WEIGHT	71	1.73	NS	NS	NS

PLANTAR-FLEXORS (PF)

PT	73	14.4	S	S	NS
CT	72	9.7	S	NS	S
M-w	73	10.1	S	S	NS
MVC	72	16.4	S	S	NS

DORSI-FLEXORS (DF)

PT	55	3.17	NS	S	NS
CT	54	3.18	NS	NS	NS
M-w	60	6.42	S	NS	S
MVC	70	17.9	S	S	NS

V. DISCUSSION

The aim of the present study was to provide a better understanding of muscle function in healthy adult subjects and in patients with myotonic muscular dystrophy (MMD) and limb-girdle muscular dystrophy (LGMD). To achieve this goal, a study was undertaken of evoked and volitional contractile properties of two opposing muscle groups in the leg, the ankle plantar-flexors (PF) and dorsi-flexors (DF). The following contractile properties were investigated under isometric conditions: (1) twitch torque, (2) twitch speed, (3) twitch potentiation, (4) voluntary muscle strength, (5) extent of motor unit activation during maximum voluntary effort and (6) muscle fatigue. Using the above contractile responses, I first sought to determine any differences in the contractile behaviour between these two opposing muscle groups in healthy subjects. Then, I investigated the influence of age (19-65 years) and sex on the above contractile properties. In that part of the study concerning patients with myotonic muscular dystrophy (MMD) and limb-girdle muscular dystrophy (LGMD), I examined the following aspects of contractile function: (1) the degree of involvement by the dystrophic process of one muscle group compared with the other (PF versus DF muscles), and the involvement of one muscle fibre type compared with the other (fast-twitch versus slow-twitch) in these two muscle groups; (2) the capacity of dystrophic patients to activate fully their muscle mass during maximum voluntary effort; and (3) the question of disproportionality between muscle electrical

response (M-wave) and its corresponding mechanical output (twitch) in dystrophic muscle. The present study constitutes the first comprehensive report of muscle contractile properties in patients with MMD and LGMD, in which adequate matching with control subjects was performed. It is also the first study which has examined the effects of muscular dystrophy in two opposing muscle groups. The present physiological investigation complements the many anatomical, biochemical and electromyographic studies of normal and dystrophic human muscles.

A. Comparison of PF and DF properties in control subjects

1. Twitch and voluntary torques

Significant differences in contractile properties were observed between the plantar-flexor (PF) and dorsi-flexor (DF) muscles. Some of these differences were expected in view of the visibly greater muscle mass and cross-sectional area of PF muscles; other differences might have been anticipated from the contrasting roles of these two muscle groups. Thus the plantar-flexors (PF) are continuously active in the standing posture (Joseph and Nightingale, 1956) and develop enormous torques during running (Winter, 1980). In contrast, the dorsi-flexors (DF) are quiescent during standing and develop relatively modest torques in walking and running. In the present study, I found the maximum voluntary torque of DF muscles and the twitch torque of the tibialis anterior (TA) muscle to be significantly smaller than those of the PF muscles. Using an ultrasonic scanning device to determine the cross-sectional area of human muscles, Ikai and Fukanaga (1968) demonstrated a significantly positive correlation between muscle

cross-sectional area and muscle strength. Recently, Bulcke et al., (1979) have disclosed, using the computed tomography scanning technique, the larger cross-sectional area and muscle mass of the PF muscles as opposed to the DF muscles.

In discussing twitch and voluntary torque development, it must be understood that the TA muscle was only responsible for approximately 42% of the maximum voluntary DF torque, the remainder being contributed by the long extensor of the toes and the peroneus tertius muscle (Marsh et al., 1981). Furthermore, twitch measurements were made only from the TA muscle, since the cathodal electrode was placed directly over its muscle belly and no contractions could be seen or palpated in the long extensor muscles of the toes. All of the PF muscles, which include the triceps surae (soleus, medial and lateral gastrocnemii), tibialis posterior, plantaris, peroneus longus and brevis and the long extensors of the toes would have contributed to voluntary plantar-flexion torque. For the PF twitch torque, however, the peroneus longus and brevis muscles, being supplied by the peroneal nerve, were not excited as the cathodal electrode was placed over the medial popliteal nerve only (Sale et al., 1982).

The PF muscles showed twitch and voluntary torque values which were nine and three times larger, respectively, than those found in the DF muscles. Throughout this study, twitch and voluntary torque measurements were taken with the TA and PF muscles positioned at, or close to, their respective optimum muscle lengths; the latter corresponded to 15 degrees of dorsi-flexion and to 20 degrees of plantar-flexion respectively (Marsh et al., 1981; Sale et al., 1982).

Testing of contractile function at optimum muscle length allowed the greatest resolution of twitch and voluntary torque measurements. Because of the difficulty of resolving the lever arm length and the direction of pull for each of the PF and DF muscles, measurement of muscle torque was preferred over that of muscle tension. Muscle torque (in units of Newton-metre, N.m.), is defined as the product of absolute muscle tension and the length of the lever arm (i.e. the perpendicular distance between the line of pull of the muscle and the axis of joint rotation). Torque measurements have the advantage of directly reflecting the functions of the PF and DF muscles, which are to cause the foot to rotate about the axis of the ankle joint.

The effect of sex on twitch and voluntary torque values were also of interest. In keeping with other studies of human muscle strength in male and female subjects (Asmussen and Heeboll-Nielsen, 1961; Tornvall, 1963; Larsson et al., 1979; Fugl-Meyer et al., 1980), men were found to be stronger than women throughout the age span covered in this study, i.e. between the ages of 20 and 65 years. In the present study, maximum PF voluntary torque was 27% lower in females than in males, a value similar to the 35% found by Fugl-Meyer et al., (1980). For DF voluntary muscle strength, a larger difference (52%) was found between male and female subjects. These differences did not depend on the degree of voluntary effort since motor unit activation (MUA) during maximal effort was similar in the male and female groups. The most probable cause of greater muscle strength in males was the relatively larger muscle masses noted in both the PF and DF muscles (Bulcke et al., (1979).

To date, there has been no study indicating differences in maximum isometric twitch tension between male and female subjects. In the present study, women were found to have significantly smaller twitch torque values, the disproportionality being 15% for PF muscles and 217% for the TA muscle. In women, the smaller TA muscle twitches were responsible for the larger ratios of maximum voluntary torque to twitch torque (MVC:PT; Table 7). Since the TA muscle was responsible for only 42% of maximum DF torque (see above), the MVC:PT ratio of this muscle was corrected by a factor of 0.42. For the PF muscles an unknown, but probably small, correction was required; thus the peroneus longus and brevis would have contributed to voluntary plantar-flexion but, being supplied by the peroneal nerve, not to the twitch. Of interest here are other studies of plantar-flexion voluntary torque (Herman and Bragin, 1967) and twitch torque (Gottlieb and Agarwal, 1978) which have shown maximum torque development with the PF muscles in a stretched position. In a unique study, in which the triceps surae (soleus, medial and lateral gastrocnemii) was completely excised from a patient with a sarcoma of the Achilles tendon, Murray and colleagues (1976) have estimated that 60% of the total plantar-flexion torque could be attributed to these muscles. Murray and collaborators also calculated the hypothetical potential torque for the triceps surae muscles and found it to be approximately 80% of the total torque.

The very much larger twitch torques developed by the TA muscles in men, as opposed to women, have already been noted. One possible mechanism for this difference would be an alteration in the length:tension relationship of DF muscles in females, as a consequence

of wearing high-heeled shoes. Animal experiments have disclosed that prolonged lengthening of muscles causes the addition of sarcomeres (Tabary et al, 1972) and it seemed possible that a similar adaptation might prevail in chronically stretched human DF muscles. This possibility was examined by comparing the curves relating maximum voluntary DF torque to ankle joint angle. It was found that in women, maximum DF torque was developed with the ankle plantar-flexed by 25 degrees; in similarly aged men, the corresponding optimal angle was only 10 degrees. However, the discrepancy in optimal joint angle was equally true of three female subjects who did not wear high-heeled shoes and of the four who did. Therefore, a second explanation for the small twitches of the TA muscle in females was considered, namely that the series-elastic component was greater in women than in men. Such a mechanism could also have accounted for the observed alterations in the length:tension relationship for DF muscles in women. An increased series-elastic component would have been expected to cause slowing of the TA twitch in women but this, however, was not the case. Similarly, it has not been possible to demonstrate differences in the length:passive torque relationship for DF muscles between men and women (A. Vandervoort, personal communication). At present then, no convincing explanation is available for the relatively small twitches of the TA muscle in female subjects.

In the present study, the age factor was not found to have a significant effect on the voluntary and twitch torque values of PF and DF muscles, as revealed by linear correlation analyses. Both twitch and voluntary torque values were seen to be maintained between the period of

20 to 55 years of age in both muscle groups; thereafter there was a tendency for these values to decline. These findings are consistent with those of Asmussen and Heeboll-Nielsen (1961) and those of Fugl-Meyer et al., (1980) who tested only the PF muscle group. Also of interest, in considering the effect of age on contractile function, are the studies of McComas et al., (1973) on the extensor hallucis brevis muscle and those of Larsson et al., (1978,1979) on the quadriceps muscle. These studies showed significant increases in twitch (McComas et al., 1973) and voluntary torque (Larsson et al., 1978,1979) during the second decade of life, most likely due to the effect of puberty and substantial muscle growth. Towards the end of the sixth decade and thereafter, muscle strength has been shown to decline as muscle atrophy and loss of functional motor units occurs (Burke et al., 1953; Campbell et al., 1973; Larsson et al., 1978,1979; Fugl-Meyer et al., 1980; Davies and White, 1981,1982). Preliminary studies on the effect of ageing (in subjects aged 65-70 years) on the PF and DF muscle groups have identified normal values of twitch torque in both TA and PF muscles as well as normal value of maximum voluntary torque in the DF muscles; only voluntary torque of PF muscles was seen to significantly decline in this group of elderly subjects (Vandervoort and McComas, 1982).

2. Twitch speed

In view of the known relationship between twitch speed and muscle fibre type (Barany, 1967), the possibility of taking muscle biopsy specimens from the control subjects was considered. However, an adequate study of muscle fibre composition would have required samples

of three muscles in each subject (soleus, gastrocnemius and tibialis anterior) and of three sites in each muscle (Elder, 1979; see below). For ethical and practical reasons, such an extensive muscle investigation did not appear justified. Instead, the assumption was made that each subject tested in the present study possessed PF (soleus and medial-lateral gastrocnemius) and DF (tibialis anterior) muscle fibre compositions similar to those found in other human subjects (see below).

In every subject tested, the TA muscle demonstrated much faster twitch contraction and half-relaxation times than did the PF muscles. However, the mean twitch contraction time of the TA muscle was still significantly greater than that found for the intrinsic muscles of the hand and foot, and for facial muscles (McComas, 1977). To some extent, differences of twitch speed between different muscles could be correlated with muscle fibre-type composition (myosin ATPase; Barany, 1967). The soleus muscle has the highest incidence of type I (slow-twitch) fibres whereas the facial muscles have the lowest incidence of this fibre-type (Johnson et al., 1973). Previous studies with muscle biopsies have exhibited considerable variation in fibre-type composition between the PF muscles (soleus, lateral and medial gastrocnemii) and the tibialis anterior (TA) muscle within the same individual; significant variations were also found for the same muscle between individuals (Edstrom and Nystrom, 1969; Johnson et al., 1973; Gollnick et al., 1974a; Edgerton et al., 1975; Fugl-Meyer et al., 1979). Elder (1979) showed that some of the discrepancies reported could be due to sampling problems, since fibre type proportions could vary from one

part of a muscle to another. He indicated that at least 3-5 sites were required to be sampled in each muscle for a reliable estimate of fibre type composition to be made. Using such a sampling technique in four adult cadavers, Elder (unpublished data) showed the soleus to possess the greatest proportion of type I (slow-twitch) fibres (mean 76%; range 63% - 81%). His examination of gastrocnemius and TA muscles revealed smaller proportions of type I fibres, the mean incidence being 63% in gastrocnemius and 64% in TA muscle respectively, with ranges for both the TA and gastrocnemius muscles of 52% to 72%. However, it is possible that factors other than myosin ATPase activity (Barany, 1967) may also have contributed to twitch speed of contraction. For example, twitch contraction times have been found to be similar in human gastrocnemius and soleus muscles (Buller et al., 1959), despite their differences in fibre-type composition (Johnson et al., 1973). Factors such as muscle 'active state' intensity and duration, as well as the amount and stiffness of the muscle series-elastic component, are likely to significantly influence twitch speed of contraction and relaxation (Desmedt and Hainault, 1968; Close, 1972; Takamori et al., 1975, 1978). The significantly slower twitch contraction times in the PF muscles of females compared with those of males are also noteworthy, but too few observations were available to indicate whether this was associated with a difference in fibre type proportions or with an increased muscle series-elastic component. Slower PF twitch contraction times in females were also observed by Sale (1979) in a group of subjects of both sexes. The lack of studies on muscle fibre-type composition and on the series-elastic component of muscles of adult sedentary male and female

subjects, preclude further speculation on the nature of this finding.

3. Twitch potentiation

In considering other contractile features of PF and DF muscle groups, a striking observation was that, following a brief maximum voluntary contraction, the value of twitch torque was appreciably enlarged. Facilitation of the twitch has been well documented following tetanic stimulation of amphibian (Colomo and Rocchi, 1965) and mammalian muscles (Brown and Von Euler, 1938; Sandow, 1967; Standaert, 1967; Botelho and Cander, 1953) and has been termed post-tetanic potentiation (PTP). In the present study, twitch potentiation was obtained following a brief maximum voluntary contraction and was termed post-activation potentiation (PAP). In the present study, this enhancement was significantly greater in the TA muscles than in the PF muscles, the mean PAP values being 144% for the TA muscles and 20% for the PF muscles. The fact that the 'potentiated' twitch contraction times were always shorter than those of the 'resting' twitches strongly suggests that potentiation could not have been due to a prolongation of the 'active state' process, but must instead have reflected an increase in its intensity. This conclusion is in keeping with those of Desmedt and Hainaut (1968) and of Rosenfalck (1974) in human muscle, and of Ranatunga (1979) in other mammalian muscles. The mechanism underlying increased intensity of the 'active state' process in the potentiated condition has yet to be elucidated; it may or may not involve higher calcium ion concentrations in the vicinity of the myosin cross-bridges (Close, 1972; Blinks et al., 1978; Ranatunga, 1979; Wallinga-de-Jonge et

al., 1981). The greater twitch potentiation observed in the TA muscles is in keeping with other observations indicating that potentiation is most marked in fast-twitch muscles (Brown and Von Euler, 1938; Ranatunga, 1979). The occurrence of twitch potentiation following a brief voluntary isometric contraction has both practical importance as well as physiological interest. From a practical standpoint it is obviously necessary to measure 'resting' twitch parameters under properly controlled conditions, i.e., after the muscle under investigation has been inactive for at least 5 to 10 minutes. Thus, preliminary studies have shown the phenomenon of twitch post-activation potentiation to last approximately 5 to 10 minutes after voluntary effort (A. Vandervoort, personal communication). From a physiological viewpoint, potentiation may be responsible for the well-known observation of greater maximum voluntary muscle strength after two or three attempts as opposed to that obtained after the first attempt. In the present study, voluntary strength measurements were consistently greater after the second or third contractions than after the first one.

B. Motor unit activation during maximum contractions of PF and DF muscles in control subjects

Before consideration of this question, it is appropriate to discuss another way in which the problem of measuring the extent of voluntary motor unit activation has been approached. Such a method has been to compare maximal voluntary torque with that developed by the same muscles during tetanic electrical stimulation (for example; Merton, 1954; Ikai et al., 1967; Edwards et al., 1977; Bigland-Ritchie et al.,

1978,1979). The difficulty with this approach is in selecting a muscle, or a group of muscles, which are entirely responsible for a particular joint movement and can be selectively stimulated. In the case of the ankle joint, for example, the peroneal nerve supplies not only all the dorsi-flexors, but also two of the plantar-flexor muscles (peroneus longus and brevis). Although the adductor pollicis muscle was chosen by Merton (1954) for his classical study, there are other muscles that can contribute to adduction of the thumb, such as the first dorsal interosseous and opponens pollicis. The complete elimination of the actions of these two latter muscles is difficult to achieve, especially during voluntary contractions. Undoubtedly, one of the best movements for the employment of the tetanic nerve-stimulation technique is extension of the knee, since the femoral nerve supplies by far the strongest extensor, the quadriceps, and only one weak flexor, the sartorius (Edwards et al., 1975,1977; Bigland-Ritchie et al., 1978,1979). However, the tensor fascia lata muscle also helps to extend the knee and is supplied by the superior gluteal nerve (Gray, 1973). Unfortunately, tetanic stimulation of the femoral nerve is not only painful but also dangerous because of the risk of dislocating the patella or of rupturing the quadriceps tendon. In one reported instance this experiment has been done and the tetanic torque achieved was found to be similar to that developed during maximal effort (Edwards et al., 1975). In contrast, one of the attractions of the twitch interpolation technique, used in the present study as an alternative to the tetanic stimulation technique, is that it can be employed for almost any muscle with an accessible nerve supply. It is also much less uncomfortable for

the subject, and the risk of muscle or tendon damage is negligible.

Experiments conducted in the present study, using the twitch interpolated technique, have shown that the motor units belonging to the TA muscle were easily and fully activated during maximum voluntary contraction (except in one subject). In contrast, motor units of the PF muscles were fully activated in only half of the subjects, usually with much more difficulty. The finding of full motor unit activation during voluntary effort is in keeping with that of Merton (1954) for the adductor pollicis muscle and that of Edwards et al., (1975,1977) for the quadriceps muscle, although in the latter instance only one subject was examined. The finding that maximum muscle tension can be achieved under volitional effort, as a result of full motor unit activation, runs counter to the findings of Ikai et al., (1967) who, like Merton (1954), tested the adductor pollicis. Ikai and colleagues (1967) found that even within the first few seconds of maximum contraction (before fatigue had set in), the tetanically-elicited torque exceeded that developed in maximum effort. Contradictory observations have also been reported by Gollnick et al., (1974b) who, on the basis of glycogen depletion studies with the quadriceps femoris, have suggested that weak isometric contractions are brought about by slow-twitch (type I) units, but that strong effort involves only fast-twitch (type II) units. This conclusion seems improbable, however, for in the many studies of motor unit firing in human muscles (Desmedt, 1981), there has been no report of motor units dropping out as the contraction became stronger (see, for example, Bigland and Lippold, 1954).

A feature of this type of experiment was that further

dorsi-flexion torque could be developed beyond the level at which all the TA motor units were maximally activated. One explanation for this apparent anomaly would be that whereas moderately strong dorsi-flexion might be achieved largely through the action of the TA muscle, maximum dorsi-flexion torque might depend more on the contribution from the long dorsi-flexors of the toes (Marsh et al., 1981). The findings obtained from the plantar-flexor muscles (PF) differed from those seen in the TA muscle in that approximately half the subjects had difficulty in obtaining full activation. This observation finds some support from clinical electromyography, for it is recognized that full EMG interference patterns are commonly not achieved in the gastrocnemius and soleus muscles during maximal plantar-flexion (A.J. McComas, personal communication). The incomplete activation of the PF muscles was unlikely to have been related to poor representation for ankle movement in the motor cortex, in view of the ease of motor unit activation in the TA muscle. An alternative explanation would depend on differences in synaptic input to the lower PF and TA motoneurons. The PF muscles have been shown to be active in standing posture (Joseph and Nightingale, 1956) and their motoneurons to receive powerful monosynaptic excitatory connections from homonymous Ia spindle afferent fibres. The latter is reflected in the ease with which H-reflexes can be elicited in human soleus (for example; Hoffmann, 1918; Magladery et al., 1951; Paillard, 1959). In contrast, the TA muscle has been shown to be inactive in the standing posture (Joseph and Nightingale, 1956) and its H-reflexes to be elicited only after voluntary contraction (Upton et al., 1971). The motoneurone pool of the TA muscle may, therefore, receive weaker

afferent inputs from the Ia spindle afferent fibres than that of the PF muscles, while the TA motoneurons may receive stronger inputs from the descending motor pathways. As a result, motor units may be more readily excitable under volitional effort in the TA muscles than in PF muscles.

C. Susceptibility of PF and DF muscles to isometric fatigue in control subjects

Fatigue experiments conducted in the present study showed the dorsi-flexor muscles to be significantly more susceptible to isometric fatigue than the plantar-flexor muscles. By the end of 60 seconds of a fatiguing contraction, the mean reduction in voluntary torque amounted to 40% of the initial value for the DF muscle group but to only 22% for the PF muscle group. At the end of 180 seconds of contraction, voluntary torque further declined to 70% for the DF muscles and to 50% for the PF muscles. The fact that the DF muscle group was less resistant to isometric fatigue than was the PF muscle group is consistent with the demonstration of a relatively greater proportion of type II (fast-twitch) fibres in the TA muscle (the main dorsi-flexor) than in the soleus muscle (the main plantar-flexor; see Edstrom and Nyström, 1969; Edgerton et al., 1975; Elder, 1979). That fast-twitch glycolytic muscle units are more susceptible to fatigue than slow-twitch oxidative muscle units was elegantly demonstrated by Burke et al., (1973) in the cat gastrocnemius muscle and by Garnett et al., (1978) in human soleus and gastrocnemius muscles. Also consistent with the findings of Garnett et al., (1978) are the results of Ochs et al., (1977) who showed electromyographically that the gastrocnemius muscles

fatigued more rapidly than the soleus muscle, following dynamic voluntary fatiguing contractions.

In the present study, clues were obtained as to whether central or peripheral sites were responsible isometric muscle fatigue. The interpolated stimulus technique was employed to detect central failure while measurements of M-wave and twitch torque, made before and immediately after the fatiguing contraction, served to detect peripheral sites of failure. In the present discussion, 'central' failure refers to a lack of motor unit activation while 'peripheral' failure encompasses defects of neuromuscular transmission, muscle fibre impulse propagation, excitation-contraction coupling, and contractile machinery. In the case of the DF muscle group, the results obtained from the interpolated stimulus technique showed no evidence for a central site of failure in the TA muscle; thus no twitch response could be detected on top of the voluntary torque recording at the end of the fatiguing effort. In the TA muscle, then, the decline of voluntary torque during fatigue appeared to be due to peripheral sites of failure. However, the use of the interpolated stimulus technique was restricted to the TA muscle and failed to provide information on the extent of motor unit activation of the remaining DF muscles during fatigue. It remains possible that fatigue of the DF muscle group resulted from a combination of peripheral failure of the TA muscle on the one hand, and central or peripheral failure in the remaining dorsi-flexor muscles, on the other.

During fatigue, the PF muscles behaved similarly to the DF group, in that no evidence was found of impaired motoneurone activation, beyond that present at the outset of the effort. That isometric fatigue

of PF and DF muscle groups was due to peripheral rather than to central failure is in agreement with the findings of Merton (1954). This investigator compared the M-wave with the twitch tension and clearly demonstrated a peripheral site of failure in the adductor pollicis muscle (see below). The lack of central failure in the TA and PF muscles during fatiguing contractions is, however, counter to the findings in the adductor pollicis muscle (Bigland-Ritchie et al., 1979; Jones et al., 1979) and in the quadriceps (Bigland-Ritchie et al., 1978). In these latter studies, evidence for central fatigue was based on the comparison between voluntary tension and that developed through tetanic stimulation and on changes in the surface electromyographic interference patterns of the muscle. Comparison of voluntary muscle tension with that obtained by tetanic stimulation, in the adductor pollicis muscle, is not without difficulty because of the synergistic actions of other muscles during effort (see above). Experiments of this kind, with the quadricep muscles, also present difficulties, since femoral nerve stimulation was employed in only one subject, the other subjects being tested with surface muscle stimulation, which yields only 50% of the total quadriceps muscle tension. Studies of muscle fatigue of the adductor pollicis muscle by Bigland-Ritchie et al., (1979) and by Jones et al., (1979) have suggested that a substantial reduction in the firing frequencies of motor units may occur during fatiguing contractions, so as to minimize failure of muscle impulse propagation. In the present study, using the twitch interpolation technique, there was no evidence for a significant lack of motor unit activation during the isometric fatiguing contraction. If a reduced motoneurone firing frequency had

occurred in the TA and PF muscles, then it was not pronounced enough to cause muscle torque to decline (fatigue), since no detectable interpolated twitch torque was superimposed on the top of the voluntary torque recording. As recently reported by Bigland-Ritchie et al., (1982) in the adductor pollicis muscle, slowing of the contractile speed, as measured by the relaxation phase of fatiguing maximum voluntary contractions, was seen to parallel the reduction of motor unit firing rate, thereby allowing maximal tension development despite the reduced excitatory drive.

In relation to peripheral sites of fatigue, the present experiments demonstrated preservation of the muscle compound action potential at a time when the twitch torque responses were significantly reduced. Such a discrepancy between the electrical (M-wave) and mechanical (twitch) responses suggested a failure of excitation-contraction coupling and/or contractile machinery during isometric fatigue. Failure of excitation-contraction coupling has long been identified in the frog skeletal muscle following prolonged repetitive stimulation of the muscle at low frequencies (Mashima et al., 1962; Eberstein and Sandow, 1963; Grabowski et al., 1972). These investigators have shown twitch tension to decline progressively to zero values, at a time when propagated muscle action potentials and muscle energy substrates for contraction were still present. That fatigue was caused by a failure of the excitation-contraction coupling, rather than to a failure of the contractile machinery, was demonstrated using the caffeine contracture test. The caffeine agent has been shown to cause release of calcium ions from the sarcoplasmic reticulum, without

affecting the contractile machinery itself (Weber and Herz, 1968). Grabowski and colleagues (1972) have shown, at a time when twitch tension had fallen to 10-20% of normal value during repetitive stimulation, the muscle fibres to develop normal contracture following the addition of caffeine, thus identifying the excitation-contraction coupling failure. In the present study, no distinction could be made between failure of excitation-contraction coupling or contractile machinery. To make such a distinction would have required taking muscle specimens from the TA and PF muscles immediately after the fatiguing contraction and submit these to the caffeine test (Wood, 1978). In 1977, Edwards et al., presented indirect evidence for excitation-contraction coupling failure in the adductor pollicis and quadriceps muscles, during submaximal and maximal fatiguing contractions. They showed, at the time when muscle action potentials were normal and muscle energy substrates were available, a long lasting type of muscle fatigue (up to 24 hours), which was manifested when the muscle was stimulated at low frequencies (20 Hz) rather than at high (100 Hz) frequencies. If excitation-contraction coupling failure is considered as a change in the amount of activation (contraction) per pulse (electrical), the better contractile responses following high frequencies of stimulation probably occurred because the amount of electrical activity (number of pulses) saturated the calcium-releasing mechanism.

D. Tension development of dystrophic PF and DF muscles

Before discussing the contractile properties of patients with

MMD or LGMD, it must be emphasized that muscle biopsies were not taken from any of the muscles tested in the present study. In some patients, needle biopsy specimens had been examined by a neuropathologist (Dr. Grooves) but these were obtained from the lateral vastus or deltoid muscles. Since these specimens were frequently normal at a time when weakness in dorsi-flexion could be demonstrated, the histological component of this study was not pursued. Instead, the dystrophic muscles were assumed to possess characteristics similar to those found in other biopsy studies (for example; Engel, 1962; Engel and Brooke, 1966; Dubowitz and Brooke, 1973; Roses et al., 1979; Bradley, 1979).

1. Patients with myotonic muscular dystrophy

Studies of muscle biopsies from patients with MMD have revealed a variety of pathological muscle changes, including atrophy and loss of type I (slow-twitch) muscle fibres, presence of subsarcolemmal masses, ringed fibres, centrally-placed nuclei, abnormalities of the tubular and sarcoplasmic membranes and interstitial fibrosis (Engel, 1962; Brooke and Engel, 1966; Dubowitz and Brooke, 1973; Harper, 1979; Roses et al., 1979). All of these muscle changes are likely to influence the contractile responses displayed by the affected muscle fibres. As anticipated, the significantly reduced twitch torques, M-waves and voluntary torques in the PF and DF (TA) muscles were consistent with the clinical observation of muscle weakness and atrophy seen in the patients. A more intriguing observation was the disproportionate involvement of PF and DF muscles in individual patients and also between patients. In some patients, usually males, the twitch and voluntary torque values of the DF muscles were virtually abolished while remaining

appreciable for the PF muscles. In other patients, usually female, the trend was in the opposite direction.

Many factors could have contributed to reduced tension generation of muscles affected by the myotonic dystrophic process. Reduced excitable muscle mass, shown by computed tomography scanning in patients with muscular dystrophy (Termote et al., 1980; Bulcke et al., 1981) and by the significantly reduced muscle compound action potentials (M-waves), as in the present study, is probably the most important factor. An impaired tension-generating capacity of the remaining excitable muscle fibres could also have contributed to reduced twitch and voluntary muscle strength. Poor tension generation by the myotonic muscle fibres would be in keeping with the demonstration of such a defect in single skinned muscle fibre of patients with DMD (Wood et al., 1978; Takagi and Nonaka, 1981). Future work involving a study of the contractile responses of skinned myotonic muscle fibres would be of value.

Abnormalities of the transverse tubular system, such as the presence of a network of proliferated tubules, is rarely seen in muscles of patients with myotonic dystrophy (Mussini et al., 1970). In contrast, prominent ultrastructural changes have been described in the sarcoplasmic reticulum and ranged from simple swelling to severe abnormalities of the reticular membrane (Mussini et al., 1979; Korenyi-Both et al., 1975). Sarcoplasmic reticulum abnormalities raise the possibility that calcium regulation for muscle contraction might be impaired. Much is known about the important role of the tubular and sarcoplasmic reticulum systems in releasing calcium ions into the

myofibrillar space, this being necessary for contraction to occur (Huxley, 1974; Desmedt and Hainault, 1968; Endo, 1977; Ebashi, 1980). A defect of the reticular membrane could significantly interfere with calcium ion release and uptake mechanisms, thereby affecting twitch and voluntary tension development in myotonic muscle fibres. In the present study, sarcoplasmic function was indirectly investigated by comparing the twitch potentiation in dystrophic and control TA and PF muscles. As a whole, the PF and TA muscles of patients with MMD showed normal twitch post-activation potentiation responses following brief voluntary contractions. This finding was interesting in that it raised the possibility that twitch potentiation did not depend on added calcium release by the sarcoplasmic reticulum (Desmedt and Hainault, 1968; Rosenfalck, 1974; Ranatunga, 1979; Wallinga-de-Jonge et al., 1981). Other possible explanations for such a discrepancy may be that structural changes in the sarcoplasmic reticulum were insignificant in the present group of dystrophic patients, or, that the remaining excitable muscle fibres in both dystrophic muscle groups were normal. Conclusive experiments will require electron-microscopic examination of single fibres tested for tension production and calcium transients. In single skinned muscle fibres, Wood and colleagues (1978) have already shown calcium regulation by the sarcoplasmic reticulum to be impaired in most fibres of patients with Duchenne dystrophy and of female carriers of this trait.

2. Patients with limb-girdle muscular dystrophy (LGMD)

As with the myotonic group, patients with LGMD showed

considerable disproportionality of muscle tension capacity of both muscle groups, in individual patients as well as between patients. For example, eleven patients showed twitch torque values for the TA muscle within normal ranges while in the remaining patients, no twitch was detectable. The involvement of the TA muscles in these patients with LGMD does not appear to be related to sex or age, since the group of nine patients was composed of five males and four females, aged between 32 and 68 years. This observation would suggest that, at a given stage in limb-girdle dystrophy, the TA muscle is either spared or severely affected. Since intermediate values of twitch torque were rarely observed, it follows that, once muscle degeneration commences in the TA muscle, it usually runs a rapid time course. In contrast, degeneration of the PF muscles, as measured by their ability to generate tension, appears to progress more slowly.

Previous studies of manual muscle strength in patients with LGMD have shown the TA muscle to be weaker than the PF muscles (Dimitrijevic and Granacin, 1968; Bradley, 1979). In the present study, in which objective and quantitative measurements of muscle strength were employed, the DF and PF muscle groups were found to be equally affected by the dystrophic process. Thus, when the whole population of patients was considered, the losses of twitch and voluntary torque were similar in the PF and DF muscles; the relative declines in M-wave amplitude were also similar in the two dystrophic muscle groups. These findings re-emphasized the need for proper muscle strength testing in patients with muscular dystrophy, using mechanical testing devices instead of the traditional manual muscle testing. Also remarkable in the present

investigation was the fact that some dystrophic patients, despite their lack of regular or stressful physical activities, still maintained normal muscle strength. For example, one of the patients with LGMD, a 34 year-old man, was able to develop greater maximum voluntary torque in the PF muscle than any of the control subjects. This observation indicates that, in this patient at least, the enlargement of the calf muscles may be a consequence of true muscle hypertrophy rather than the pseudohypertrophy traditionally postulated. The muscle weakness which characterized patients with LGMD is undoubtedly associated with a reduced excitable muscle mass and this is reflected in the present study by the significantly reduced M-waves; it was also shown by Termote et al (1980) using the computed tomography scanning technique. Future work, using such a muscle scanning technique, is required to determine conclusively whether muscle enlargement in individual patients is due to true hypertrophy or to pseudohypertrophy.

E. Involvement of type I (slow-twitch) and type II (fast-twitch) muscle fibres by the dystrophic process

The issue of muscle fibre type involvement in human muscular dystrophy is an important one for it relates to the hypothesis of 'fibre-type specificity' in muscular dystrophy. This hypothesis rests on findings obtained from two animal models of muscular dystrophy: the avian (chicken) model (Cosmos, 1966; Cosmos, 1970; Cosmos et al., 1979; Wilson et al., 1979) and the murine (mouse) model (Brust, 1966; Butler and Cosmos, 1977). In the dystrophic chicken, Cosmos and colleagues have clearly shown the fast-twitch muscles to be affected by the

dystrophic process while the slow-tonic muscles were spared the expression of dystrophic phenotypes. To date, there has been no investigation of the phenotypic expression of dystrophy between fast-twitch and slow-twitch muscle fibres in the avian model. In the dystrophic mouse, however, comparisons of fibre type involvement have been made between fast-twitch and slow-twitch muscles (Brust, 1966; Butler and Cosmos, 1977). In the 129/Rej dy/dy strain of mouse, the fast-twitch glycolytic fibres (located in the crown portion of the tibialis anterior muscle) have been shown to be preferentially affected. In the C57BL/6J dy2j/dy2j strain, however, the fibres most susceptible to dystrophy are the slow-twitch fibres located in the core portions of the soleus and tibialis anterior muscles. Eventually, however, fibres of both types become extensively involved by the dystrophic process.

1. Patients with myotonic muscular dystrophy

Evidence for preferential involvement of slow-twitch muscle fibres in human myotonic dystrophy was first reported by Engel and Brooke (1966). They noted, in approximately half of the cases examined, that slow-twitch fibres (type I) were both atrophied and reduced in number, and that fast-twitch fibres (type II) were hypertrophied (see also Dubowitz and Brooke, 1973; Harper, 1979; Roses et al., 1979). In keeping with these histological observations, the present study has demonstrated briefer twitch contraction times in dystrophic TA and PF muscles, suggesting preferential involvement of slow-twitch (type I) fibres in myotonic muscular dystrophy. The present finding of preferential slow-twitch (type I) muscle fibre involvement by the

myotonic process must be weighed, however, against the total elimination of contractile responses in both fast-twitch and slow-twitch fibres of some of the tibialis anterior muscles. As with the animal models of muscular dystrophy, selective fibre-type involvement in human muscular dystrophy may be dependent on the stage of the disease. Future work could involve the investigation of twitch contraction time in patients grouped according to the onset of the disease.

Alternatively, serial observations could be made on individual patients, with correlative fibre-typing of muscle specimens obtained by needle biopsy from TA and soleus muscles. Although measurements of twitch speed cannot rival muscle biopsy in determining muscle fibre composition, it is, nevertheless, a non-invasive technique which provides some information on this point. However, fibrosis and other gross structural abnormalities in these muscles could also affect the time course of the twitch. In the present study, the ratio between maximum voluntary torque (MVC) and twitch torque (PT) was used to assess the relative changes in the muscle series-elastic component in control subjects and dystrophic patients. The mean MVC:PT ratios of both the TA and PF muscles were seen to be normal in the dystrophic patients, suggesting that changes in the series-elastic component had no significant effect on the measurements of twitch contraction time and half-relaxation time. An adequate determination of the series-elastic component in human muscle in situ is difficult. My approach to this problem was to measure the maximum voluntary torque to twitch torque (MVC:PT) ratio in both PF and DF muscle groups. This ratio is influenced by the muscle series-elastic component in that during a

single maximal twitch, much of the contractile tension is expended in stretching the elastic elements within the muscle and tendons, rather than developing optimal tension at the attachments of the tendons. During maximum voluntary contraction, however, there is sufficient time for the elastic component to be fully stretched and for maximum tension to be developed. Thus, changes in the series-elastic component are expected to affect the MVC:PT ratio, since twitch torque, but not maximum voluntary torque, is affected by the elastic elements. Another approach to this problem would have been to measure the passive length:tension relationship of both PF and DF muscles. This technique consists of passively stretching the muscles from a shortened to a lengthened position, while recording the passive resistance (tension) encountered during the movements of the joint. Thus, a stiffer series-elastic component would yield a greater passive tension than normal for similar increments in muscle-tendon length. Although both techniques would yield information pertaining to muscle elasticity, they would fail to identify where this elasticity resided. Recently, Foidart et al., (1981) have investigated collagen localization of normal and dystrophic muscles, using biopsied specimens from the biceps brachii. They showed that muscle contractures resulted from increased muscle fibrosis in muscles of patients with Duchenne dystrophy. Foidart and colleagues (1981) have shown the fibrosis to be caused by an accumulation of type I and type III collagen in the perimysial and endomysial layers of the muscle. Type I collagen has been shown to be prominent in the tendon while type III collagen is abundant in the skin (Fietzeck and Kunh, 1976). As stated by Foidart and colleagues,

collagen is probably one of the major contributors to the elastic and tensile properties of the muscle-tendon complex. To the best of my knowledge, there has been no study of fibrosis and collagen localization in muscles of patients with myotonic dystrophy.

2. Patients with limb-girdle muscular dystrophy

Previous studies of muscle biopsies of patients with LGMD have provided evidence of preferential involvement by the disease of fast-twitch (type II) muscle fibres as opposed to slow-twitch (type I) fibres (Dubowitz and Brooke, 1973; Bradley, 1979). On theoretical grounds, the twitch contraction times would be expected to be prolonged in these dystrophic muscles. In the present study, twitch contraction times of both dystrophic TA and PF muscles were not seen to be significantly different from those of the control subjects, suggesting that both types of muscle fibres were equally affected. The above findings are in agreement with those of Desmedt (1967) who showed normal values of twitch contraction and half-relaxation times in the adductor pollicis muscle of patients with LGMD. The results obtained in the present investigation were contrary to those of Sica and McComas (1971) who showed prolonged contraction and half-relaxation time values in the extensor hallucis brevis of patients with LGMD. The discrepancy between their findings and those of the present study may be explained in several ways. For example, the present investigation was based on a larger group of patients who were more adequately matched to control subjects. As with the patients with MMD, the MVC:twitch ratios in both the DF and PF muscle groups of LGMD patients were normal, thereby suggesting that any alterations in the series-elastic component had no

significant consequences on the measurement of twitch contraction time. The lack of agreement between the results of the present investigation and those of Sica and McComas (1971) may also have reflected the different muscles chosen for investigation.

F. Relationship between muscle tension development and its electrical response in dystrophic PF and TA muscles

1. Patients with myotonic muscular dystrophy

In a normal muscle, the cross-sectional area is mainly occupied by myofibrils (Adams, 1973), but this is not always true in muscles affected by myotonic dystrophy. As shown by Engel (1962) and by Engel and Brooke (1966), a proportion of myotonic muscle fibres are characterized by the presence of subsarcolemmal masses which are devoided of contractile material. On theoretical grounds, muscle fibres with subsarcolemmal masses would be expected to present a disproportion between tension development and muscle electrical response. The presence of subsarcolemmal masses would reduce the contractile responses of fibre but would not interfere with the ability of the fibre to propagate impulses. My approach to this problem was to compare maximum muscle electrical response (M-wave) with its contractile output (twitch torque). In the present investigation, the mean twitch:M-wave ratios were found to be similar, for the TA and PF muscles, between the control and dystrophic subjects. However, a striking observation was that in three patients, M-waves were associated with no detectable twitches in the TA muscle. The latter finding is the first to suggest an electro-mechanical uncoupling in muscles of patients with MMD.

2. Patients with limb-girdle muscular dystrophy

Studies of contractile function in patients with LGMD by Desmedt (1967) and by Takamori et al., (1975;1978) have disclosed contractile abnormalities at a time when no alteration of the muscle action potentials (M-waves) was present. The above investigators have examined the twitch time course (Takamori et al., 1975,1978) and the staircase phenomenon (Desmedt, 1967) in the adductor pollicis muscles of patients with LGMD. Takamori and collaborators (1975,1978) observed a markedly reduced rate of twitch tension development while Desmedt (1968) showed little, if any, potentiation of the twitch after repetitive stimulation (2 Hz, positive staircase) in the dystrophic adductor pollicis muscle. On the basis of these results, the above authors have postulated a disorder of excitation-contraction coupling in muscles affected by the limb-girdle dystrophic process. An excitation-contraction coupling disorder could reflect an impaired ability of the sarcoplasmic reticulum to release calcium ions into the myofibrillar space. In the present study, the mean twitch:M-wave ratios of TA and PF muscles were similar in patients with LGMD and in control subjects. Furthermore, the extent of post-activation potentiation (PAP) of the twitch after voluntary effort was also within the normal range in the dystrophic muscles. Together, these findings indicated normal electro-mechanical coupling in the PF and TA muscles of patients with LGMD, and did not support the conclusions reached by Desmedt (1967) and Takamori et al., (1975,1978) in their studies of the adductor pollicis muscle. Because of the considerable variability of pathological muscle changes between

patients, however, it is difficult not to exclude a disorder of excitation-contraction coupling in occasional patients or in a small proportion of muscle fibres. All that can be said is that partial uncoupling does occur in LGMD, and that it is not a prominent feature of the TA and PF muscles. The discrepancy between the present results and those of Desmedt (1967) and of Takamori and colleagues (1975,1978) may be due to the fact that different muscles were investigated and that in the present investigation, a larger number of patients, covering a greater age span, were investigated. Furthermore, Desmedt's (1967) study lacked information on the number, sex and age of his patients, while Takamori and colleagues only investigated patients aged 20 to 39 years. In neither of these studies were the control subjects matched for age, sex, weight and height.

G. Use of available muscle mass during maximum voluntary contractions of PF and DF muscles in patients with MMD and LGMD

Although considerable muscle weakness was anticipated in patients with LGMD, it remained possible that, during maximum voluntary contraction, motor units were not activated as fully as in the normal subjects. This possibility was explored using the interpolated stimulus technique, previously employed by Merton (1954), on the adductor pollicis muscle. In the case of the TA muscle, patients with MMD and LGMD resembled control subjects in being able to activate their tibialis anterior muscles fully. The results for the PF muscles differed, however, in that only 28% of the patients with myotonic dystrophy could realize their maximum potential torque; this value was significantly

different from the value of 48% obtained with the matched control subjects. In the case of the PF muscles of patients with LGMD, 35% of both affected patients and control subjects were able to activate their motor units fully.

During the course of maximum voluntary isometric strength testing, I observed that most patients with MMD or LGMD were only able to develop a fraction of their ultimate voluntary torque at the first attempt; instead several repetitions were required before their maximum strength could be achieved. The fact that motor unit activity could be increased by repeated voluntary effort during one experimental session, indicated that the failure to achieve greater muscle strength was not a consequence of any structural changes in the descending motor pathways or in their synaptic connections. It also indicated that, in patients with moderately severe muscle weakness, the relatively few movements attempted throughout the day may well render motoneurons transiently incapable of sudden maximal activation. This conclusion is in keeping with those reached by Fulgsang-Frederiksen and Scheel (1978) and by Sale (1979) who have studied the effects of muscle inactivity in healthy adult subjects. Fulgsang-Frederiksen and Scheel (1978) have suggested that the rapid increase of muscle strength, seen after the first day following the removal of a plaster cast, was due to a transient inability of some motor units to be activated during voluntary effort. Thus, using coaxial EMG needles to explore the affected muscles, they showed that the volitional interference patterns were reduced during the phase of weakness and improved as strength returned. Further support for their conclusion was that the increase in muscle strength was too

large and happened too rapidly to be due to an increase of muscle cross-sectional area in atrophic muscle fibres. Using the reflex potentiation technique introduced by Upton and colleagues (1971), Sale (1979) showed decreased reflex potentiation of thenar muscles in arms immobilized by plaster casts. This reduced reflex potentiation correlated with reduced muscle maximum strength, but contrasted with the preservation of normal twitch torques. Sale (1979) postulated that a reduced ability to recruit and fire motor units may have caused the reduction in reflex potentiation following muscle inactivity. The observation in the present study, that some dystrophic patients generated greater muscle strength after repeated trials, has therapeutic implications, for it suggests the possibility of better muscular performance through the adoption of appropriate exercise regimes. It also suggests that muscle strength in patients with muscular dystrophy may sometimes be underestimated, unless several attempts are made by the patients during strength testing.

H. Susceptibility to isometric fatigue of PF and DF muscles in patients with MMD and LGMD

Of all the aspects of contractile function, studies of muscle fatigue have been most neglected in human muscular dystrophy. This is rather surprising since, apart from complaining of muscle weakness, patients with muscular dystrophy also complain of muscle fatigue. After an extensive search of the literature, I have found only one study of muscle fatigue in human dystrophic patients, that of Blank et al., (1981). In the study, Blank and colleagues asked six patients with LGMD to sustain an isometric contraction (20% of maximum voluntary tension)

until complete exhaustion. With a teflon-coated needle electrode inserted into the belly of the biceps brachii muscle, Blank and collaborators showed the electromyographic response (compensatory recruitment of motor units) to be similar in both dystrophic and control muscles, following sub-maximal isometric fatiguing contractions. Unexpected in the present study was the fact that patients with MMD and LGMD showed normal fatigue behaviour following maximum voluntary contractions lasting 60 seconds. No significant differences were seen in either the extent or the rate of decline of voluntary torque, the DF muscles presenting, in control subjects, much less resistance to fatigue than the PF muscles.

As with the control subjects, the major sites for isometric fatigue in both the DF and PF muscle groups of patients with LGMD were peripheral rather than central, as motor unit activation was well maintained until the end of the fatiguing contraction. Immediately after the end of the fatiguing contraction, the M-waves of TA and PF muscles were spared at a time when the twitch torques were very much reduced. The measurement of muscle compound action potential (M-waves) reflects the integrity of neuromuscular transmission and of muscle impulse propagation following isometric fatiguing contraction. Twitch torque, however, depends not only on adequate excitation of muscle fibres but also on effective excitation-contraction coupling, and contractile tension generation. Thus, comparisons between the M-waves and twitch torques indicated whether fatigue was due to failure at the neuromuscular transmission or plasmalemma on the one hand, or at sites of excitation-contraction coupling and/or contractile machinery, on the

other. In the present study, the findings pointed to a disorder of excitation-contraction coupling and/or contractile machinery, as the major cause of isometric muscle fatigue in patients with MMD and LGMD. No distinction could be made between these two sites of possible failure; further experiments would require the study of isolated muscle fibres in which contractures would be produced by caffeine or some other agent (Wood, 1978).

Finally, the extent of recovery of both twitch and voluntary strength after one minute of rest following fatigue was seen to be similar to that observed in the control subjects. These findings would suggest adequate recovery mechanisms in muscles of patients with MMD and LGMD.

I. Distinction between muscle contractile properties of patients with MMD and LGMD

One of my aims in conducting the present study was to identify any distinction between the contractile muscle behaviour of patients with MMD and LGMD. Such a distinction, based on testing of twitch and volitional muscle performance, would be an useful addition to the existing anatomical, biochemical and electromyographic diagnostic tools for human muscular dystrophy, particularly in mildly affected patients not exhibiting the classical features of either condition. Unfortunately, no statistically significant differences could be discerned between the contractile properties of muscles of patients with MMD and LGMD. This finding was undoubtedly a consequence of the considerable variability of PF and DF contractile responses observed

within the same patient and also between patients. The above finding, however, does not imply that differences in muscle involvement do not exist between patients with well-established syndromes of MMD and LGMD. Apart from the characteristic clinical features of patients with myotonic dystrophy (for example, frontal baldness, cataract, gonadal atrophy), there is the well known preferential involvement of the distal muscles, as opposed to the proximal muscle involvement of patients with LGMD.

VI. CONCLUSIONS

The general purpose of the present study was to provide a better understanding of muscle contractile function in healthy subjects and in patients with myotonic (MMD) or limb-girdle muscular dystrophy (LGMD). To fulfil this aim, twitch and voluntary contractile responses were investigated in the ankle plantar-flexor (PF) and dorsi-flexor (DF) muscles. The following conclusions relate to eleven specific questions (see section THE PRESENT STUDY and below).

Control group: thirty-one men and fifteen women

The first two questions asked in the present investigation were: (1) are twitch properties of TA and PF muscles different and (2) are PF and DF muscle groups equally strong? The present study has disclosed clear differences in the twitch properties between these two opposing leg muscle groups. In contrast to the plantar-flexor (PF) muscles, the tibialis anterior (TA) muscle demonstrated smaller twitch torque, shorter twitch contraction and half-relaxation times, and marked twitch post-activation potentiation. This is the first time that twitch potentiation has been demonstrated following a brief maximum voluntary contraction in normal and dystrophic human muscles. The PF muscles were three time stronger than the DF muscles when maximal voluntary contractions were compared; the mean PF twitch torque was nine time as large as that of the TA muscle.

The third question to be considered was: "can motor units of TA

and PF muscles be fully activated during the course of a maximum voluntary isometric effort?". The present study, in which the interpolated stimulus technique was used, has clearly shown that motor units belonging to the TA muscle were easily and fully activated by almost all subjects. In contrast, motor units comprising the PF muscles were fully activated in only half of the subjects and usually with greater difficulty. The present investigation is the first to have validated and employed the interpolated stimulus technique for the study of motor unit activity of PF and TA muscles during maximum voluntary contractions.

The fourth question to be addressed was: "are the DF and PF muscle groups equally susceptible to isometric fatigue during sustained maximum voluntary contractions?". Results from the present study have disclosed that the PF muscles were more resistant to fatigue than were the DF muscles. In relation to the controversial issue of the mechanism of fatigue, the present investigation has identified level of excitation-contraction coupling and/or contractile machinery as being the major site(s).

The fifth question to be dealt with was: "what are the influences of age and sex on the contractile properties of these two muscle groups?". Women were different from men in developing smaller DF and PF torques, both during maximal voluntary effort and following indirect stimulation. The twitch contraction times of PF muscles were longer in women than in men. Maximum voluntary isometric strength of PF and DF muscles began to decline in the sixth decade of life. Within the fifth and sixth decades, twitch contraction times of PF muscles were

prolonged. There was no significant effect of age on the ability to activate motor units and on muscle fatigue behaviour.

Dystrophic groups: twenty-five patients with MMD and twenty patients with LGMD

The two following questions are particularly important for they relate to the hypothesis of 'muscle fibre-type specificity' in muscular dystrophy. Thus the sixth question was: "are the DF and PF muscle groups similarly affected by the dystrophic process?". The present study has clearly shown that in any one patient at a given stage, the dystrophic process (MMD or LGMD) is capable of virtually destroying one muscle group while sparing another, regardless of their respective functions and fibre-type compositions. The seventh question is a related one, namely: "is there preferential involvement by the dystrophic process of either fast-twitch (type II) or slow-twitch (type I) muscle fibres in either of the muscle groups?". On the basis of the twitch speeds, it was concluded that the myotonic dystrophic process preferentially affected slow-twitch (type I) fibres in both TA and PF muscles. In contrast, there was no evidence for preferential involvement of one fibre-type over the other in muscles of patients with LGMD.

The eighth question was: "can patients with MMD or LGMD make full use of their available muscle mass during the course of a maximum effort?". The results indicated, in some patients with MMD, that there was a significant inability to activate motor units during the first few attempts. Following additional attempts, patients became able to make

full use of their remaining excitable muscle mass. The present investigation is the only one to have provided insight into the ability of dystrophic patients to activate their available muscle mass.

The ninth question to be considered was: "is the tension generated by the dystrophic muscle proportional to its electrical response?". The present results of twitch torque:M-wave ratio and of twitch potentiation showed no evidence for electro-mechanical uncoupling, in PF and TA muscles of most patients with MMD or LGMD. In some patients there did appear to be uncoupling.

With regard to the tenth question: "what are the isometric fatigue behaviours of dystrophic PF and DF muscle groups?", the conclusions were similar to those of control subjects. In patients with either MMD or LGMD, the DF muscles were less resistant to fatigue than the PF muscles, and sites of fatigue were peripheral at the level of the excitation-contraction coupling and/or contractile machinery.

As far as the last, eleventh, question was concerned: "can patients with MMD or LGMD be distinguished on the basis of their contractile properties?" the answer was negative, mainly because of the considerable variability of contractile responses observed between patients.

To summarize, the present investigation is the first to have comprehensively examined the contractile properties of two antagonistic leg muscle groups, and this has been achieved both in control and in dystrophic subjects. In contrast to other studies of muscle contractile function in human dystrophy, the present study is the first to have

adequately matched control subjects for important variables such as age, sex, weight and height. The present investigation of 25 patients with MMD and of 20 patients with LGMD is more substantial than any other previous studies of this kind. Since these patients were only ones with MMD or LGMD known to the muscular dystrophy clinic, there was no known bias of selection. Furthermore, their ages ranged from 19 to 68 years.

The present protocol of investigation provides, in a non-invasive way, comprehensive and quantitative information about the contractile properties of human muscles. It must therefore be considered an important adjunct to the existing methods of monitoring the time course of human dystrophy, and of assessing any therapeutic benefits.

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DEFINITION OF TERMS

1. Active state: conceptual term which reflects the intensity and time course of the tension generating capacity of the contractile machinery, in the absence of the series-elastic component.

2. 'Back response': mechanical response due to re-stimulation of intra-muscular nerve endings elicited by synchronous electrical activity, such as in a twitch. The mechanical response to a single nerve stimulus, therefore, is not a true twitch, but a double contractile response with distorted features.

3. Contraction time (CT): period of time from the onset of twitch torque (or tension) to maximum torque development.

4. Peak twitch torque (PT): maximum twitch torque obtained following the delivery of a maximum electrical stimulus to the nerve.

5. Half-relaxation time (1/2 RT): period of time taken for maximum twitch torque to drop half of its maximum value.

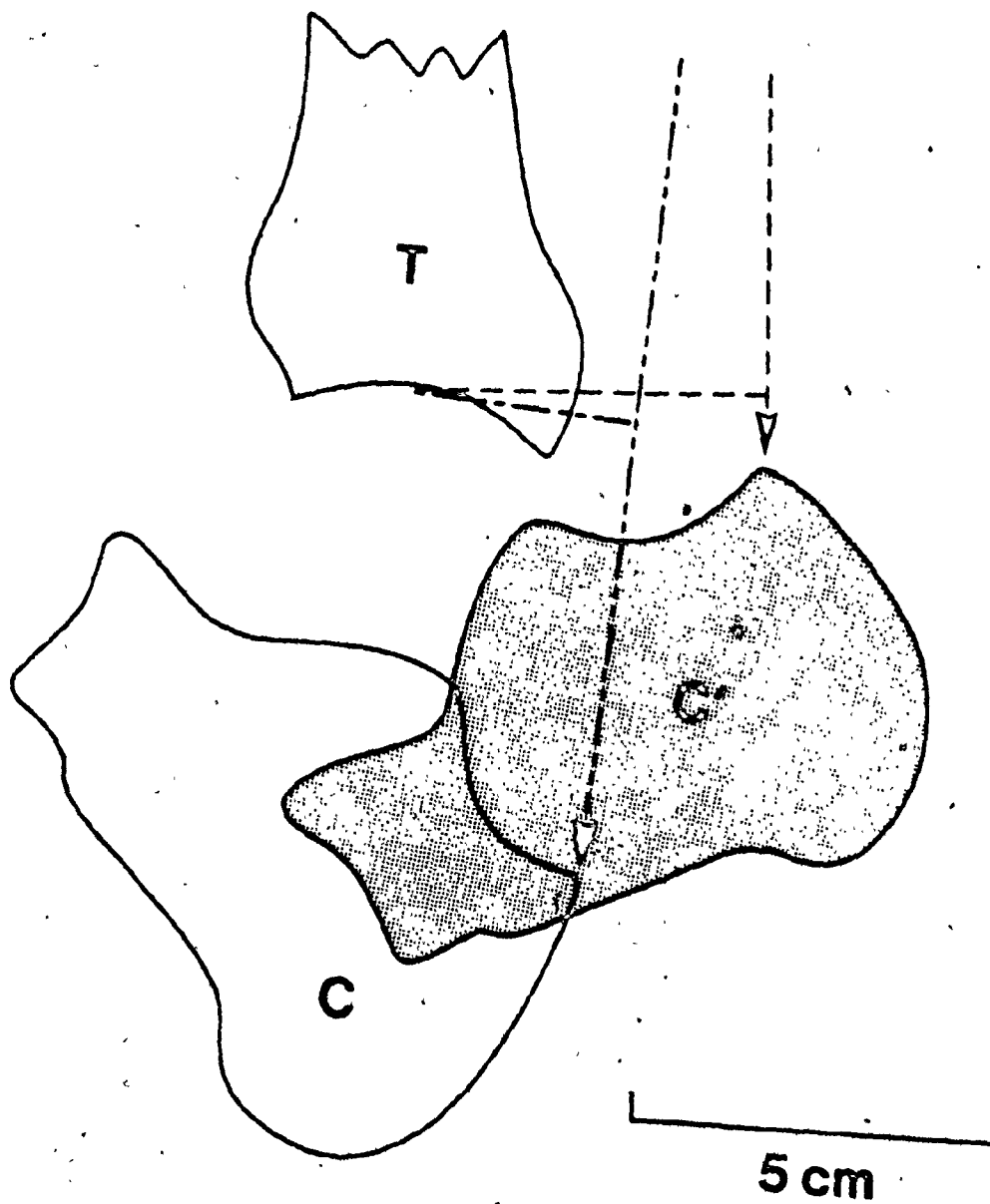
6. Muscle compound action potential (M-wave): the evoked electrical impulse activity resulting from a single maximal stimulus to the appropriate motor nerve.

7. Post-activation potentiation (PAP): enlargement of twitch torque value after (5 seconds of) maximum isometric voluntary contraction.

8. Staircase phenomenon: progressive decline (negative staircase) followed by progressive enlargement (positive staircase) of twitch torque following nerve stimulation given at low rates, such as 2 to 3 per second.

Appendix I

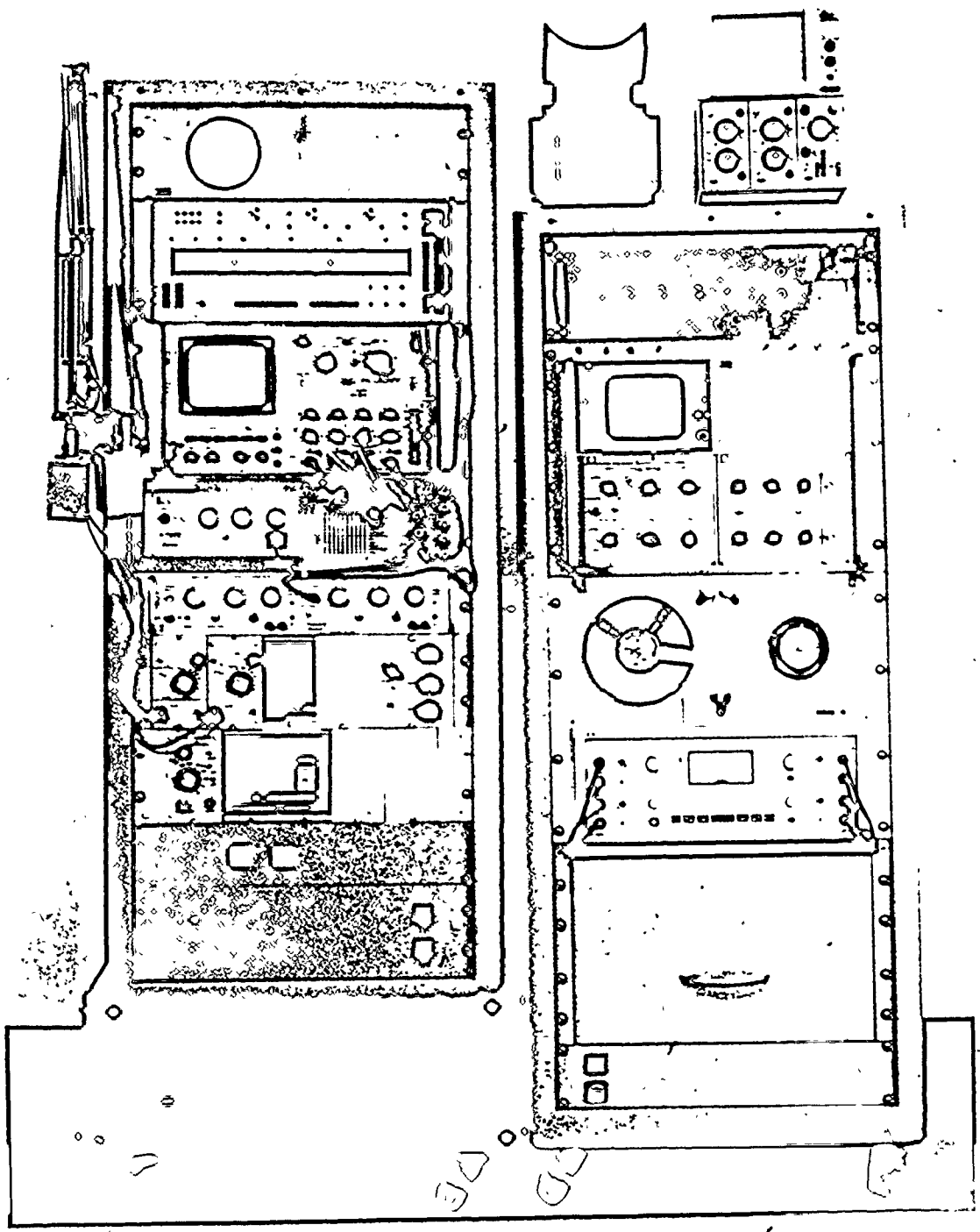
Superimposed tracings of radiographs showing the position of the calcaneum (C,C') relative to tibia (T) with the ankle fully dorsi-flexed or plantar-flexed (talus omitted). Arrows indicate the posterior margin of insertion of the Achilles tendon. The interrupted lines show the respective lever arms, and directions of muscle pull, in the dorsi-flexed and plantar-flexed positions (see text). Note the longer lever arm with the ankle joint almost fully plantar-flexed.



Appendix II

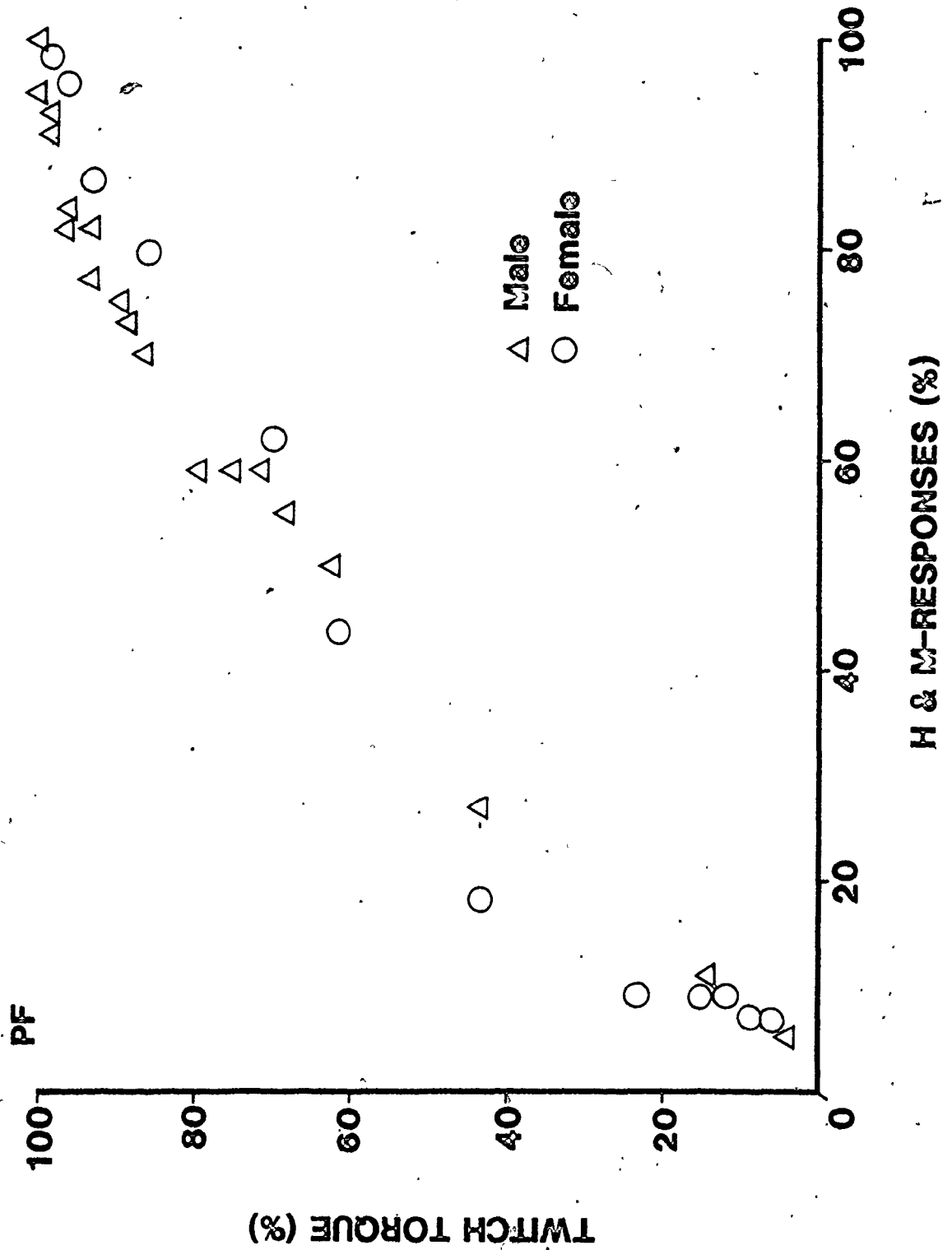
This photograph shows the major pieces of equipment used in this study, except for the ankle torque-measuring devices (see Figures 1 and 2).

Left: from top to bottom; (1) loudspeaker, (2) digitimer (Devices Ltd., type 3290), (3) Hewlett-Packard oscilloscope (141B) incorporating time-base (1422A) and plug-in amplifiers (1404A), (4) gated pulse generator (Devices Ltd., type 2521) and switch box, (5) two high voltage stimulators (Devices Ltd., type 3070), (6) two low-noise EMG amplifiers and audio-amplifier (laboratory-built). Right: from top to bottom; (1) Polaroid camera and portable oscilloscope (Tektronix Inc.), (2) signal analyzer (Hewlett-Packard, model 5480B and (3) magnetic tape recorder (Hewlett-Packard).



Appendix III

Twitch torque as a function of combined reflex (H) and motor (M) responses (expressed in % of maximum values) in two control subjects, using the same stimulating and techniques described in the Subjects and Methods section. The values of twitch torque and electrical responses were obtained by progressively increasing the stimulus intensity until maximum values were obtained. The almost linear relationship between these two parameters indicated that the amplitude of the muscle compound action potential is a satisfactory index of excitable muscle fibre mass.



Appendix IV

Summary of reproducibility of measurements made on PF and DF muscles of five subjects, on two separate days.

1. Calculation of method error (ME):

$$ME = \sqrt{\sum (d - \bar{d})^2 / 2 (n - 1)}$$

2. Calculation of coefficient of variation (CV) in %:

$$CV = \frac{ME}{(\bar{x}_1 + \bar{x}_2) / 2} \times 100$$

d= differences between the two measurements in each subject

\bar{d} = mean difference

n= number of subjects

\bar{x}_1 = mean results of the first testing session

\bar{x}_2 = mean results of the second testing session

2

PARAMETERS		COEFFICIENTS OF VARIATION (%)	
Height		0.18	
weight		0.44	
		PF	DF (TA)
Resting	PT	3.51	3.90
	CT	4.01	4.16
	1/2 RT	7.50	1.90
	M-w	13.2	25.5
Potentiated	PT	8.84	7.83
	CT	3.95	7.30
	1/2 RT	8.26	6.20
	M-w	5.92	14.88
MVC		4.94	3.45
MUA		4.31	-
MVC after fatigue		3.63	8.99
Fatigue; control	PT	10.7	23.4
	control M-w	9.16	21.2
	MVC at 60s	17.26	14.72
	MUA at 60s	5.6	-
After fatigue;	PT	6.61	27.2
	M-w	20.4	25.2
	MVC	2.87	4.97