THE EFFECTS OF AGEING AND NUTRITIONAL STATUS ON VOLUNTARY MUSCLE FUNCTION TESTS USING HUMAN ADDUCTOR POLLICIS MUSCLE

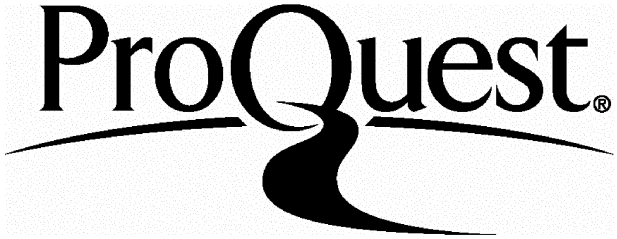
Stuart Alexander Bruce

A thesis presented for the degree of Doctor of Medicine in the University of London

Department of Physiology, University College London

& Department of Medicine for the Elderly, Conquest Hospital, St. Leonards-on-Sea

1993



ABSTRACT

Maximum voluntary force and cross-sectional area (CSA) of adductor pollicis muscle have been measured to examine the weakness associated with ageing and that associated with subnutrition, in six groups of subjects: 1) fit young, 2) fit elderly, 3) subnourished young, 4) elderly hip fracture patients, 5) post-menopausal women not receiving hormone replacement therapy, 6) post-menopausal women on hormone replacement therapy.

In normally nourished young adults no sex difference was found in the force produced for a given cross-sectional area of adductor pollicis muscle. Likewise subnourished young adults produced the same force/CSA as their normally nourished counterparts. Pre-menopausal women and the subnourished produced lower forces but this was because they had smaller muscles.

In contrast the elderly had a lower force/CSA. This reduction was particularly marked in those with osteoporotic fractures. As women are more prone to these fractures we predicted that a sex difference might be found with ageing and we have demonstrated this to be in the time-course of the decline in force/CSA. In women the decline was clearly related to the menopause. In men it was more gradual and its onset later.

Possible causes for a low force/CSA are:

1) incomplete muscle activation - the force is not maximal. This was excluded in our weak elderly subjects using twitch interpolation.

2) replacement of the muscle with non-contractile tissue - the CSA is artefactually

large. This was excluded by showing that the force obtained during stretch of the actively contracting adductor pollicis muscle is greater as a proportion of the isometric force in weak post-menopausal women than in young adults. This therefore suggests that the low force/CSA in these subjects is due to:

3) a change in cross-bridge function.

Finally we found that the force/CSA in post-menopausal women is maintained by oestrogen replacement therapy suggesting that the change in cross-bridge function is hormonally mediated.

CONTENTS

DEDICATION 9

ACKNOWLEDGEMENTS 10

INTRODUCTION 12

CLINICAL MUSCLE FUNCTION 13

VOLUNTARY MUSCLE FUNCTION TESTING 16

HAND-GRIP 19

PLANTAR-FLEXORS 20

KNEE-EXTENSORS 20

ADDUCTOR POLLICIS 27

SKELETAL MUSCLE FUNCTION AND SUBNUTRITION 29

HUMAN SKELETAL MUSCLE AND AGEING 34

A NOTE ON THE PRESENTATION OF DATA REVIEWED IN THIS SECTION 34

VOLUNTARY MUSCLE FORCE 35

a) HAND-GRIP 35

b) KNEE-EXTENSORS 42

c) CALF MUSCLES 48

d) ELBOW-FLEXORS 50

e) SUMMARY 50

MUSCLE SIZE 52

WHAT IS THE CAUSE OF THE WASTING? 58

a) FIBRE ATROPHY 58

b) FIBRE LOSS 58

i) HISTOLOGICAL STUDIES OF MUSCLE 58

ii) MOTOR-UNITS 63

FORCE AND CROSS-SECTIONAL AREA IN HUMAN AGEING MUSCLE . . . 67

a) KNEE-EXTENSORS 67

b) ANKLE PLANTAR FLEXORS 70

c) BICEPS 71

d) SUMMARY 71

POSSIBLE CAUSES OF A REDUCED FORCE/CSA 72

a) REPLACEMENT OF MUSCLE BY NON-CONTRACTILE TISSUE . . 72

b) INCOMPLETE ACTIVATION 76

i) COMPARING MAXIMAL VOLUNTARY WITH MAXIMAL STIMULATED CONTRACTIONS 76

ii) INTERPOLATING TWITCHES DURING A MAXIMAL VOLUNTARY CONTRACTION 77

c) A CHANGE IN MYOSIN ISOFORMS 78

d) METABOLIC CHANGES 81

OTHER CONTRACTILE PROPERTIES OF STIMULATED MUSCLE 90

STUDIES OF AGING ANIMAL MUSCLE 93

a) WASTING 93

i) FIBRE NUMBER AND SIZE 93

ii) MOTOR UNITS 94

b) FORCE/CSA 95

POSSIBLE CAUSES OF A REDUCED FORCE/CSA 97

a) REPLACEMENT OF MUSCLE WITH NON-CONTRACTILE TISSUE 97

b) INCOMPLETE ACTIVATION 97

c) A CHANGE IN MYOSIN ISOFORMS 98

d) METABOLIC CHANGES 101

CONCLUDING INTRODUCTORY REMARKS 104

METHODS 106

1. FORCE MEASUREMENT 106

2. CROSS-SECTIONAL AREA MEASUREMENT 112

3. TESTING FOR FULL ACTIVATION 122

4. MEASUREMENTS OF FORCE AT DIFFERENT VELOCITIES OF STRETCH DURING A MAXIMAL VOLUNTARY CONTRACTION 124

5. STATISTICS 128

SUBJECTS 129

RESULTS 130

1. FORCE AND CROSS-SECTIONAL AREA MEASUREMENTS IN YOUNG MALES AND FEMALES 130

2. NUTRITION STUDY 132

a) MVF/CSA 132

b) MVF/HEIGHT 134

c) MAXIMAL HANDGRIP/ARM MUSCLE AREA 134

d) MAXIMAL RELAXATION RATE 137

e) FATIGUE 137

3. COMPARING FORCE AND CROSS-SECTIONAL AREA BETWEEN YOUNG AND VERY ELDERLY SUBJECTS 138

4. ACTIVATION STUDY OF WEAK VERY ELDERLY SUBJECTS 141

a) YOUNG SUBJECTS 141

b) ELDERLY SUBJECTS 143

5. FORCE AND CROSS-SECTIONAL AREA IN VERY ELDERLY HIP FRACTURE PATIENTS 147

6. THE TIME-COURSE OF THE DECLINE IN FORCE/CSA IN MEN AND WOMEN 149

7. THE EFFECT OF HORMONE REPLACEMENT THERAPY ON FORCE/CSA IN WOMEN 151

8. THE EFFECT OF APPLYING STRETCH DURING A MAXIMAL VOLUNTARY CONTRACTION IN WEAK POST-MENOPAUSAL WOMEN . 153

DISCUSSION 155

FORCE/CROSS-SECTIONAL AREA MEASUREMENTS IN NORMALLY NOURISHED YOUNG ADULTS 155

a) ANATOMICAL MODEL 155

b) SIMULATED FORCE AND CROSS-SECTIONAL AREA MODEL . . 167

MUSCLE FUNCTION AND NUTRITIONAL STATUS 171

MUSCLE FUNCTION AND AGEING 175

TWITCH INTERPOLATION IN ELDERLY SUBJECTS 176

MUSCLE FUNCTION AND OSTEOPOROSIS 178

THE TIME-COURSE OF THE DECLINE IN MVF/CSA WITH AGE 180

SEX HORMONES AND MUSCLE 181

THE RELATIONSHIP BETWEEN MUSCLE ENERGY METABOLISM AND FORCE/CSA 184

THE STRETCH EXPERIMENT 185

THE STRETCH EXPERIMENT IN AGEING MUSCLE 195

CONCLUSION 204

REFERENCES 208

SUPPORTING PUBLICATIONS . . . . . *after 243*

for Carole and James and Hannah

This is, therefore, the intensest rendezvous.

It is in that thought that we collect ourselves,

Out of all the indifferences, into one thing:

Wallace Stevens

ACKNOWLEDGEMENTS

This study has its origin in discussions I had with Dr Gordon Sladen about the difficulties of individual quantitative nutritional assessment, in particular in the elderly. He drew my attention to the work of Jeejeebhoy's group wherein I saw the opportunity to combine a clinical study with an enthusiasm for the physiology of skeletal muscle kindled during my intercalated BSc course at UCL by association with the likes of Sir Andrew Huxley, Sir Bernard Katz, Prof Doug Wilkie, Prof Brian Jewell and most closely Prof Roger Woledge.

The results presented here are those of a collaboration. I make no apology for this. It was perhaps one of my wider purposes to demonstrate that such a collaboration (between academic and clinician, moreover district hospital clinician) can not only bear fruit but also ask fundamental bio-medical questions in the context of applied research. This was something I had aspired to as a student and which was firmly discouraged by the academic clinical teachers with whom I discussed it at the time.

My principal collaborator is Roger Woledge. Indeed without his initial enthusiasm and insight into the project it is unlikely to have got beyond the stage of being a "good idea". His contribution will be evident in all aspects of the work presented but in particular the computer modelling would not have been realised without his help. His patient comments on the manuscript have greatly added to its clarity. It goes without saying that the remaining confusions and obscurities are my responsibility. My other main collaborator is Dr Suzanne Phillips, a practical scientist of much ability and enthusiasm who it has been a great pleasure to watch grow and mature throughout the

duration of the project. Dr Mike Hutchinson and Dr Simon Johnson helped greatly at the start of the anatomical study and Mr Nick Siddle with the menopause study. Mr David Newton, Ms Karen Rook, Dr Rashbal Ghottaora, Dr Aziz Sheik, Ms Shirley Rice, Ms Jackie Ashmore and Mr James Rowbery helped at various stages with data collection and Dr Michael Wilson by writing the extension to the Nicolet PC31 computer programme used in the nutrition study. The photographic assistance of Mr Wilf Francis at UCL and of the Medical Illustration Unit of the Hastings and Rother NHS Trust is gratefully acknowledged as is the technical assistance of Mr Duncan Farquharson. Fig 1 is reproduced by kind permission of The Cambridge University Press. Finally the project would not have been possible without generous financial support from Action Research, South-East Thames Regional Health Authority and Research into Ageing.

INTRODUCTION

At the very beginning of the journey, already far off the main highway, as I walked along the path that leads to Galta, past the little grove of banyan trees and the pools of foul stagnant water, through the Gateway fallen into ruins and into the main courtyard bordered by dilapidated houses, I also had no idea where I was going and was not concerned about it.

Octavio Paz - The Monkey Grammarian (cf. p 204)

In this study voluntary muscle function tests are used to examine the weakness associated with ageing and that associated with subnutrition. Some of the problems of interpreting muscle function tests are discussed. Results are described which have been obtained using new methods for measuring force and cross-sectional area (CSA) of the adductor pollicis (AP) muscle in six groups of subjects: 1) fit young, 2) fit elderly, 3) subnourished young, 4) elderly hip fracture patients, 5) post-menopausal women who have not received hormone replacement therapy and 6) post-menopausal women on hormone replacement therapy. These new methods are also used to elucidate possible mechanisms of the muscle weakness associated with ageing. The objectives of this project are primarily bio-medical, rather than clinical or functional. This is relatively unusual in the setting of clinical geriatrics. It is therefore hoped that the more clinical direction that the project has taken in its later stages will be seen to have justified the initial approach. Moreover in a political climate where obtaining health service funding for bio-medical research has been more difficult than for more obviously clinical or operational projects (D. Lowe, Regional Statistician, South-East

Thames Regional Health Authority, 1986 - personal communication) I would hope to have justified the support received and to encourage others to beat a similar path.

CLINICAL MUSCLE FUNCTION TESTING

There are established tests for measuring muscle function in the clinical setting of assessing specific muscle diseases (Edwards et al., 1977). The most widely used test is the force-frequency curve. This depends on the principle that the force generated by a muscle as a result of supramaximal stimulation is a function of the frequency of stimulation (Edwards, 1978). The muscle may be stimulated via its motor nerve or parts of large muscles such as quadriceps may be stimulated directly (Edwards et al., 1977). The shape of the curve is remarkably constant for different muscles (Moxham et al., 1981) and is independent of the amount of muscle stimulated (Edwards et al., 1977). The use of electrical stimulation eliminates the possibility that the results obtained are influenced by varying motivation between subjects, or of the same subject on different occasions, which may be the case when voluntary muscle function tests are used (Young & Edwards, 1977). However the force-frequency curve cannot be used to measure the degree of weakness because relative rather than absolute force is measured. It is also difficult to interpret deviations from the usual shape of the curve in terms of the possible mechanisms within the muscle which might lead to the observed functional changes. The fusion of a tetanus and therefore the shape of the force-frequency curve depends largely on the relaxation rate (Jones & Round, 1990). Relaxation is itself a complex phenomenon on which the influence of different factors

is known to vary depending on the experimental conditions (Woledge et al., 1985, Lannergren & Arner, 1992). Relaxation rate is dependent both on the kinetics of cross-bridge turnover and on the rate of removal of calcium ions. Activation, which depends on the release of calcium and is discussed in more detail in the next section, must also be crucial to the shape of the force-frequency curve. Thus for tetanic fusion to occur the relaxation rate has to be slow enough for relaxation not to have occurred before the next action potential arrives, and the generation of more force must also be possible within that time. Therefore the shape of the force-frequency curve depends both on the rates of release and of removal of calcium and also on the kinetics of cross-bridge turnover.

The force-frequency test is cumbersome to perform at the bedside and there is prejudice against stimulated tests. This is typified by Fig 1 which is taken from Duchenne's Méchanisme de la Physionomie Humaine. This was the first series of published physiological experiments to be illustrated by photography. The photograph reproduced shows Duchenne engaged in stimulating the left corrugator supercilii muscle of a young female subject who thereby exhibits "resigned suffering on the left side of her face, while on the right she discloses sorrowful contemplation" (Duchenne, 1862; the published English translation (see reference) is distinctly inelegant. I have therefore amended it.). There is a feeling that the information gained from stimulated tests does not justify the discomfort inflicted on the patient, particularly when more general problems involving muscle weakness rather than specific muscle diseases are being investigated. For example, in studies of the nutritional status of the elderly (Wickham et al., 1989), and of surgical patients (Klidjian et al., 1980, Hunt et al., 1985) or in studies of falls in the elderly (Askham et al., 1990) the only test of muscle

Fig 1

Duchenne de Boulogne and a Young Religious

function reported was of a voluntary maximal hand-grip using a hand-held dynamometer.

VOLUNTARY MUSCLE FUNCTION TESTING

Two problems have to be addressed when interpreting voluntary muscle function tests.

1) the comparison of the force measurement between subjects. It has long been recognised that the solution to this problem depends on the ability to make a concomitant measurement of muscle size since the force that a muscle exerts is proportional to its cross-sectional area (Weber, 1846 cited by Haxton, 1944).

2) the reproducibility of the force measurement. Maximal voluntary contractions are used. The force measured will represent the full capacity of the muscle to produce force only if all the fibres in the muscle are maximally activated throughout the duration of the measurement. The sequence of events in activation is as follows (Carlson & Wilkie, 1974, Woledge, Curtin & Homsher, 1985, Rüegg, 1986). The arrival of an action potential at the end-plate of the motor nerve of all vertebrate twitch muscle fibres causes a large transient increase in the probability of the quantal release of acetyl choline. Synchronous release of a large number of quanta results in depolarisation of part of the muscle membrane producing an end-plate potential. The end-plate potential initiates a propagated muscle action potential. The surface membrane of the muscle fibre has invaginations forming a system of branched tubes called T-tubules. These run transversely into the fibres and, together with the terminal

cisternae of the sarcoplasmic reticulum (SR), form structures called triads. The SR is a network of closed tubules of irregular shape surrounding each myofibril. It sequesters calcium ions allowing the muscle to relax, a process that requires ATP. It is also from the terminal cisternae of the SR that calcium is released in response to propagation of the muscle action potential along the T-tubule system (Ashley et al., 1991). The signal from the T-tubule to the SR which initiates calcium release is uncertain. Binding of calcium by troponin allows the interaction of actin and myosin resulting in the production of force. It is generally considered that, within individual unfatigued fibres, the calcium released during a high-frequency tetanus is sufficient to saturate all the troponin binding sites (Westerblad et al., 1991). Thus if low force is due to a reduced calcium release secondary to fewer action potentials, more force would result from applying electrical stimulation at unphysiologically high frequencies resulting in additional action potentials in the muscle. Calcium release will then rise to a maximal level i.e. that sufficient to saturate all the troponin binding sites.

This can be tested by comparing maximal voluntary with maximal stimulated contractions from the same muscle under the same recording conditions. However this tends to be poorly tolerated; indeed eliciting maximal tetanic force in quadriceps by stimulating the femoral nerve has been described as "an alarming procedure" (Rutherford et al., 1986) and Davies and White (1983) found that when the triceps surae muscle of the calf was stimulated at varying frequencies via its motor nerve only two of their twenty subjects were able to accept supramaximal tetanic stimulation at 100 Hz, most subjects being unable to tolerate supramaximal stimulation above 20 Hz. In Davies and White's study (1983) the ratios of the stimulated forces produced ($P_0$20/$P_0$100) by these two subjects were seventy-six per cent and ninety-one per cent

i.e. tetanic force at 20 Hz was maximal in neither subject. The alternative method of verifying whether activation is maximal is by interpolating stimulated twitches during voluntary contractions (Merton, 1954). Merton found that the size of the twitch response in human adductor pollicis muscle from stimulating the ulnar nerve was inversely proportional to the degree of voluntary activation of the muscle. Thus the stimulated twitch was maximal with no voluntary contraction, was fifty per cent when the voluntary contraction was fifty per cent of MVC, and there was no visible twitch response when the voluntary contraction was maximal.

Merton (1954) reported using this technique at the patient's bedside and McComas and colleagues (1983) found that interpolated twitches elicited by stimulation of the tibial nerve during plantarflexion of the foot and by stimulation of the common peroneal nerve during dorsi-flexion, was well tolerated by patients. McComas and colleagues (1983) also described interpolating stimulated twitches during dorsi-flexion by direct stimulation of the tibialis anterior muscle. Direct stimulation of the muscle was the method favoured by Rutherford and colleagues (1986) for interpolating twitches to assess the degree of activation of the knee-extensors as they found that femoral nerve stimulation was not well-tolerated by "inexperienced subjects". Despite direct stimulation only activating up to sixty per cent of the muscle, the relationship between the size of the twitch and the degree of voluntary activation was the same for direct stimulation as for femoral nerve stimulation.

Thus the ideal voluntary muscle test has the following characteristics:

1) the measured force must derive from one muscle or a well-defined group of muscles

so that the appropriate muscle size can be assessed

2) the motor nerve should be accessible for interpolating stimulated twitches and should not supply other muscles, particularly not antagonists

3) the measurement of muscle force must have a good correlation with that of muscle size

4) the movement required to produce a maximal contraction must be simple to explain to the subjects and straightforward for them to perform.

HAND-GRIP

Of these requirements only the fourth is fulfilled by hand-grip. It is a complex movement involving many forearm, finger and thumb muscles. It is difficult to conceive of a method for verifying its maximality. Where an attempt has been made to correlate it with a measurement of muscle size this has been indirect. Probably for this reason the correlations between force and muscle size have been relatively weak:

Maclennan and colleagues (1980), between grip and fat free mass, males - $n = 158$, $r = 0.327$, $P < 0.001$, females - $n = 112$, $r = 0.166$, NS,

Phillips (1986), a "weak positive" correlation between grip and arm muscle circumference in 82 female subjects,

and Kallman and colleagues (1990) who studied 864 male subjects, $r = 0.60$, $P < 0.0001$ between grip and arm muscle circumference, and $r = 0.58$, $P < 0.0001$ between grip and creatinine excretion.

PLANTAR-FLEXORS

Repeatable MVF measurements are obtainable from the plantar-flexors of the calf for young adults (Davies & White, 1982), children (Davies et al., 1983) and the elderly (Davies & White, 1983, Pearson et al., 1985, Vandervoort & McComas, 1986). Cross- sectional area of these muscles may be calculated using an anthropometric technique (Jones & Pearson, 1969) or by ultrasound (Vandervoort & McComas, 1986). Vandervoort and McComas did not measure CSA in all their subjects and do not publish a correlation between force and CSA. Published correlations between MVF and the anthropometric measurement of CSA vary from $r = 0.91$ (Davies et al., 1983) to $r = 0.62$ (Pearson et al., 1985) and doubts about the general applicability of this area measurement have been expressed (Bassey et al., 1988). It has also been found using interpolated twitches, that it is difficult to maximally activate the planter-flexors as opposed to the dorsi-flexors (Belanger and McComas, 1981). This may contribute to the inconsistencies in the correlations between force and CSA for this muscle group.

KNEE-EXTENSORS

Measurement of MVF of the knee-extensors using specially designed muscle-testing chairs (Edwards et al., 1977, Maxwell et al., 1984) is accepted in clinical practice (Edwards, 1978). With the reservations noted above, the motor nerve is accessible for stimulation (Rutherford et al., 1986) and the muscles' CSA may be measured using computer-assisted tomography (CAT-scanning) (Maughan et al., 1983, Chapman et al., 1984), ultrasound (Young et al., 1984, 1985) or estimated anthropometrically (Hyatt et al., 1990).

Correlations between force and CSA in young adults have been relatively poor however. Using CAT-scanning a significant correlation between MVF and CSA ($r = 0.69$) was found for male subjects (Chapman et al., 1984). In contrast, using ultrasound no significant correlation was found between MVF and CSA for young male subjects (Young et al., 1985). The interpretation of the significance of the correlation has also proved ambiguous. In their original publication Maughan and colleagues (1983) demonstrated significant correlations between MVF and CSA for both male and female subjects. Comparing mean ratios of MVF and CSA measurements using Student's t test for unpaired data, they showed no difference in force/CSA between male and female subjects. Winter and Maughan (1991), drawing on Tanner (1949), reanalysed the 1983 data comparing regression lines using analysis of covariance. By this method a significant difference between males and females was shown. The conclusion was drawn that Tanner's general criticism of ratio standards as "misleading" had been upheld and that, in this particular case, differences had been concealed and underlying mechanisms obscured (Winter & Maughan, 1991).

Tanner's theoretical critique was based on his own measurements of stroke volume (SV) and body weight (W) in male human subjects. He pointed out that the use of a ratio standard implied that the relationship between the two variables is a proportional one described by the equation:

$$SV = k.W \quad (\text{i.e. } y = mx)$$

whereas assuming a linear relationship between them the best fit for his data was given by the equation:

$$SV(cm^3) = 0.32 \times W(kg) + 79.5 \quad (\text{i.e. } y = mx + c).$$

Tanner appears to have been concerned with the use of such standards to predict "normal" ranges, particularly in clinical practice. Using his example he showed that measured values for heavy men would be lower, and those for light men higher, than the "normal" values predicted on the basis of the ratio standard. He was able to quote examples from the literature where heavy people were said to have relatively low SV's whereas thin people were described as having "essential hyperkinemia".

It will have been noted that the only difference between Tanner's two equations is the presence of the intercept. Data from Maughan and colleagues (1983) and Young and colleagues (1984 & 1985) have been redrawn (Figs 2 and 3 - regression lines and their 95% confidence limits are shown). In these studies and another in which knee-extensor force and CSA is compared (Chapman et al., 1984) there are large positive intercepts for male subjects. In Maughan and colleagues study there is also a large positive intercept for female subjects though in both Young and colleagues' (1984) and Chapman and colleagues' (1984) studies the intercept for females is relatively small.

Relationship between knee-extensor MVF and CSA of fit young male and female subjects (re-drawn from Maughan et al. 1983)

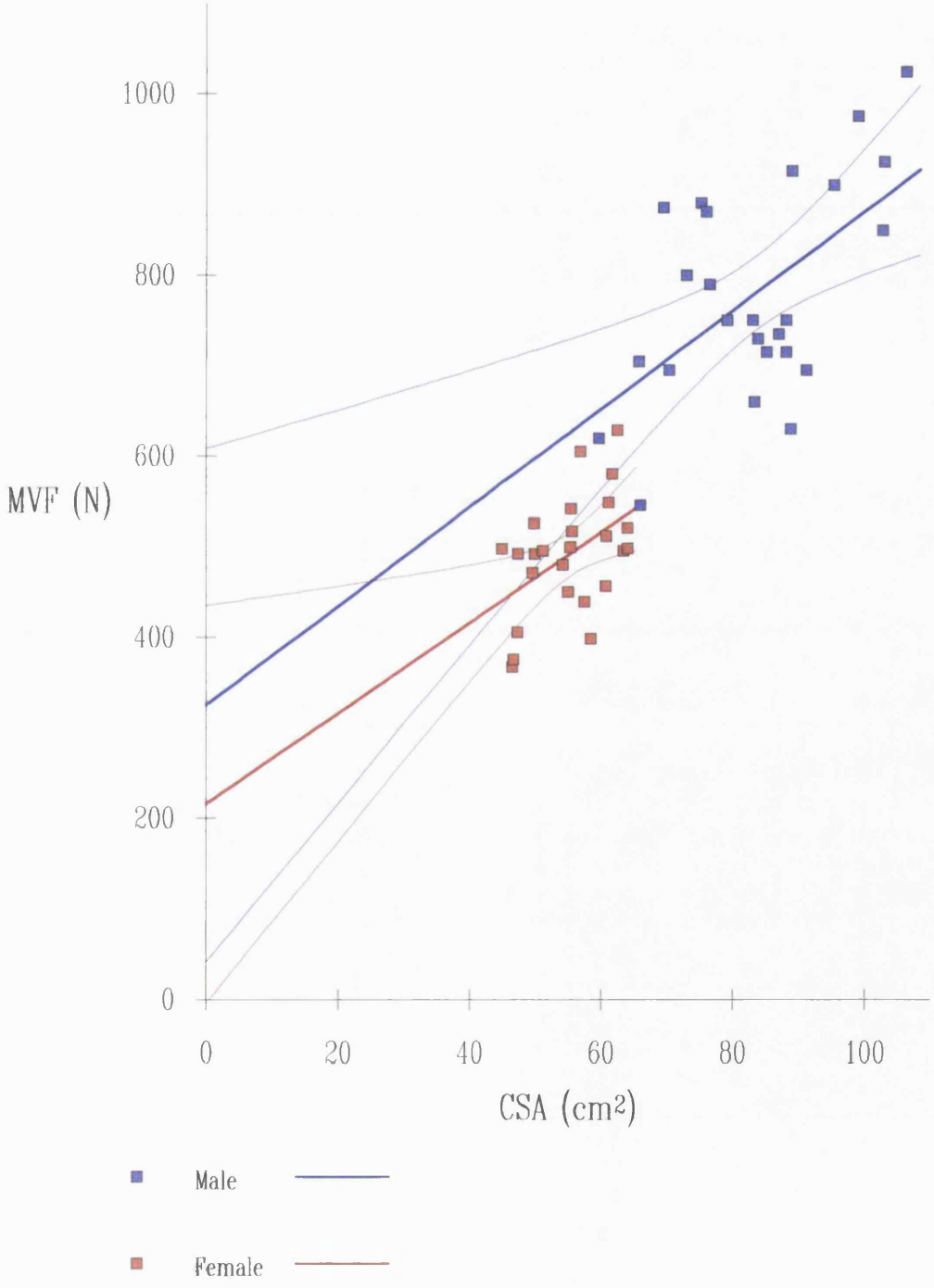
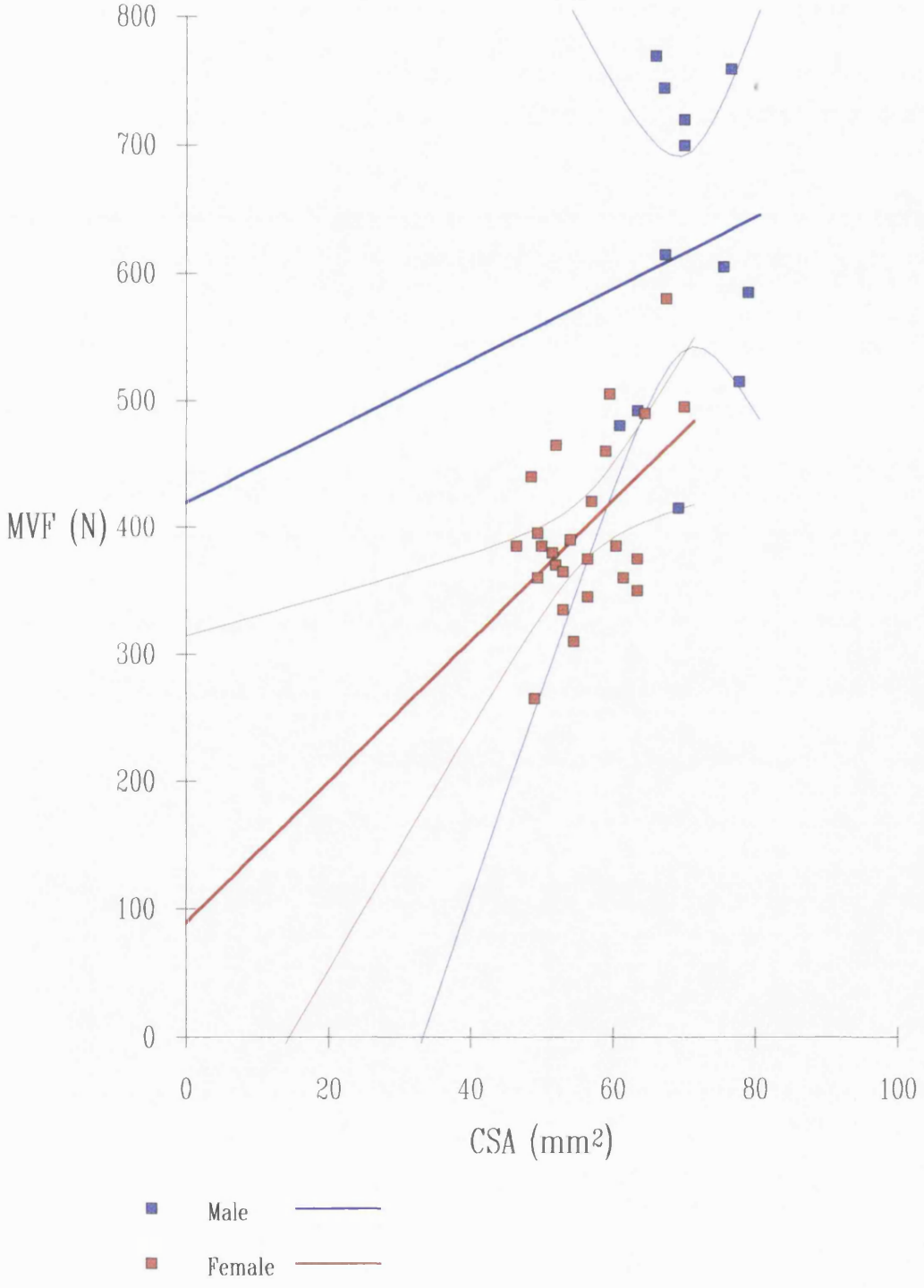


Fig 3

Relationship between knee extensor MVF and CSA of fit young male and female subjects (re-drawn from Young et al. 1984 & 1985)



One possible reason for these intercepts is that the force recorded by a transducer acted on by a limb is not a simple multiple of that exerted by the individual muscle fibres because these are connected to a "lever" whose ratio is variable between subjects. In pennate muscles such as quadriceps the angle of pennation affects the overall lever ratio (Haxton, 1944) and changes in muscle size lead to changes of the pennation angle (Binkhorst and van't Hof, 1973). For measurements of knee-extensors using published methods (Edwards et al., 1977, Maxwell et al., 1984) another variable length lever is that between the point of attachment of the muscles and the point of application of the force transducer. In a small study of young males comparing MVF of knee-extensors with a CAT-scan estimate of CSA, taking this factor into account appeared to explain some of the residual variance around the regression line (McCullagh et al.,1984) although one would expect the influence of this factor to be small relative to that of changes in pennation angle (Huxley, 1980).

Another possible factor contributing to the positive intercepts is that large muscles may not be fully activated during a maximal voluntary contraction in apparently normal subjects. Using twitch interpolation, Rutherford and colleagues (1986) found evidence of incomplete activation of knee-extensors in ten per cent and of biceps brachii in twenty-eight per cent of their subjects. Also using twitch interpolation, Belanger and McComas (1981) found that fifty per cent of their subjects were unable to fully activate the triceps surae muscle of the calf. Rutherford and colleagues (1986) described three groups of subjects whose knee-extensors were weak, 1) those who could not completely activate because of pain
2) those who were weak because of loss of contractile tissue but who could activate all of the remaining muscle and 3) those in whom twitch interpolation produced evidence

of incomplete activation but in whom there was no apparent reason (those with inhibition without pain). Teleologically "inhibition without pain" could be seen as a safety feature as it is said that the knee joint can be damaged by tetanic stimulation of the femoral nerve (Belanger & McComas, 1981). As male subjects tend to be larger, the effects of variability in lever ratio and of any protective inability to fully activate the knee-extensors would be more likely to affect male rather than female subjects thereby increasing the variance and introducing a non-linearity into the data. Against this argument however is the observation that all eight competing athletes tested as part of Rutherford and colleagues' study (1986), were able to fully activate their knee-extensors, and that inhibition without pain has been found to be rare in further studies of activation of knee-extensors with larger numbers of subjects (O. Rutherford, 1993 - personal communication)

In Fig 2 there is almost no overlap between the observations from the groups of male and female subjects. Despite inconclusive evidence, it seems more likely that the difference shown in MVF/CSA by Winter and Maughan (1991) is due to fitting a linear model to non-linear data from two non-overlapping groups rather than any sex-difference in the cross-bridge function of young adults. (This is discussed further on pp. 167-169).

It is clearly important to study large muscles and to be able to interpret the results. Specific disorders of muscle more often affect proximal muscles (Edwards et al., 1977) and the effects of disuse are more likely to be seen in leg muscles (Bassey et al., 1988). However if one is interested in elucidating possible differences in force-generating capacity, it becomes crucial that the measurement of muscle force

should have a more consistently good correlation with that of size than has so far been achieved with large muscles.

ADDUCTOR POLLICIS

Use of the adductor pollicis muscle (AP) is well established in experimental (Merton, 1954) and clinical practice (Edwards et al., 1977). Adduction of the thumb is a straightforward movement to perform and the motor nerve (the ulnar nerve) is easily accessible at the wrist. The only other muscle of the thumb supplied by this nerve is first dorsal interosseous (FDI) which makes a small contribution to the movement measured, whether voluntary or stimulated. It has been shown that AP can be fully activated voluntarily (Merton, 1954). When investigating the effects of subnutrition and of ageing, both of which might be expected to have generalised effects on muscles, the use of a small hand muscle is quite reasonable. It is also a positive advantage to minimise disuse as a factor; even bedridden patients will continue to use thumb muscles in the activities of daily living. However it has been difficult to isolate the maximal force exerted by adductor pollicis from possible augmentation by the long flexors of the thumb and there was no means of measuring its CSA (Edwards et al., 1977).

Therefore the force measuring technique of Merton (1954) modified by Edwards and colleagues (1977) has been further modified by us to reduce, as far as possible, the augmentation of the force by other muscles and the length of the lever between the point of attachment of the muscle and the point of application of the force transducer. We have also devised a simple means of estimating the CSA of the muscle and

demonstrated good correlations between this estimate and CAT and magnetic resonance imaging (MRI) scans of the muscle taken in the same plane of the hand. Reports of these methods have been published (Bruce et al., 1986a & 1989).

SKELETAL MUSCLE FUNCTION AND SUBNUTRITION

Fasting leads to profound effects on homeostatic mechanisms (Hardy, 1983). These include:

1) depression of insulin secretion and consequent inhibition of uptake of glucose to tissues other than brain

2) enhanced release of glucagon, glucocorticoids, growth hormone and, if severe, adrenaline which stimulate a) glycogenolysis, b) protein breakdown and gluconeogenesis, and c) breakdown of stored fat, releasing free fatty acids.

The only substances available for gluconeogenesis are amino-acids which, during fasting, are derived from the breakdown of protein. Although the relative rate of resynthesis of myofibrils (approximately ten per cent per day) is less than that of liver protein (over fifty per cent per day), the overall amount of protein turnover in muscle is two to three times greater than that in the liver (Daniel et al., 1977). This is because the body's skeletal muscle tissue weighs some twenty times more than the liver. Thus skeletal muscle may be seen as an important homeostatic regulatory organ in periods of subnutrition in that it is the main provider of amino-acids for gluconeogenesis.

Loss of myofibrillar and other muscle proteins would lead one to anticipate changes in skeletal muscle function as a consequence of changes in nutritional status. The observation of weakness and wasting of muscle as a consequence of protein-calorie-malnutrition is commonplace (Shizgal et al., 1986). Weakness of hand-grip has been shown to correlate with nutritional status as assessed by body composition in surgical

patients (Forse and Shizgal, 1980), and to be a good predictor of post-operative complications (Klidjian et al., 1980, Hunt et al., 1985). Another clinically important consequence of the muscle weakness associated with subnutrition is found in patients requiring ventilation. Many of these patients are subnourished and respiratory muscle function is known to be a critical factor in the response to ventilation and its withdrawal (Marini, 1991).

Changes in the function of adductor pollicis in response to stimulation of the ulnar nerve were described in ten patients who were subnourished as a result of various gastro-intestinal disorders (Lopes et al., 1982). The reported changes were:

1) an abnormal force-frequency relationship with proportionately higher force generation at low frequencies of stimulation
2) prolonged relaxation
3) increased fatiguability during a 30 s tetanus.

In this study improvement was noted in the muscle functions of four patients who were re-examined after treatment for four weeks with total parenteral nutrition. Similar reversible changes were described in six obese patients tested before and after two weeks treatment with a 400 kcal diet, followed by two weeks fasting and finally by two weeks refeeding (Russell et al., 1983a), and also in six patients with anorexia nervosa before and after refeeding (Russell et al., 1983b).

The results in subnourished subjects were repeatable (Newham et al., 1986, Lennmarken et al., 1986a, Brough et al., 1986, Chan et al., 1986). However, there are inconsistencies which prevent complete acceptance of the interpretation that abnormalities of muscle function provide "sensitive and specific indicators of

malnutrition" (Brough et al., 1986). Newham (1986) has pointed out that the association between increased fatiguability and both an abnormal force-frequency relationship and a slowing of maximal relaxation rate (MRR) is hard to explain because a lower tetanic fusion frequency tends to be associated with relative fatigue resistance (Jones and Round, 1990). Fatiguability was not reported in later studies extolling this technique for nutritional assessment (Brough et al., 1986, Chan et al., 1986). As Newham (1986) also commented a test which produces similar results in subnourished patients and obese subjects following a two week fast, is not providing any absolute measurement of nutritional status. The results in obese subjects proved the most difficult to repeat. Neither Newham and colleagues (1986) nor Lennmarken and colleagues (1986b) were able to detect changes in contractile properties in adductor pollicis with dieting in obese subjects, the former following two weeks of a 450 kcal diet, the latter six months after gastroplastic surgery when the subjects had lost a mean of nineteen per cent of their pre-operative body weight.

During a detailed comparison of these tests with measurements of body composition by multiple isotope dilution, eight normally nourished subjects were found to have abnormal muscle function after a 48-hour fast which returned to pre-fast levels six hours after re-feeding (Shizgal et al., 1986). In this study differences in body composition in all sixty-five patients studied were found to correlate poorly with changes in muscle function. On the basis of the results it was argued that the apparently specific abnormalities of muscle function described in subnourished subjects had reflected the availability of acute energy stores rather than changes in nutritional status. This would also seem to be suggested by the study where eight subnourished surgical patients underwent 48 hours intravenous loading with glucose and potassium

(Chan et al., 1986). In that study, in addition to measuring the force-frequency relation and relaxation rate of adductor pollicis, muscle glycogen was estimated in biopsy samples obtained from quadriceps femoris before and after treatment. The abnormal force-frequency relation and relaxation rate improved with glucose-potassium loading and a significant increase in muscle glycogen was shown. Respiratory exchange ratio also increased significantly from 0.79 ($\pm$0.02) to 0.95 ($\pm$0.01) consistent with a switch from protein catabolism to glucose oxidation (Ulmer, 1989).

As mentioned above (pp. 13-14) the shape of the force-frequency curve depends largely on the relaxation rate (Jones and Round, 1990). An association between changes in the force-frequency relation and prolonging of relaxation is therefore predictable. The rate of removal of calcium ions during relaxation is dependent on the removal of free calcium from the sarcoplasm by the sarcoplasmic reticulum. This process is energy dependent and energy supply is known to affect relaxation in both mammalian (Edwards et al., 1975) and amphibian muscle (Dawson et al., 1980). In two studies comparing metabolic and functional changes in muscle induced by hypocaloric dieting, raised total intracellular calcium was shown in biopsy material from humans (Russell et al., 1984a) and rats (Russell et al., 1984b). These studies also demonstrated abnormal force-frequency relations and slowing of relaxation in the individuals biopsied. Thus the simplest explanation for the observed changes in the force-frequency relation with subnutrition and refeeding is that the availability of energy for calcium pumping is affecting the uptake of calcium by the sarcoplasmic reticulum during relaxation. This could be 1) by directly affecting the number of pump molecules or 2) by accumulation of metabolic products or depletion of substrate inhibiting the calcium pump.

However the rat study also reported an almost six fold elevation of muscle lactate and three-fold increase in pyruvate (Russell et al., 1984b). The presence of the former might be expected to lower intracellular pH, another factor known to result in slowing of relaxation in amphibian muscle (Curtin and Edman 1989). Changes in intracellular pH (Curtin and Edman 1989 & Curtin 1990) and in pyruvate (Phillips et al.,1993b) could also affect the relationship between force and CSA. Lennmarken and colleagues (1986a) and Brough and colleagues (1986) reported changes in muscle function with changes in nutritional status without any significant alteration in muscle bulk assessed by arm-muscle-area. It is perhaps surprising therefore that in none of the studies quoted above was any attempt made to directly correlate force and cross-sectional area of the muscle studied which might be expected to shed light on the mechanism of the weakness associated with subnutrition.

We have therefore measured MVF and CSA of adductor pollicis in subnourished patients and compared the results with those from normally nourished healthy subjects. Normalised relaxation rates after a brief maximal voluntary contraction (MVC) and fatigue during a MVC sustained for 30 s were also measured. These results have been published (Bruce et al., 1989a). The relationship between adductor pollicis MVF and CSA is compared with that between maximal hand grip and arm muscle area.

HUMAN SKELETAL MUSCLE AND AGEING

Muscle weakness is an inevitable accompaniment of ageing. "Remember now your creator in the days of your youth before the evil days and years draw nigh when you will say, I have no pleasure in them. While the sun, or the light, or the moon or the stars be not darkened, nor the clouds return after the rain. Then your arms, that have protected you, will tremble and your legs, that were strong, will grow weak." (Ecclesiastes 12 vv 1 - 3). The functional consequences of these changes are also well recognised. "You will be afraid of high places and walking will be dangerous. Your hair will turn white; you will hardly be able to drag yourself along" (Ecclesiastes 12 v 5) - *translation adapted from the King James Version and United Bible Societies Edition.*

A NOTE ON THE PRESENTATION OF DATA REVIEWED IN THIS SECTION

I have attempted to clarify the summaries of the results from the studies reviewed in this section by presenting many of them graphically, the reported percentage changes being plotted against age. For the sake of clarity, lines have been included joining the various points though it is of course realised that these are not continuous variables. Below each of these graphs is a table presenting the *numbers of subjects* in each age group in the respective studies.

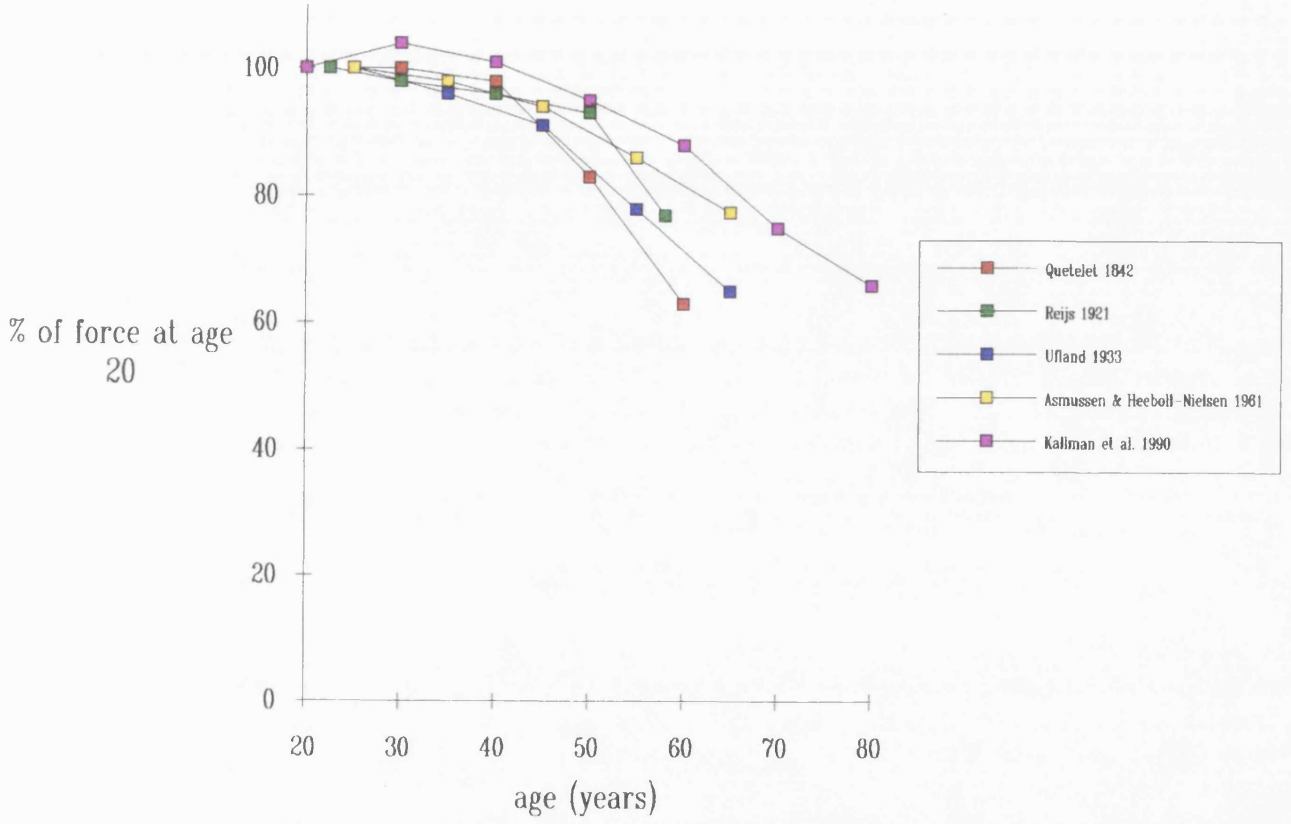
VOLUNTARY MUSCLE FORCE

a) HAND-GRIP:

Despite hand-grip being an unsatisfactory measurement, for the reasons argued above, studies of the decline in the force of a maximal grip with age are important for two reasons. The first reason is that there have been studies quantifying decline in hand-grip with age published over the past 150 years, since that by Quetelet (1842). Fig 4 summarises the results of five cross-sectional studies showing the decline in hand-grip with age in men and Fig 5 those from two studies of women. There is an overall loss of force of 25-40% from age 20 to the end points of the studies quoted. However as Larsson (1982) has pointed out, in more recent studies force appears to be maintained into later years. There is no apparent difference between men and women in the studies shown. Quetelet (1842) had been unable to demonstrate any appreciable decline in grip in women but attributed this to his female subjects having hands that were too small to effectively produce maximal contractions on his dynamometer.

Fig 4

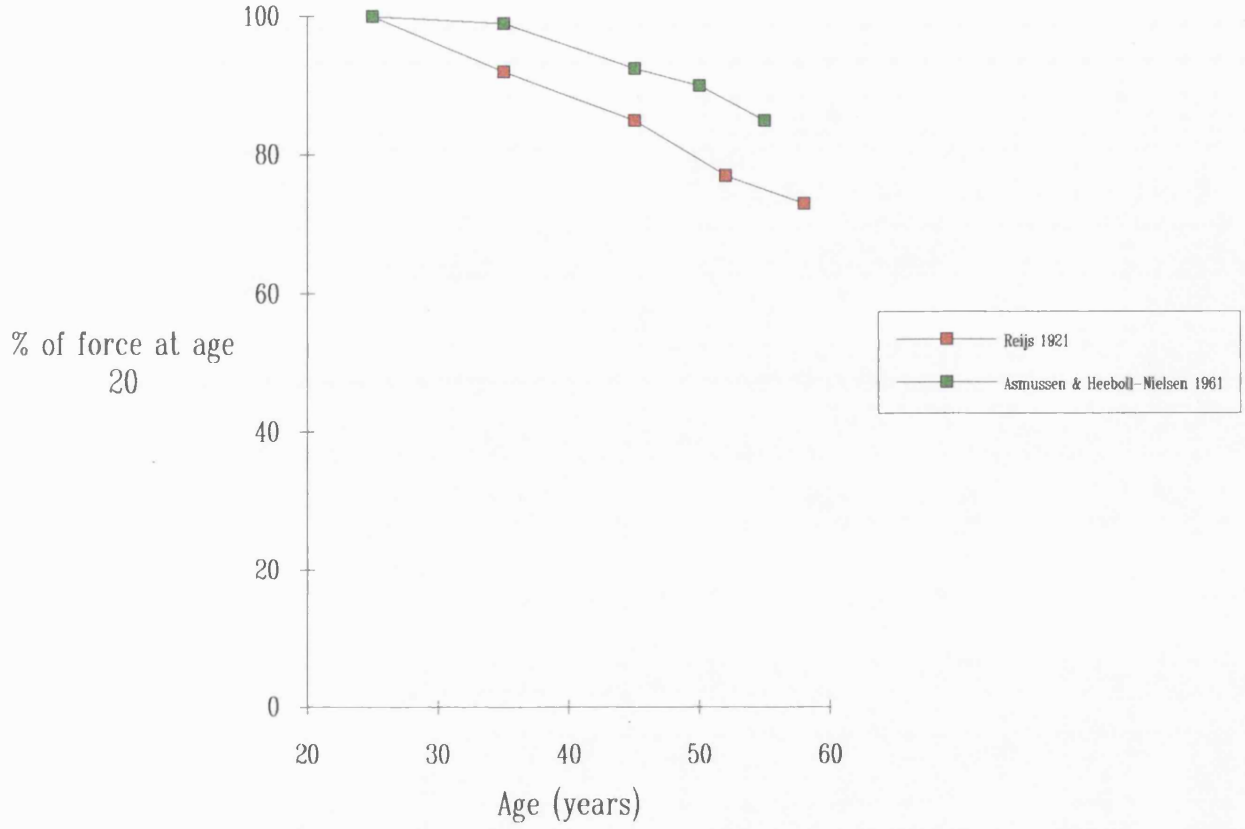
Force of maximal grip in men with respect to age 1842–1990



Study	20s	30s	40s	50s	60s	70s	80s
Quetelet 1842	"at least 10 subjects in each group"					-	-
Reijs 1922	n = 1112				-	-	-
Ufland 1933	1132	1098	976	531	79	-	-
Asmussen & Heeboll-Nielsen 1961	"20 - 40 subjects in each group"					-	-
Kallman et al. 1990	55	115	130	187	158	155	42

Fig 5

Force of maximal grip in women with respect to age 1921 & 1961



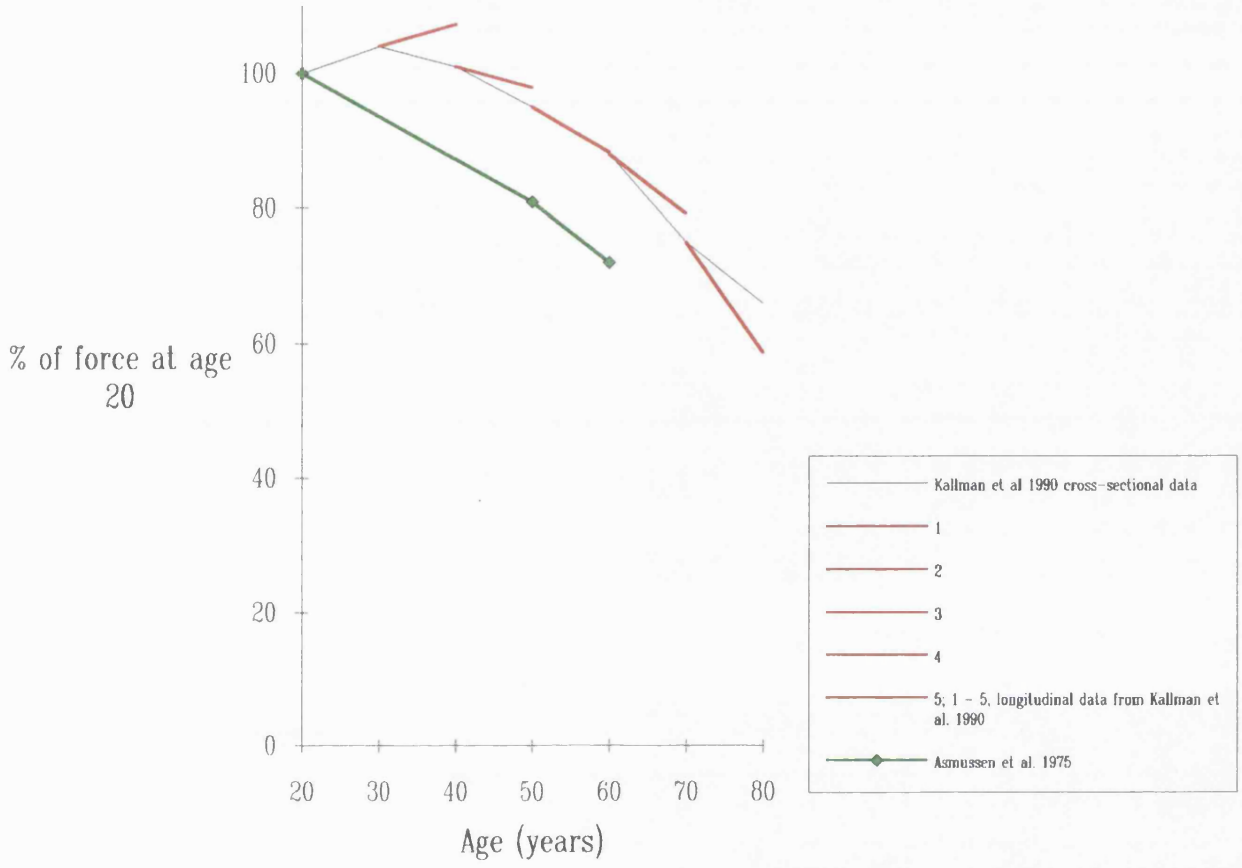
Study	20s	30s	40s	50s	60s
Reijs 1922	n = 888				-
Asmussen & Heeboll-Nielsen 1961	"20 - 40 subjects in each group"				

The second reason for the importance of studies of the effects of age on hand-grip is that there have been longitudinal as well as cross-sectional studies. Fig 6 summarises results from two of these. A group of twenty-five Danish physical education students were tested first in 1930-35 when their mean ages were 23.5 (women, n = 6) and 23.9 (men, n = 19). They were re-tested about thirty years later and again after a further ten years (Asmussen et al., 1975). Despite all the subjects remaining physically active throughout the study there were highly significant declines in hand-grip for both sexes between each test period. The other study (Kallman et al., 1990) was of different design, five cohorts being followed for an average of nine years each, but obtained similar results.

A five year longitudinal follow up study of 261 randomly selected elderly in Edinburgh (148 female) was not so conclusive however (Milne & Maule, 1984). The subjects were aged 62 - 90 at the start of the study and the authors confirmed the cross-sectional association between age and the decline in muscle force on both occasions when the subjects were tested. However, the changes in hand-grip over the five years of the study were not significant. This may have been because their measurements had very large standard deviations. Although longitudinal studies are, in principle, more likely to demonstrate true physiological changes due to ageing, rather than those which might be due to genetic, nutritional or environmental factors (Davies, 1983), the test procedure has to have the power to detect what may be quite small changes.

Fig 6

Force of maximal grip with respect to age – longitudinal data



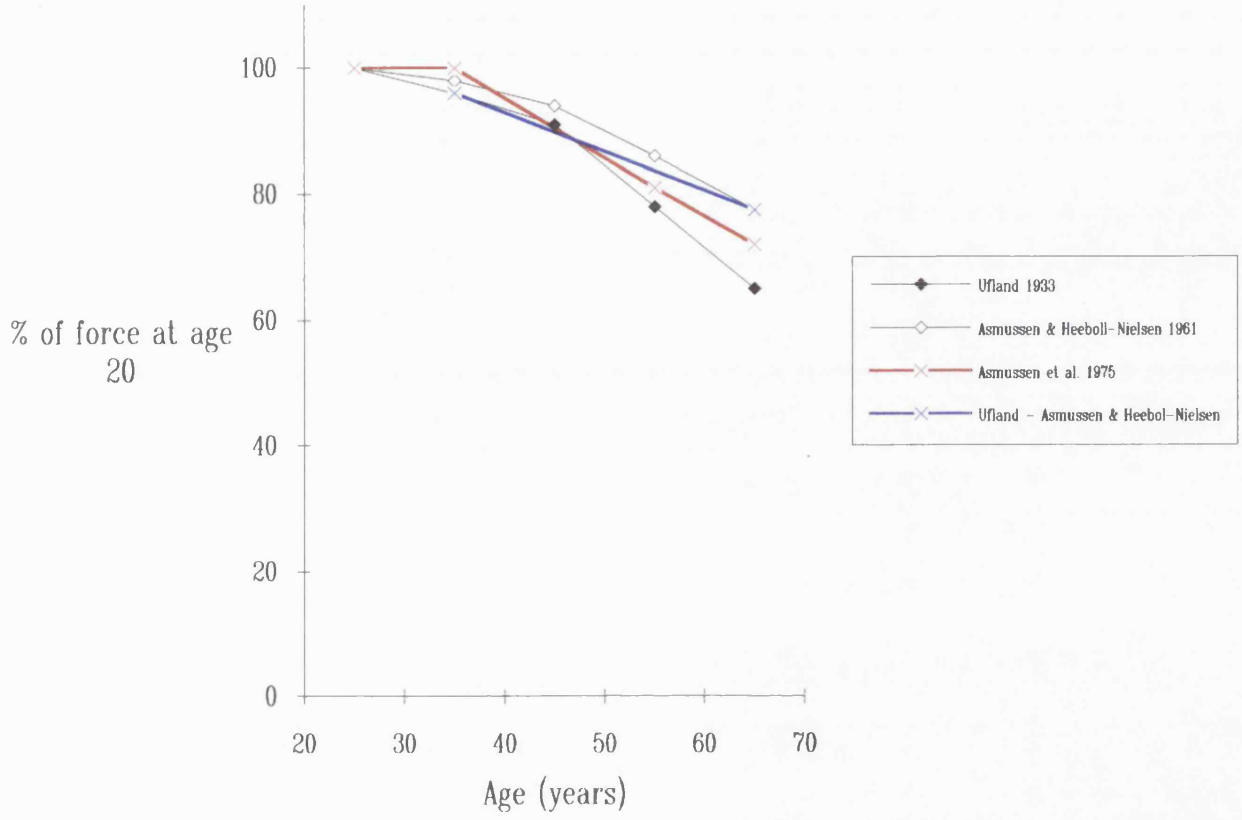
Study	20s	30s	40s	50s	60s	70s	80s
Asmussen et al. 1975	n = 25					-	-
Kallman et al. 1990	55	115	130	187	158	155	42

Asmussen and colleagues forty-year longitudinal study (1975) shows a steeper decline in hand-grip than one might expect from examining the cross-sectional studies. Fig 7 shows results from this study plotted with those from Ufland (1933) and those from Asmussen and Heebol-Nielsen (1961). The red line is data from the longitudinal study assuming that there would have been no loss of hand-grip up to age 35. The blue line joins the 35 year old's point from Ufland's study with the 65 year old's from Asmussen and Heebol-Nielsen's published 30 years later. The red line shows a steeper decline than the blue line. Assuming that the forces at age 35 are comparable between studies this suggests that cross-sectional studies may underestimate declines in force in individuals. Improvements in general health and nutrition during this century would lead one to anticipate higher forces in younger cohorts in later series thus widening rather than narrowing the gap between them and the older cohorts.

Decline in the force of maximal hand-grip has been shown to correlate with functional assessments such as manual dexterity (Hyatt et al., 1990) and with prognosis when tested on admission to hospital (Phillips, 1986). Correlations with mental test score have been inconsistent. An association with mental impairment in institutionalised elderly was reported by Denham and colleagues (1973) but Milne and Maule (1984) failed to confirm this in their study of elderly women randomly selected from the population of Edinburgh.

Fig 7

Force of maximal grip with respect to age in men – comparison of cross-sectional & longitudinal studies



Study	20s	30s	40s	50s	60s
Ufland 1933	1132	1098	976	531	79
Asmussen & Heeboll-Nielsen 1961	"20 - 40 subjects in each group"				
Asmussen et al. 1975	n = 25				

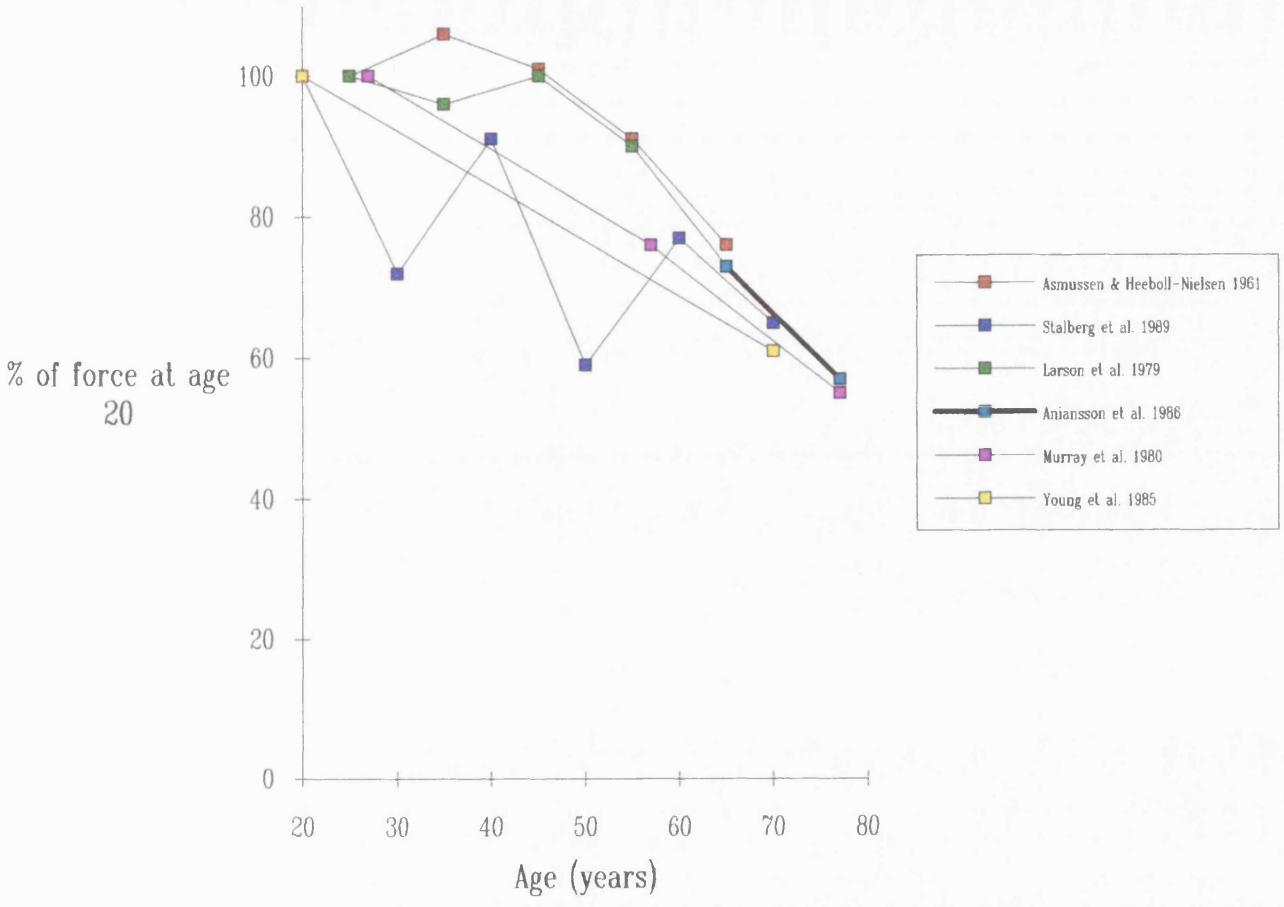
b) KNEE-EXTENSORS:

Similar percentage declines in force have been reported with knee extensors, the most extensively studied proximal muscle group. Fig 8 summarises the results of six cross-sectional studies of isometric MVF of knee extensors with respect to age in men and Fig 9 of five studies of women. Performance during dynamic contractions was also reduced (Figs 10 & 11). The age effect on dynamic contractions was reported to be greater in women than men (Aniansson et al., 1981) but in that study results from the elderly subjects were compared with published studies on young subjects rather than with observations by the authors themselves and methodological differences could account for the effects assumed to be due to age. No great sex differences are apparent in the figs 8 - 11. Stalberg and colleagues' results are rather inconsistent both with the other studies summarised and within the study itself. In this study each age-group contains less than ten observations, which is probably too small to obtain consistent results with this muscle group.

Figs 8 & 10 also show results from a longitudinal study of twenty-three elderly men tested first in 1975-76 and subsequently in 1983 (heavy line on figure), significant declines in MVF and isotonic torques were reported (Aniansson et al., 1986). However in a seven-year longitudinal study of ten women (aged 72 - 82 years) and four men (aged 72 - 77 years), (Grieg & Young, 1991) the small observed loss of MVF (- 0.3% per year) was not statistically significant (heavy line on Fig 9).

Fig 8

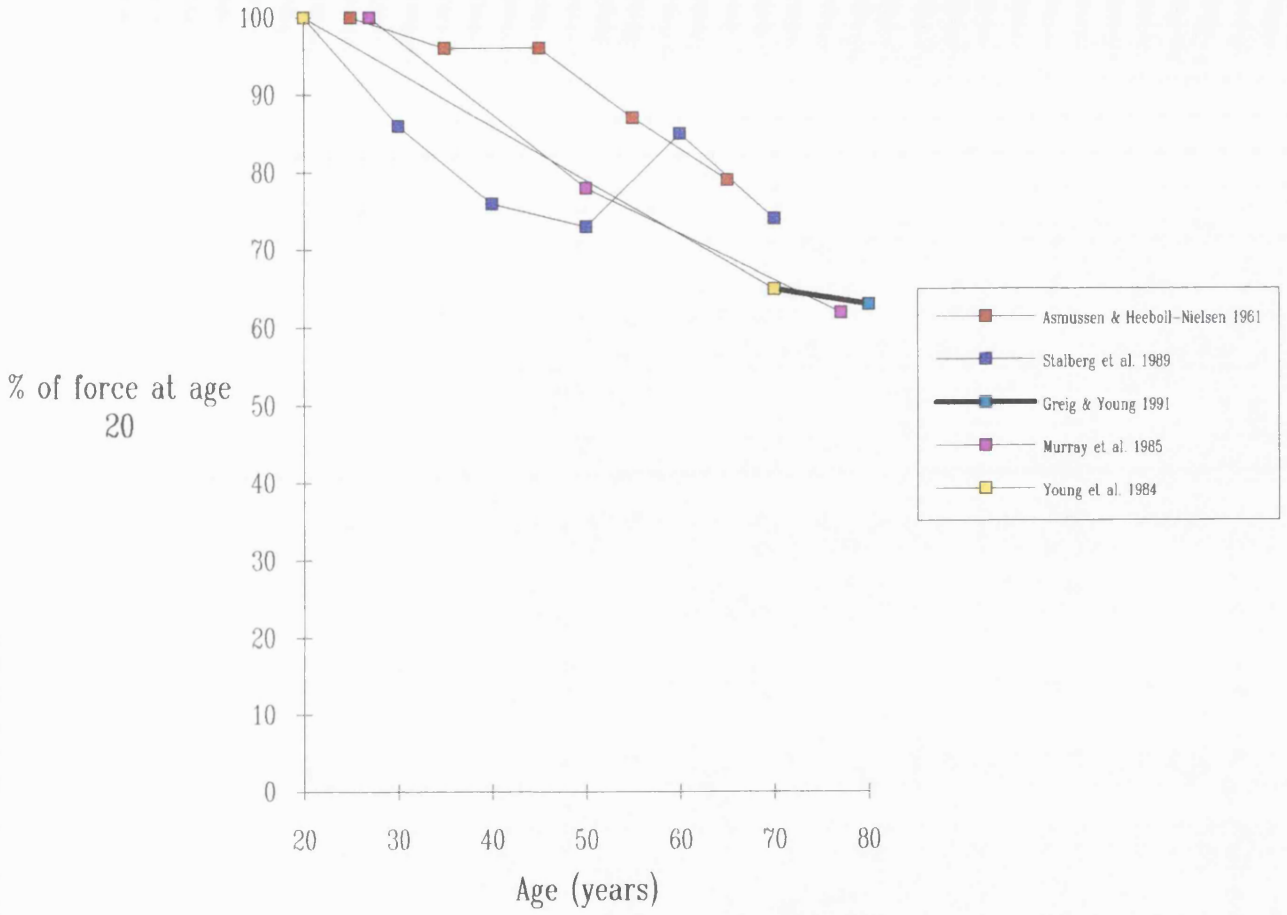
Isometric MVF of knee-extensors with respect to age in men



Study	20s	30s	40s	50s	60s	70s
Asmussen & Heeboll-Nielsen 1961	"20 - 40 subjects in each group"					-
Stalberg et al. 1989	4	6	6	5	5	7
Larson et al. 1979	11	11	10	12	16	
Aniansson et al. 1986	-	-	-	-	n = 23	
Murray et al. 1980	24	-	-	24	-	24
Young et al. 1985	12	-	-	-	-	12

Fig 9

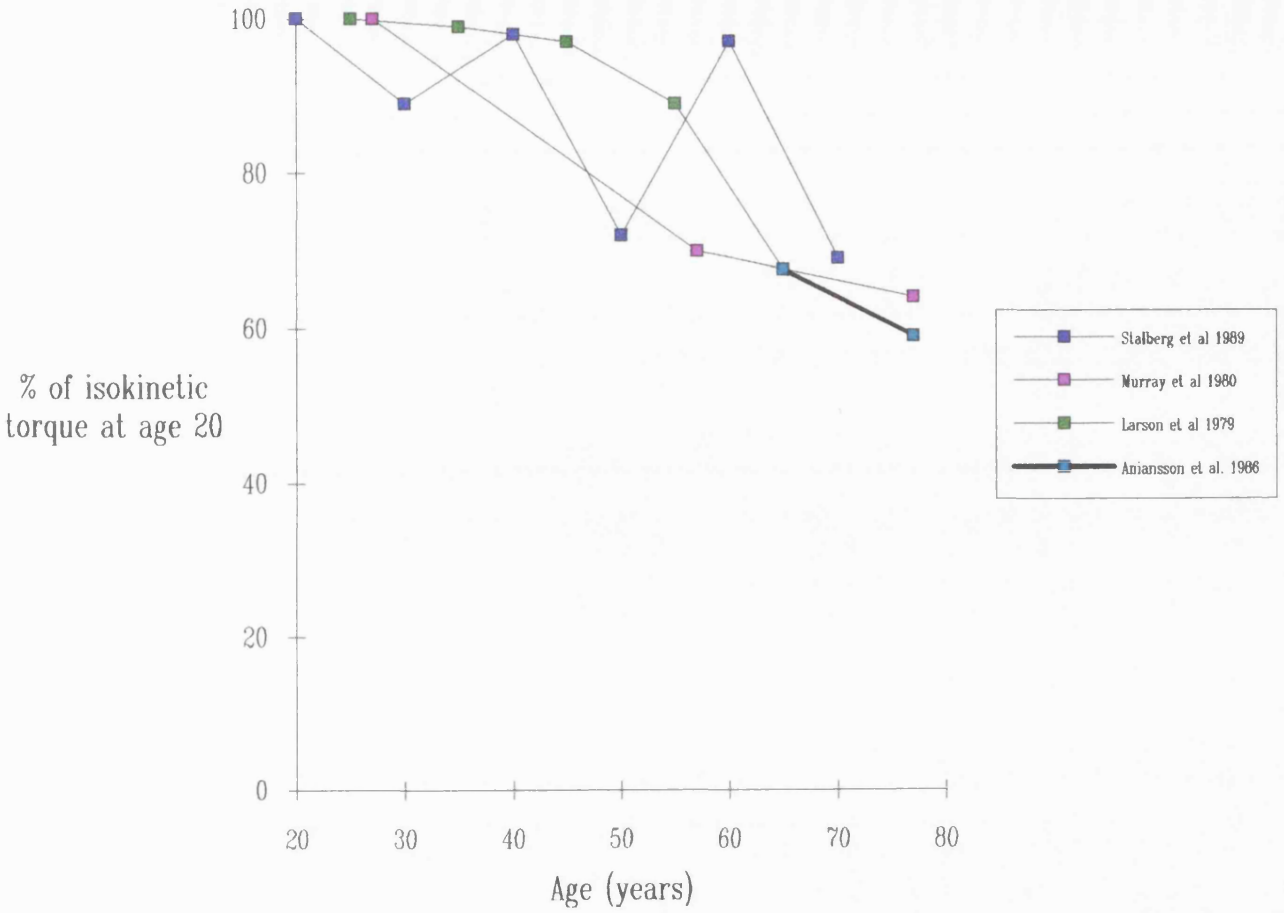
Isometric MVF of knee-extensors with respect to age in women



Study	20s	30s	40s	50s	60s	70s
Asmussen & Heeboll-Nielsen 1961	"20 - 40 subjects in each group"					-
Stalberg et al. 1989	5	4	6	6	6	4
Grieg & Young 1991	-	-	-	-	n = 14 (male = 4)	
Murray et al. 1985	24	-	-	24	-	24
Young et al. 1984	25	-	-	-	-	25

Fig 10

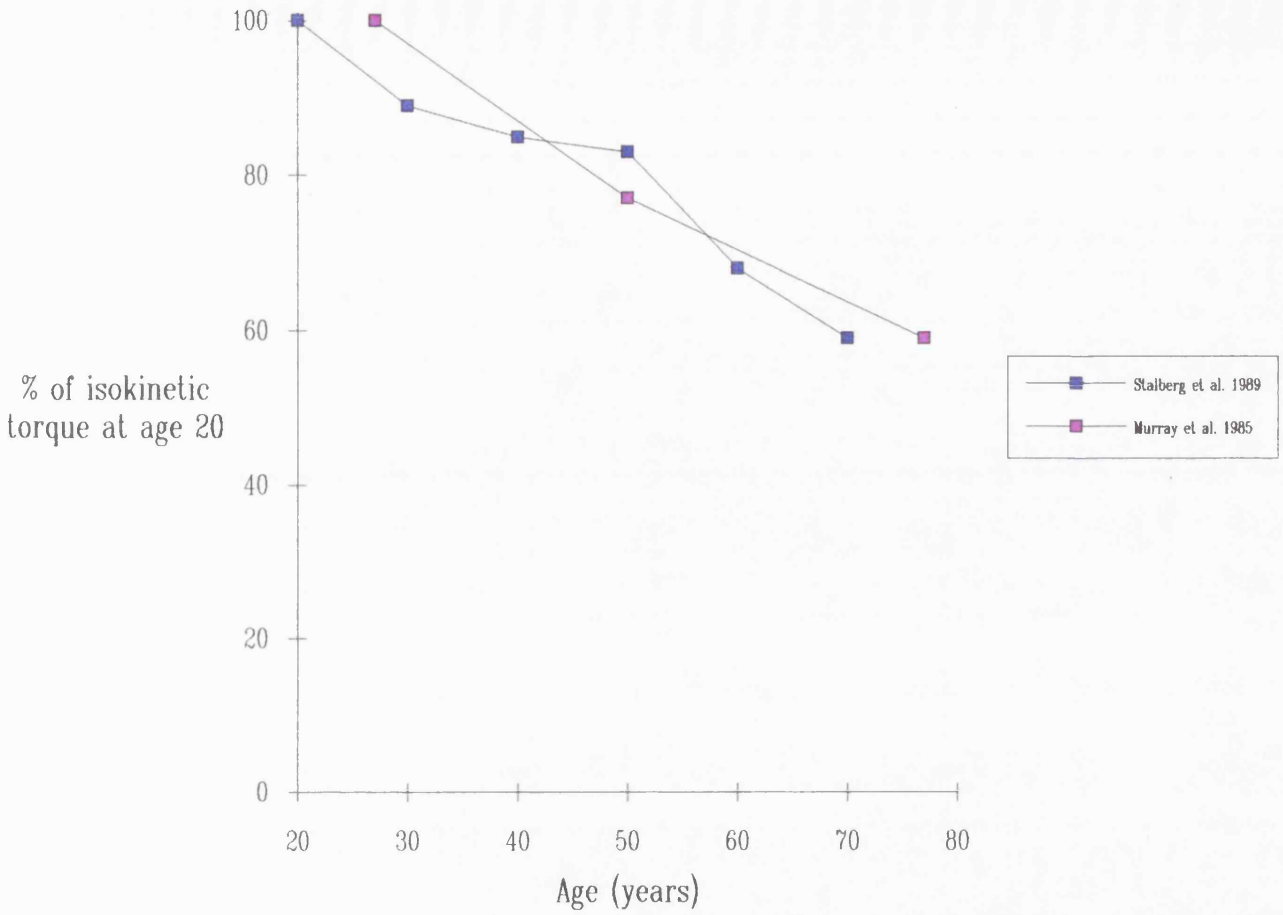
Knee-extensor isokinetic torque with respect to age in men



Study	20s	30s	40s	50s	60s	70s
Stalberg et al. 1989	4	6	6	5	5	7
Murray et al. 1980	24	-	-	24	-	24
Larson et al. 1979	11	11	10	12	16	-
Aniansson et al. 1986	-	-	-	-	n = 23	

Fig 11

Knee-extensor isokinetic torque with respect to age in women



Study	20s	30s	40s	50s	60s	70s
Stalberg et al. 1989	5	4	6	6	6	4
Murray et al. 1985	24	-	-	24	-	24

Weakness of the quadriceps muscle group has again been shown to correlate with assessments of function, being significantly correlated with Barthel index, and activities of daily living (ADL) score (Hyatt et al., 1990). It has also been suggested by Young (1986) that an 80 year old women has to make a maximal quadriceps contraction to enable her to rise unaided from a toilet seat, though he has subsequently come to modify his view that it is possible to predict the functional performance of individual elderly people by the application of theoretical standards (Skelton & Young, 1993).

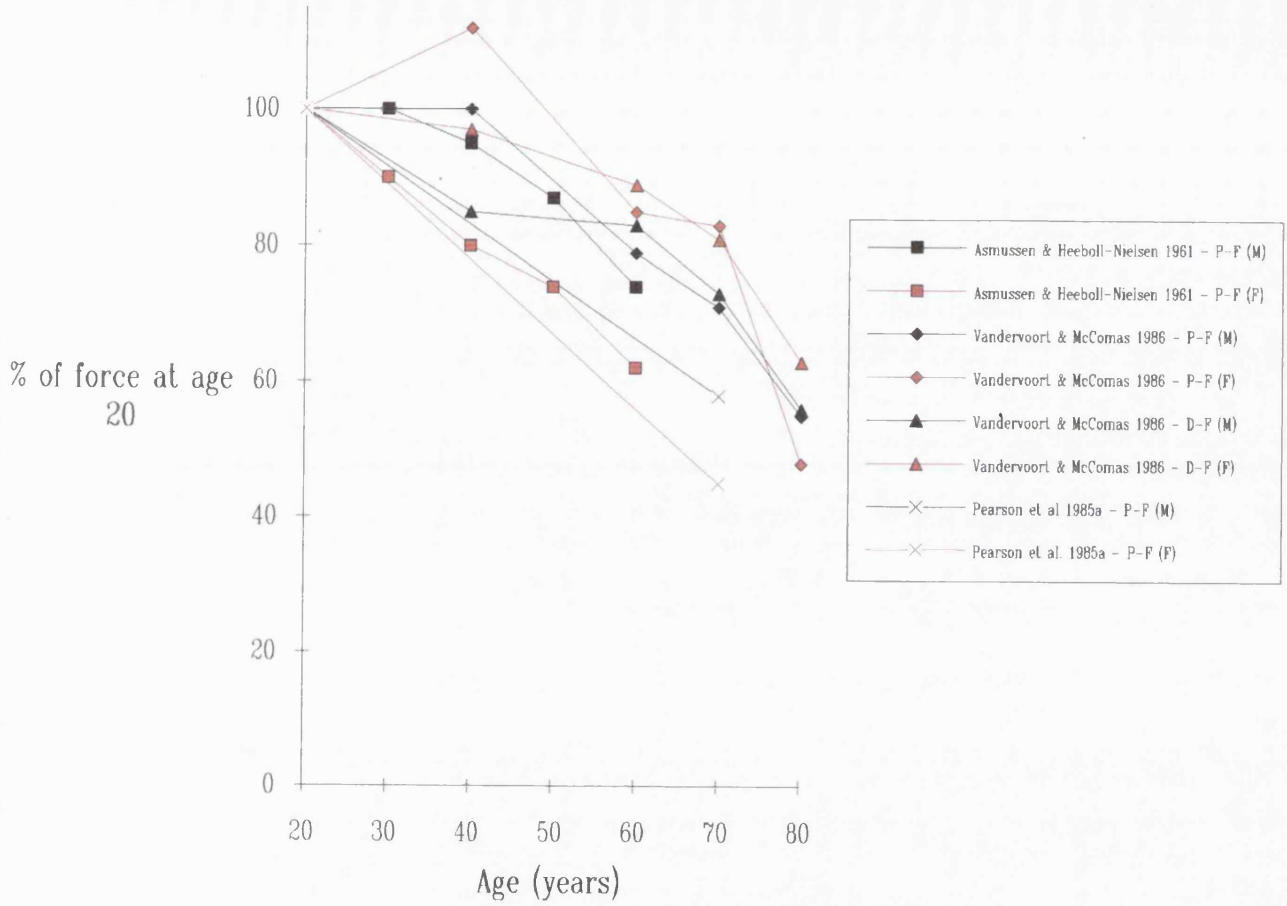
c) CALF-MUSCLES

The same 30-40% decline in force is seen with distal muscle groups of the leg (Fig 12). Here studies reporting results from both men and women are plotted together (females in red) to emphasise the difficulty in getting a clear idea of any sex difference from such data. Decline in force of triceps surae muscle was found in a large group of elderly men (n=84) and women (n=100) and the reduction in women was reported to be significantly greater than in men (Pearson et al., 1985a). However the results from both elderly groups were compared with those from only eleven subjects aged 20-24 all of them male. An added effect of age in both these elderly groups, whose age range was 65 to 90 year was subsequently reported, in that MVF declined significantly with age in both sexes (Pearson et al. 1985b).

The other two studies quoted in Fig 12 report results from cohorts of both sexes and more equal numbers. (Asmussen & Heebol-Nielsen, 1961 - black & red □ on fig 12) seem to agree with Pearson and colleagues' report suggesting a greater age-related decline in force of plantar-flexors of women than men and one which starts at around the age of 30 years. However this was not found in Vandervoort and McComas's study (1986) where no sex difference is apparent in the decline in force of either plantar- or dorsi-flexors. It is tempting to attribute Pearson and colleagues (1985a) result simply to the women having smaller muscles. Confusingly however comparison between force and calf muscle area in this study revealed no difference between elderly men and women.

Fig 12

MVF of calf muscles with respect to ageing



In fig 12 red symbols and lines indicate observations on females

Study	20s	30s	40s	50s	60s	70s	80s
Asmussen & Heeboll-Nielsen 1961 (M & F)	"20 - 40 subjects in each group"					-	-
Vandervoort & McComas 1986 D-F & P-F (M)	11	-	10	-	13	16	13
Vandervoort & McComas 1986 D-F & P-F (F)	11	-	10	-	10	9	8
Pearson et al. 1985a (M)	11	-	-	-	-	84	-
Pearson et al. 1985a (F)	11 (male)	-	-	-	-	100	-

d) ELBOW-FLEXORS

The effect of ageing on elbow-flexor MVF has not been so extensively studied, the only large study being Ufland's in men published in 1933. This is plotted in Fig 13 with three more recent studies comparing results from young and elderly male subjects.

Also plotted in this figure is McDonagh and colleagues' (1984) comparative findings in the planter-flexors. In their study the effects of ageing appeared more profound in this distal leg muscle group than in the proximal arm muscles.

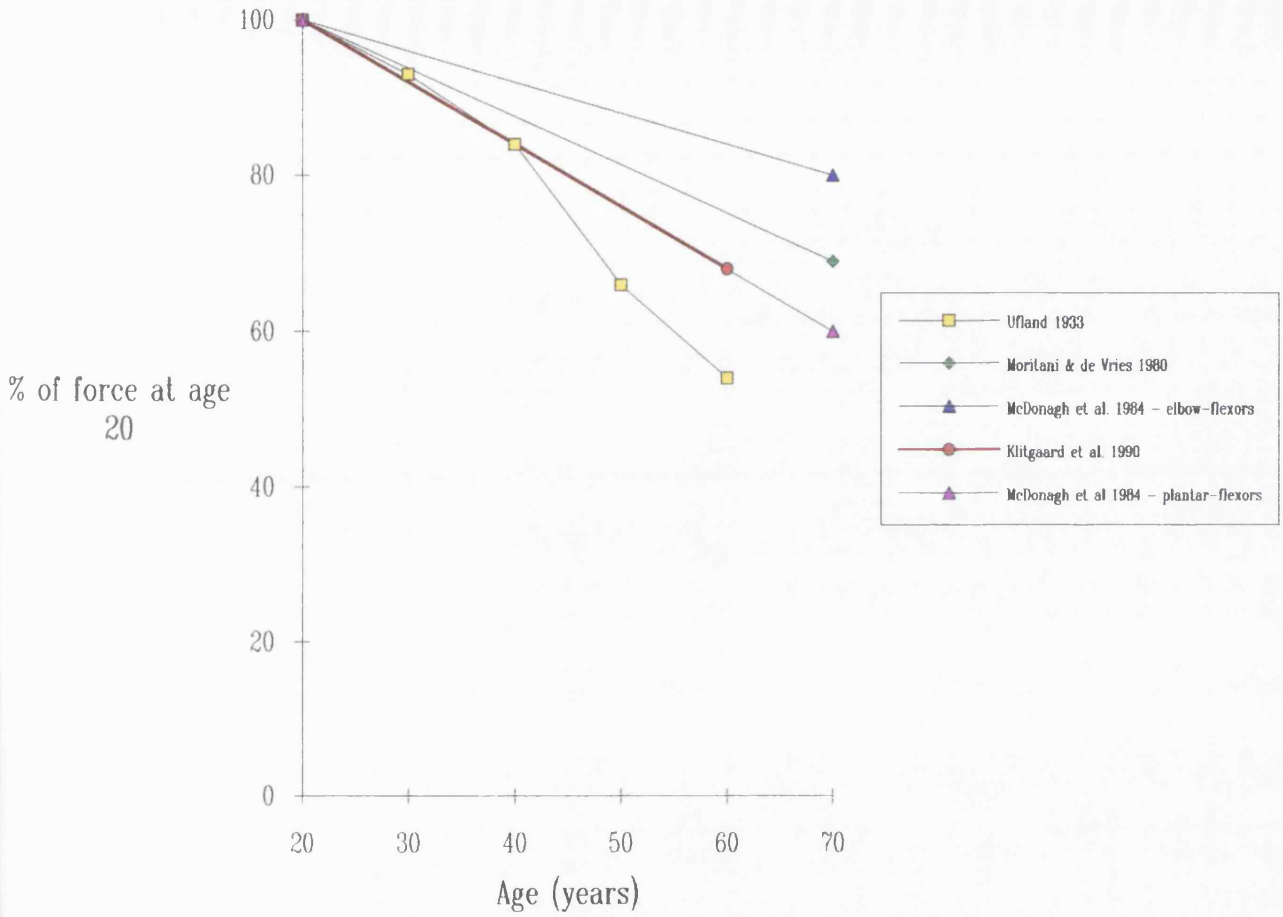
e) SUMMARY

All the studies of decline in muscle force with age show a 20 - 40 per cent decline in adults over a period of 30 - 40 years. Cross-sectional studies may tend to underestimate this decline in individuals. Most of the studies show little change with age up to 40 - 50 years though some show a progressive decline from age 20. No consistent sex differences have been demonstrated. Performance during dynamic contractions seems to be affected to a similar extent as isometric contractions. Leg muscles may be more susceptible to effects of ageing than those of the arm.

As all these are studies of muscle force without consideration of muscle size they give no information about whether the decline in force with age is due to loss of muscle, or to changes within the muscle or to some combination of these factors.

Fig 13

MVF of elbow-flexors in men with respect to age 1933-1990



Study	20s	30s	40s	50s	60s	70s
Ufland 1933	921	830	749	442	72	-
Moritani & de Vries 1980	5	-	-	-	-	5
McDonagh et al. 1984	9	-	-	-	-	11
Klitgaard et al. 1990	6	-	-	-	7	-

MUSCLE SIZE

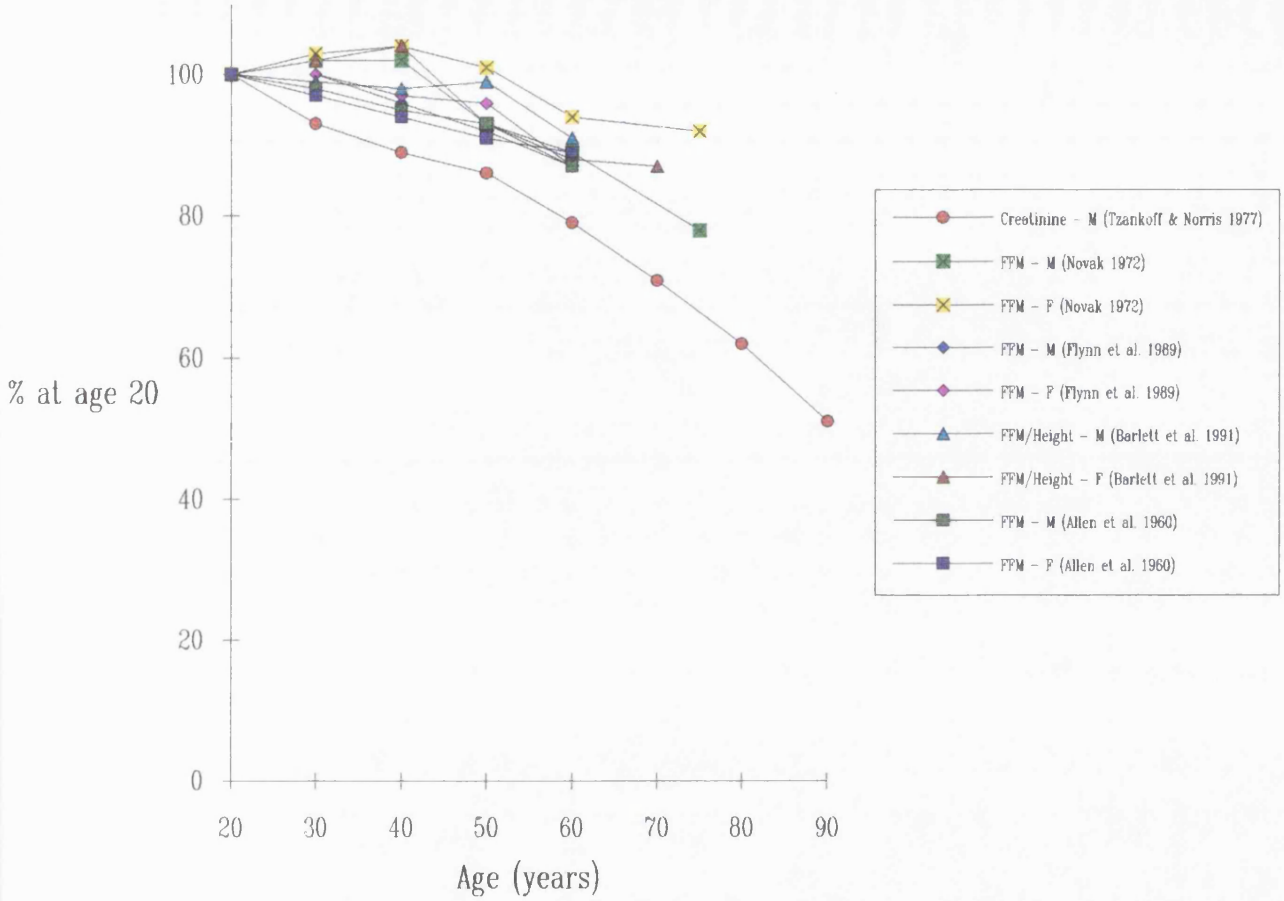
Wasting is equally as commonplace an association of ageing as muscle weakness:

> the sixth age shifts
> Into the lean and slippered pantaloon,
> With spectacles on nose and pouch on side,
> His youthful hose, well saved, a world too wide
> For his shrunk shank, and his big manly voice,
> Turning again toward childish treble, pipes
> And whistles in his sound;
>
> *(As You Like It - Act II, scene 7)*

Cross-sectional studies of overall muscle mass deduced from fat-free mass (FFM) calculated by means of total body potassium (Allen et al., 1960, Novak, 1972, Flynn et al., 1989) and densitometry (Bartlett et al., 1991) or from creatinine excretion (Tzankoff & Norris, 1977), show a decline amounting to as much as one third of total muscle mass over fifty years (Fig 14). Creatinine excretion seems to decline more rapidly with age than the other indicators of muscle mass. Decline in renal function would be expected to exert an effect in the opposite direction so it may be that the rate of formation of creatinine by unit mass of muscle also declines with age.

Fig 14

Estimates of overall muscle mass with respect to age



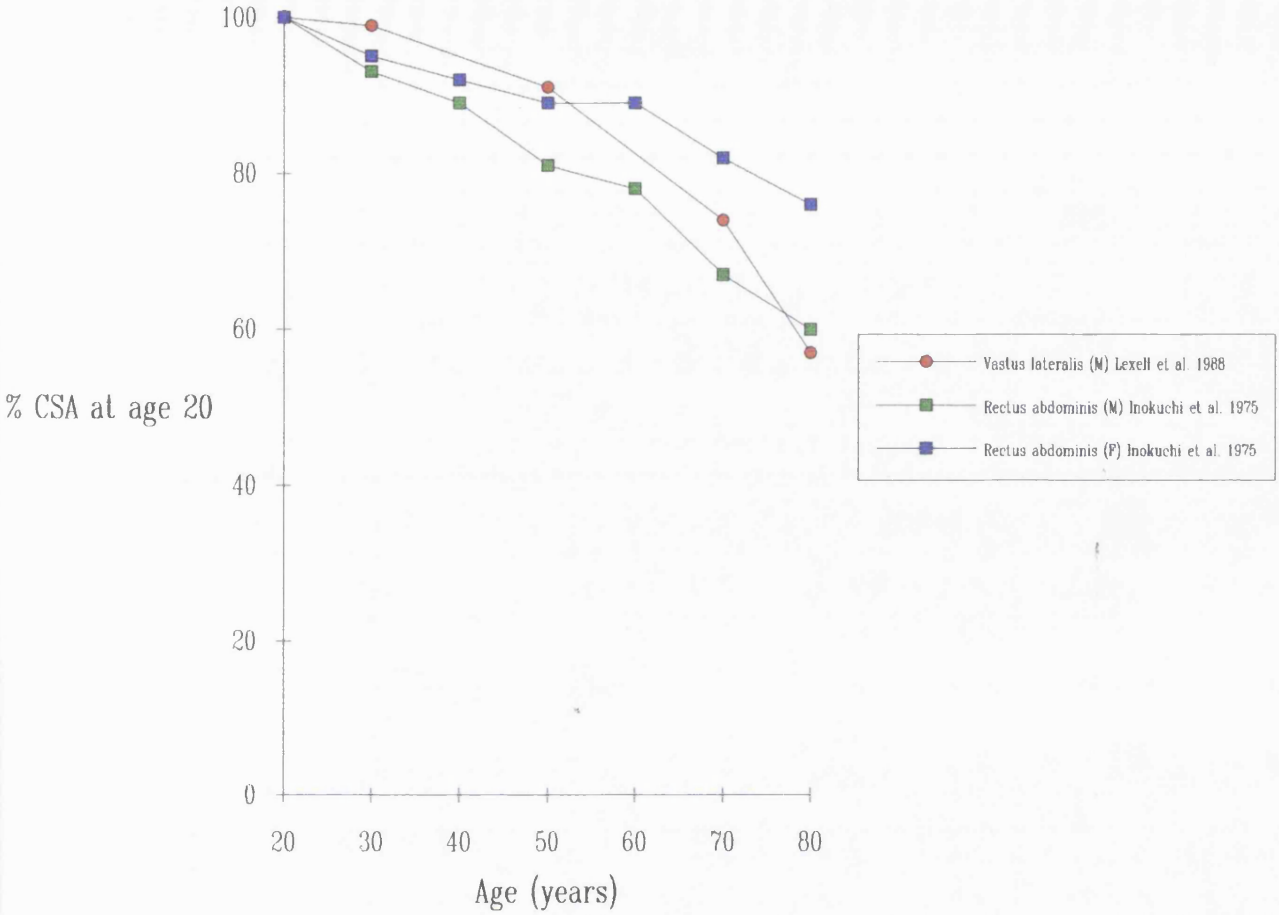
Study	20s	30s	40s	50s	60s	70s	80s	90s
Tzankoff & Norris 1977	14	127	154	215	172	162	103	12
Novak 1972 - M	27	58	33	37	42	18		-
Novak 1972 - F	89	33	44	72	54	13		-
Flynn et al. 1989 - M	-	104	184	173	103	-	-	-
Flynn et al. 1989 - F	-	11	14	20	16	-	-	-
Bartlett et al. 1991 - M	135	35	52	41	19	-	-	-
Bartlett et al. 1991 - F	237	115	80	57	19	23	-	-
Allen et al. 1960 - M	243	258	122	46	30	4		-
Allen et al. 1960 - F	86	60	42	23	18	3	-	-

The Baltimore ageing study also reports results of a longitudinal eighteen year follow-up of their subjects (Flynn et al., 1989). Lean-body mass related to height declined significantly from age 40 in men. Although there was a trend towards a decline in women after the age of 50, standard deviations were large and the number of observations relatively small. The differences do not appear to be significant, contrary to the view expressed in the discussion section of their paper. A cross-sectional study from Gothenburg showed a decline in total body potassium of around ten per cent for males but no significant change for females (Steen et al., 1977). Fat-free mass calculated from anthropometric measurements showed no decline with age in either a cross-sectional study of 158 men and 112 women aged 65 - 90 years (MacLennan et al., 1980) nor in a longitudinal study of seventy-three manual workers followed for up to five years after retirement (Patrick et al., 1982), possibly because the test was too insensitive to detect changes of the size one might anticipate.

Direct measurements of muscle CSA from post-mortem material have shown declines of about a third, between the ages of 20 to 80 years, in vastus lateralis from males (Lexell et al., 1988) and rectus abdominis from males and females (Inokuchi et al., 1975) (Fig 15).

Fig 15

Post-mortem changes in muscle CSA with respect to age



Study	20s	30s	40s	50s	60s	70s	80s
Lexell et al. 1988	9	9	-	8	-	9	8
Inokuchi et al. 1975 (M)	5	5	4	5	5	5	5
Inokuchi et al. 1975 (F)	5	5	5	5	5	5	5

In vivo cross-sectional studies comparing CSA of specific muscle groups in young and elderly subjects are shown in table 1.

Table 1

Study	Davies et al. 1986		Young et al. 1985	Young et al. 1984	Hyatt et al. 1990		Klit-gaard et al. 1990		Mori-tani & de Vries 1980	Vander-voort & McComas 1986	
Muscle	Triceps surae		Quads	Quads	AMA	TMA	Quads	Biceps	Biceps	Triceps surae	
Method	Anthr.		Ultra-sound	Ultra-sound	Anthr.		CAT		Anthr.	Ultrasound	
Sex	M	F	M	F	M & F		M		M	M	F
Numbers of Subjects (Young)	12	8	12	25	30		6		5	11	11
Numbers of Subjects (Old)	20	11	12	25	92		7		5	13	8
Age (Young)	22	22	25	24	33		28		22	22-31	
Age (Old)	70	69	75	74	77		68		70	82-100	
% decline in CSA	14	1 - NSD	25	33	9	19	24	20	+11 - NSD	23	33

Abbreviations: Anthr. = anthropometric; CAT = computer-assisted tomography; Quads = knee-extensors; AMA = arm muscle area; TMA = thigh muscle area; CSA = cross sectional area; NSD = no significant difference

Significant declines in arm and calf muscle areas measured anthropometrically were found within a group of 84 males aged 65 - 87 years, but not in a group of 100 women of similar age, in a cross-sectional study (Pearson et al., 1985b). Doubts have been expressed by Bassey and colleagues (1988) about the method used to estimate CSA of calf muscles in the study by Pearson and colleagues (1985b) and that of Davies and colleagues (1986) quoted in table 1 which also gave a non-significant result in the females. The results for biceps are particularly inconsistent, one study actually reporting the elderly to be larger although not significantly so (Moritani and de Vries, 1980). A CAT-scan follow up study of fourteen (10 female) of the subjects initially measured by ultrasound in Young and colleagues' studies (1984 & 1985), showed a decline in CSA of knee-extensors of 0.8% (95% C.I. = - 1.6 to - 0.04) per year over a period of seven years (Grieg & Young, 1991).

SUMMARY

Most studies demonstrate a loss of muscle mass of the order of 20 - 30 per cent. Thus at least part of the decline in muscle force with age appears to be due to loss of muscle bulk. The extent of the contribution of this factor to the overall loss of force may vary between individuals and between muscle groups in the same individual. For example, it has seemed harder to show significant changes in female than in male subjects and arm muscles may again be less affected than leg muscles.

WHAT IS THE CAUSE OF THE WASTING?

Muscle wasting is due to fibre loss or fibre atrophy or both.

a) FIBRE ATROPHY

Overall fibre atrophy is demonstrated by the finding of a significant decline in alkali soluble protein per unit DNA content of muscle (Forsberg et al., 1991). There is general agreement that there is a decline in fast twitch type II fibre area with age but that there is no significant decline in the area of slow twitch type I fibres (Figs 16 & 17).

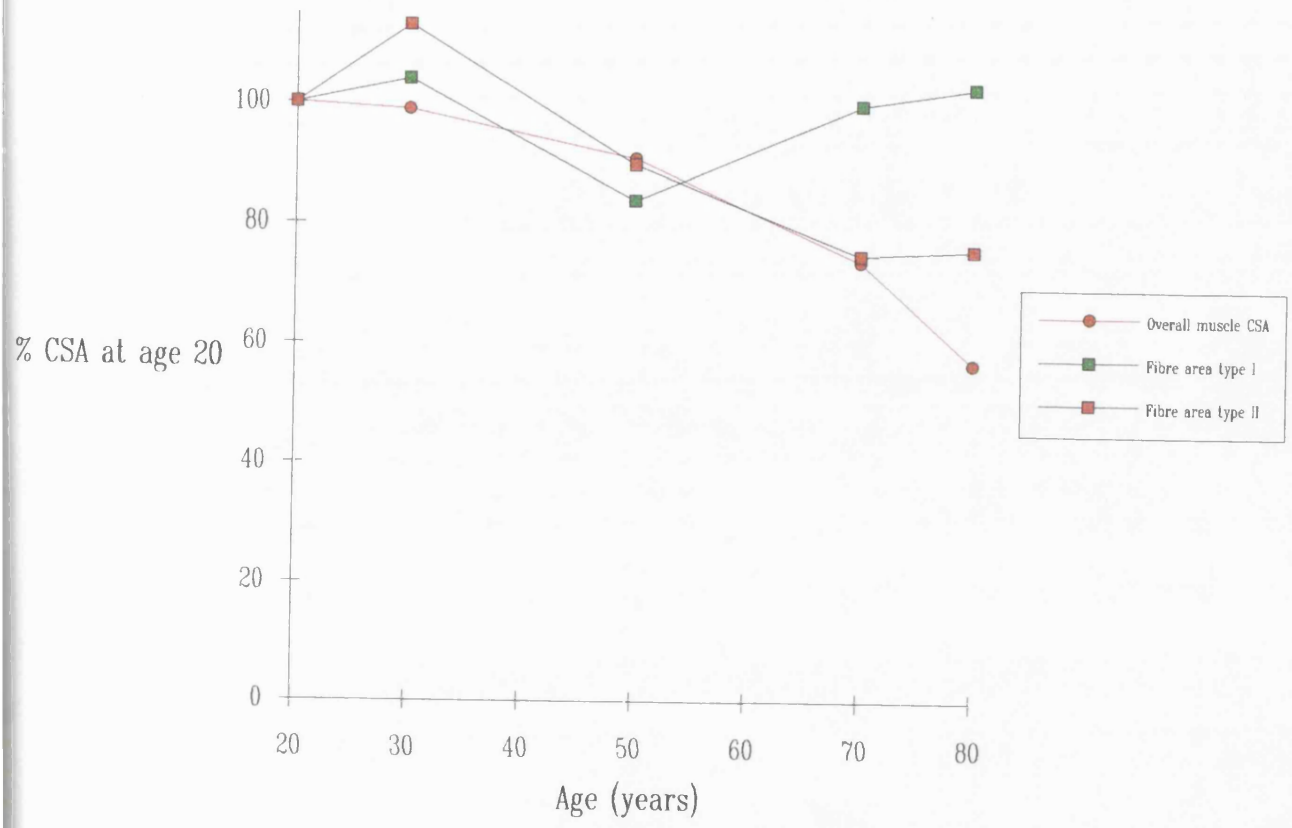
b) FIBRE LOSS

i) HISTOLOGICAL STUDIES OF MUSCLE

A descriptive post-mortem study of deltoid, biceps brachii, rectus femoris, gastrocnemius and extensor digitorum brevis (EDB) (Jennekens et al., 1971) reported loss of both type I and type II fibres. Decline in fibre numbers has been estimated quantitatively in vastus lateralis (Lexell et al., 1988) (Fig 18) and rectus abdominis (Inokuchi et al., 1975) (Fig 19). Some doubts are raised by the method of estimating fibre number in Lexell and colleagues' study since they took no account of pennation when measuring muscle CSA. Thus they would have tended to underestimate the decline in fibre numbers with age if as one would predict the older muscles were less pennate. Inokuchi and colleagues (1975) found a very marked and consistent fibre

Fig 16

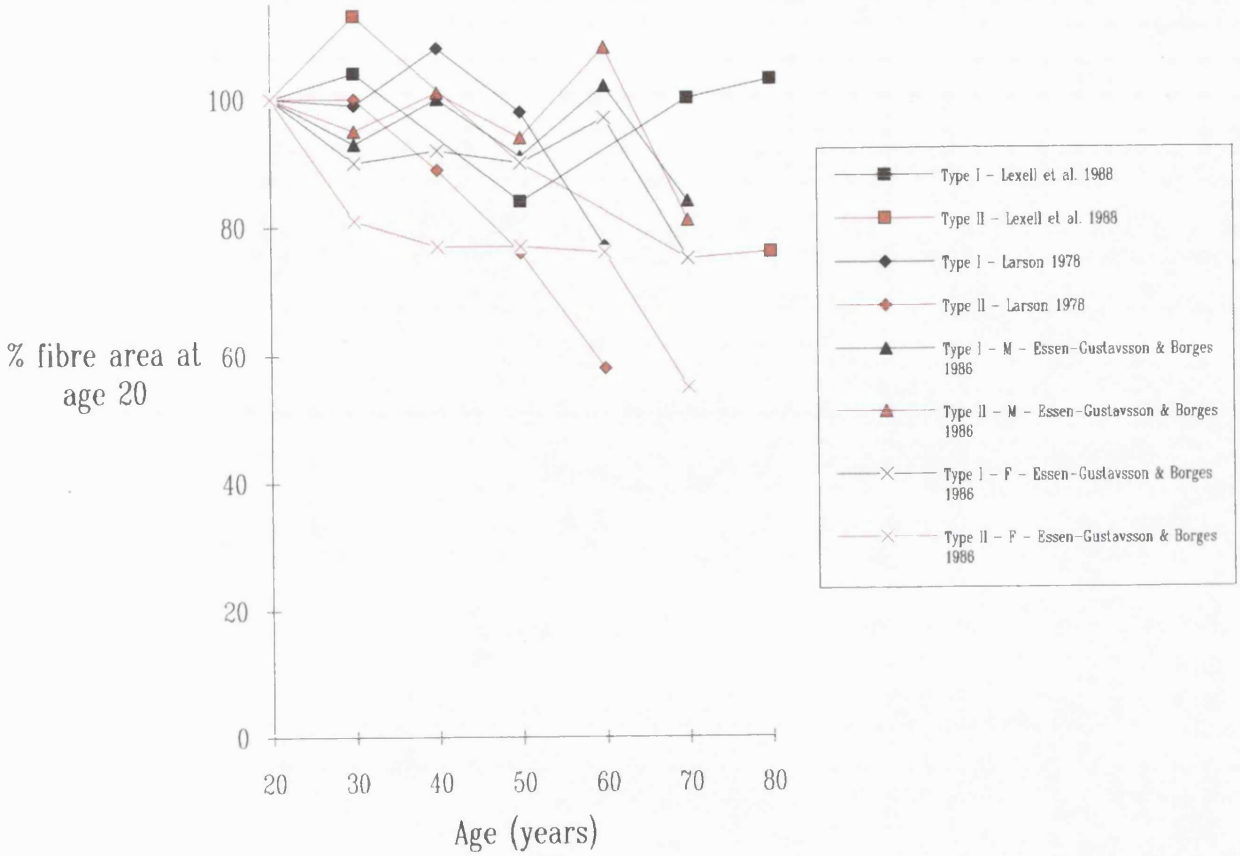
Comparison between overall decline in muscle CSA and relative change in type I & II fibre areas, with respect to age, in knee-extensors (Lexell et al., 1988)



Study	20s	30s	40s	50s	60s	70s	80s
Lexell et al. 1988	9	9	-	8	-	9	8

Fig 17

Changes in the areas of type I & II fibres in knee-extensors, with respect to age

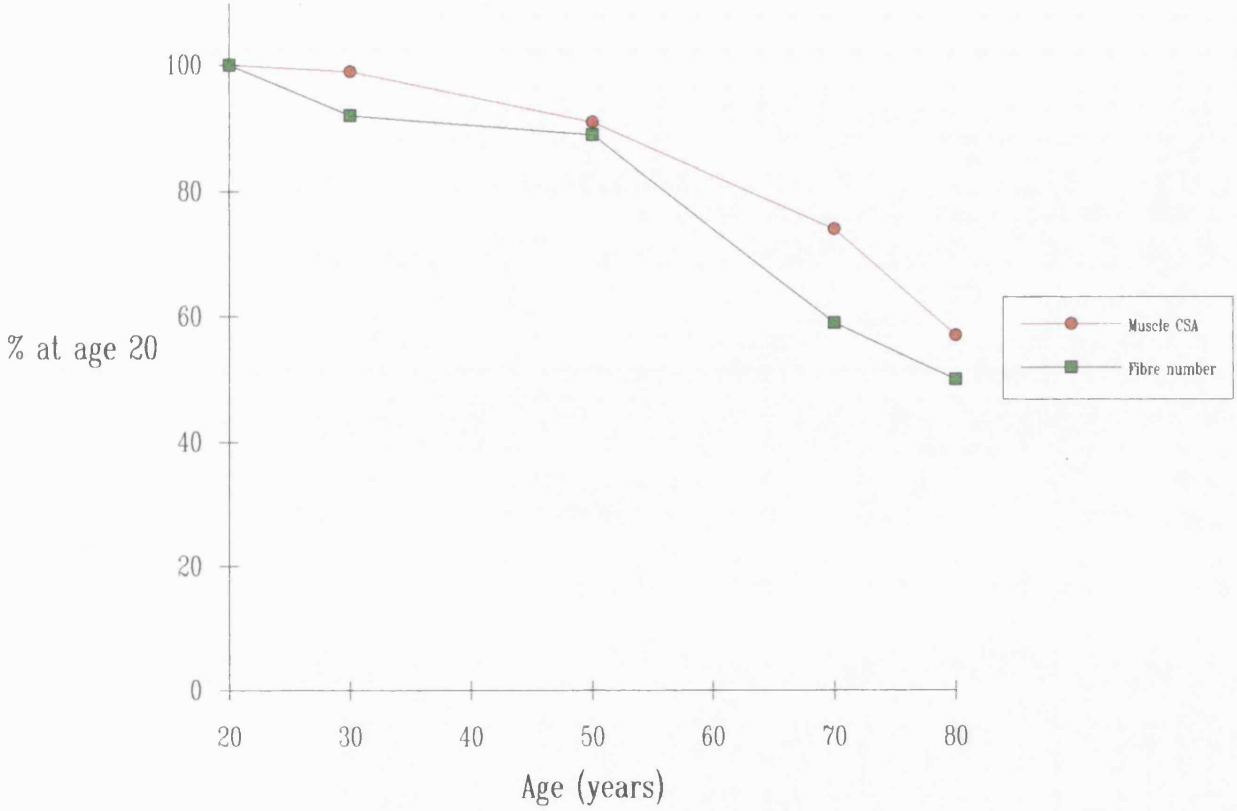


In Fig 17 change in type II fibre area is indicated by red symbols and lines

Study	20s	30s	40s	50s	60s	70s	80s
Lexell et al. 1988	9	9	-	8	-	9	8
Larson 1978	11	12	10	12	10	-	-
Essen-Gustavsson & Borges 1986 (M)	4	6	6	5	5	7	-
Essen-Gustavsson & Borges 1986 (F)	5	4	6	6	6	4	-

Fig 18

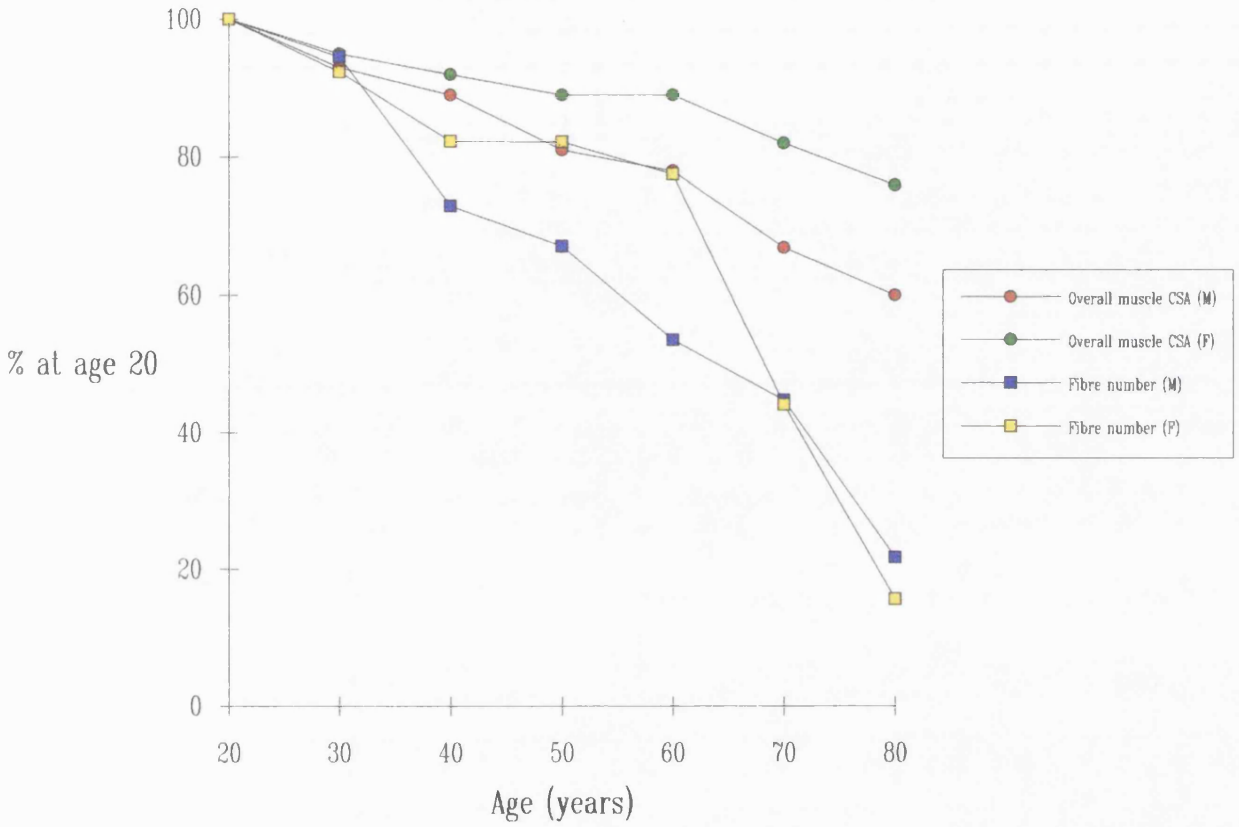
Comparison between declines in overall muscle CSA and fibre number, with respect to age, in knee-extensors (Lexell et al., 1988)



Study	20s	30s	40s	50s	60s	70s	80s
Lexell et al. 1988	9	9	-	8	-	9	8

Fig 19

Comparison between declines in overall muscle CSA and fibre number, with respect to age, in the rectus abdominis muscle (Inokuchi et al., 1975)



Study	20s	30s	40s	50s	60s	70s	80s
Inokuchi et al. 1975 (M)	5	5	4	5	5	5	5
Inokuchi et al. 1975 (F)	5	5	5	5	5	5	5

loss with age in the rectus abdominis muscle of both sexes, though their methodology has to be taken largely on trust and the number of specimens in each age group is small.

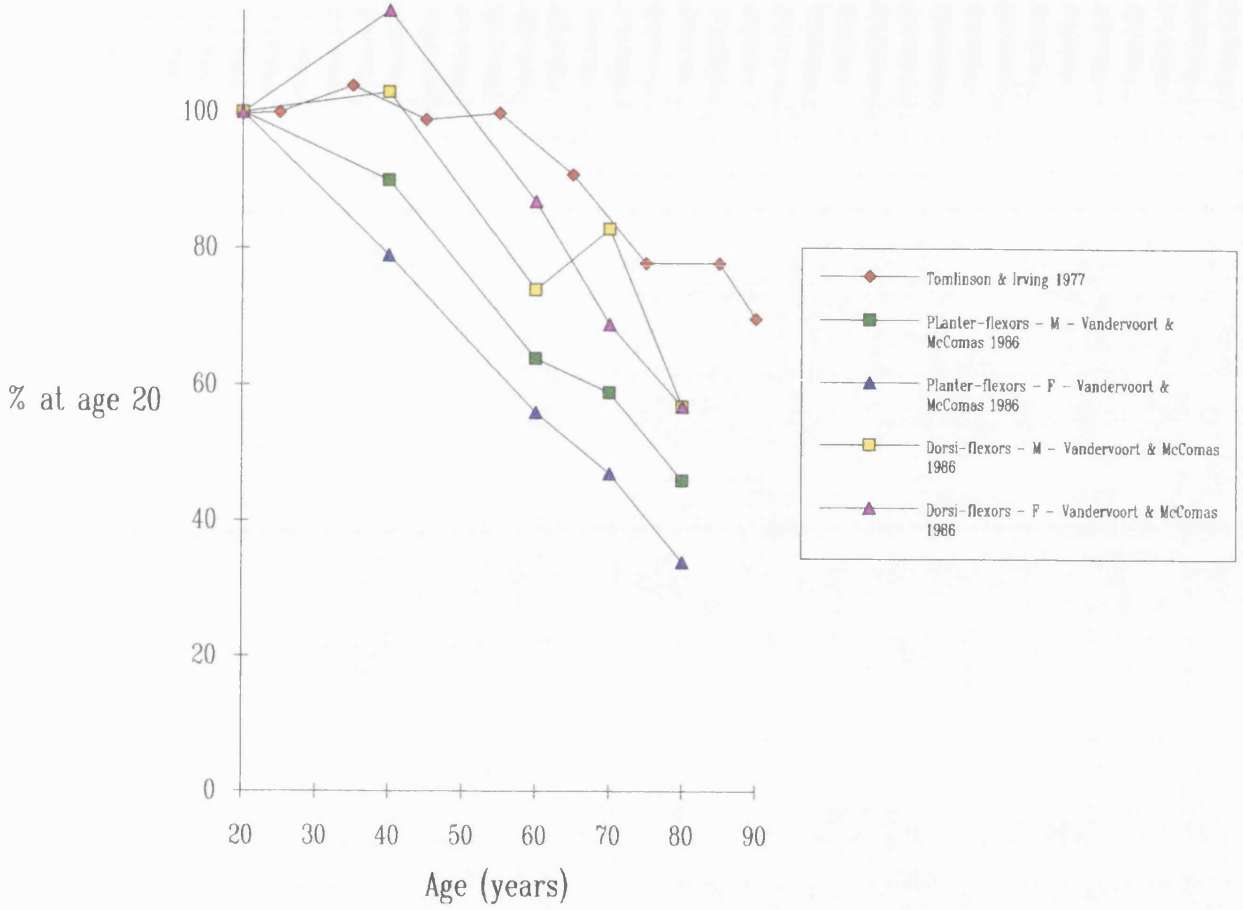
The conclusion that fibre numbers significantly decline with age raises the question whether there is a concomitant loss of motor units or whether a primary degenerative process of muscle is occurring (Gutman & Hanzlíková, 1976)

ii) MOTOR-UNITS

The decline in motor unit numbers with age has been investigated histologically and electrophysiologically. Fig 20 summarises the results of one of each of these studies. In a post-mortem study of spinal cord sections from subjects aged 13 to 95 motor neurone numbers were found to be well preserved up to 60 years of age. A progressive decline, though with much individual variation, was reported thereafter (Tomlinson & Irving, 1977). The results of the electrophysiological study are comparable with no significant loss of motor units up to age 60 but a significant decline thereafter (Vandervoort & McComas, 1986). Motor unit numbers were also found to be reduced in earlier studies of extensor digitorum brevis (EDB) (Campbell et al., 1973) soleus (Sica et al., 1976) and the thenar muscles supplied by the median nerve (Brown, 1972). Surviving motor units in elderly subjects tended to be larger than in young for EDB (Campbell et al., 1973) but not for soleus (Sica et al., 1976). Motor unit contraction time was prolonged and there was also a significant decrease in threshold firing rates of motor units from first dorsal interosseous (FDI) in elderly subjects (Newton et al.,1988).

Fig 20

Decline in motor unit numbers with age



Study	20s	30s	40s	50s	60s	70s	80s	90s
Tomlinson & Irving 1977 (M & F)	n=12 (age 11-40)		n=11 (age 41-60)		n=9 (age 61-80)		n=14 (age 81-95)	
Vandervoort & McComas 1986 D-F & P-F (M)	11	-	10	-	13	16	13	-
Vandervoort & McComas 1986 D-F & P-F (F)	11	-	10	-	10	9	8	-

This evidence raises the question as to why neuropathic changes are generally absent in biopsy studies from ageing muscle (Grimby & Saltin, 1983) e.g. from vastus lateralis (Aniansson et al., 1981). An exception was a Japanese study (Tomonaga, 1977) but details of the biopsy technique used are not given. Grimby and Saltin suggest that with the small samples generally obtained by needle biopsy techniques one would not expect to find evidence of a process that is patchy and affecting only a relatively small number of fibres at any one time. Jennekens and colleagues (1971) reported neuropathic changes and evidence of denervation and re-innervation in post-mortem samples (characterised by groups of atrophic fibres with clumps of pyknotic nuclei between areas with fibres of normal size, and enclosed fibres - fibres of one type completely surrounded by fibres of a similar type). Neuropathic changes were more marked in distal than proximal muscles (also reported by Tomonaga) supporting Grimby and Saltin's contention that sampling error may be the reason for missing neuropathic changes in needle biopsy specimens from knee-extensors. In Tomonaga's study it is hard to see how specimens of some of the muscles examined could have been obtained ethically during life. Despite being described as a biopsy study it is therefore possible that this is also a post-mortem study where much larger specimens could have been examined.

Evidence such as the above led Grimby and Saltin (1983) to conclude that "there appears no reason to postulate qualitative changes in muscle or muscle fibres with age, i.e. changes in contractile properties". This seems naive. Loss of motor units alone is unlikely to account for the decline in muscle force with age. Jennekens and colleagues (1971) emphasised striking differences in the degree to which the muscles were affected by the reported changes. In all the subjects studied, changes were more

marked in EDB than in the other muscles. Apart from EDB, one of the subjects, a 78 year old male, had muscles histologically indistinguishable from a young adult's. Also in a report of ninety-one subjects aged 65-94 (58 female) no correlation was found between motor unit number and age (Denham et al., 1980). Motor units are probably lost progressively throughout life as Grimby & Saltin (1983) observe, albeit to an accelerated extent after the age of 60, by a process primarily disturbing the neuromuscular connection (Gutman & Hanzlíková, 1976). However muscle strength increases during childhood to a peak in young adults (Shephard, 1969). When the independent influence of type II fibre area on force was eliminated by multiple regression analysis, age still had a negative partial correlation with force (Larsson 1978). In Kallman and colleagues' study (1990) there was no relationship between the slope of creatinine excretion versus age and the slope of hand-grip versus age and thirty-eight per cent of the individual variation in hand-grip could be independently explained by age compared with sixteen per cent by forearm circumference. As emphasised on page 16 muscle force is proportional to cross-sectional area (Weber, 1846, cited by Haxton, 1944). Thus a qualitative change in contractile properties must lead to a change in the amount of force produced for a given cross-sectional area. To answer the question "does age produces such changes?" direct measurements comparing muscle force and cross-sectional area are required.

FORCE AND CROSS-SECTIONAL AREA IN HUMAN AGEING MUSCLE

Tables 2 & 3 summarise the details of subjects, methods and results from seven studies reporting force and cross-sectional area in groups of young and elderly subjects.

a) KNEE-EXTENSORS (table 2):

Young and colleagues (1984) found no difference between young and elderly women either when mean values of MVF/CSA or when regressions were compared. A nineteen per cent reduction in mean MVF/CSA in elderly men was found though, as noted above (p 21), the regression relationship between force and cross-section area did not achieve significance for the young men (Young et al., 1985). The decline in force quoted in Hyatt and colleagues' study (1990) is an over-estimate. Their value for knee-extensor MVF in young subjects (438 N) derives from an earlier publication from the same group (Shaunak et al., 1987). This number appears to be simply the average of the mean MVF from male subjects (551 $\pm$ 107 N, n = 69) and that from the female subjects (325 $\pm$ 86 N, n = 67) in the earlier study. However women outnumber men by more than 2:1 among the elderly subjects (64 females, 28 males) in Hyatt and colleagues study (1990). Thus if a simple average value for both sexes together was to be used $\approx$390 N would have been more appropriate. Klitgaard and colleagues' (1990) data is rather hard to understand. They report a reduction in "specific tension" in knee extensors compared to young controls for sedentary elderly men and publish histograms of maximal isometric torque (units N.m), CSA (units cm^2) and of specific tension (units N/cm^2). However it is not stated how the values of specific tension were arrived at. They do not appear to be force/CSA assuming force

Table 2

Study	Hyatt et al. 1990	Young et al. 1985	Young et al. 1984	Klitgaard et al. 1990	
Muscle	Quads	Quads	Quads	Quads	Biceps
Method - Force	MVF	MVF	MVF	MVF	
Method - CSA	Anthro-pometric	Ultrasound	Ultrasound	CAT	
Sex	M & F	M	F	M	
Number of subjects (Young)	30	12	25	6	
Number of subjects (Old)	92	12	25	7	
Age (Young)	33	25	24	28	
Age (Old)	77	75	74	68	
Force N (Young)	438	621±34	-	-	-
Force N (Old)	235.6±91.4	377±21	-	-	-
CSA cm^2 (Young)	171.5±35.1	70.8±1.61	-	80.1	15.3
CSA cm^2 (Old)	138.2±35.5	53.2±1.83	-	(60.9)	(12.2)
Force/CSA N/cm^2 (Young)	2.5	(8.7)	7.1±0.2	-	-
Force/CSA N/cm^2 (Old)	1.7	(7.1)	6.9±0.24	-	-
% decline(Force)	46	39	35	-	-
% decline(CSA)	19	25	33	24	20
% decline (Force/CSA)	32	19	1 (NSD)	20	15

All are cross-sectional studies and comparisons are of ratio standards. Means ± SD are given. Numbers without brackets are quoted direct from respective references. Numbers in brackets are derived from those quoted or measured from published histograms

Table 3

Study	Moritani & de Vries 1980	Davies et al. 1986		Vandervoort & McComas 1986	
Muscle	Biceps	Triceps surae		Triceps surae	
Method - Force	MVF	$P_0$50		MVF	
Method - CSA	Anthro-pometric	Anthropometric		Ultrasound	
Sex	M	M	F	M	F
Number of subjects (Young)	5	12	8	11	11
Number of subjects (Old)	5	20	11	13	8
Age (Young)	22	22	22	22-31	
Age (Old)	70	70	69	82-100	
Force (Young)	(392.8N)	1620 ± 237 N	1256 ± 179 N	171±34 N.m	113±35 N.m
Force (Old)	(271.7N)	950± 190 N	823 ± 207 N	94±30 N.m	54±23 N.m
CSA cm^2 (Young)	58.2±3.2	102±11	79±10	36.5±5.3	31.1±2.0
CSA cm^2 (Old)	64.7±4.97	88±11	78±14	28±5.1	20.9±3.8
Force/CSA (Young)	(6.7 N/cm^2)	(15.8) N/cm^2	(15.8) N/cm^2	4.7 $N.m/cm^2$	3.6 $N.m/cm^2$
Force/CSA (Old)	(4.2 N/cm^2)	(10.7) N/cm^2	(10.5) N/cm^2	3.4 $N.m/cm^2$	2.6 $N.m/cm^2$
% decline(Force)	31	42	35	45	52
% decline(CSA)	NSD	14	1	23	33
% decline (Force/CSA)	40	41		28	28

All are cross-sectional studies and comparisons are of ratio standards. Means ± SD (Davies et al., 1986, Vandervoort & McComas, 1986) or ± SEM (Moritani & de Vries, 1980) are given. Numbers without brackets are quoted direct from respective references. Numbers in brackets are derived from those quoted or measured from published histograms.

to have been measured at the ankle with a lever arm between knee and ankle of approximately half a metre. They also have two different values for the percentage declines in force/CSA in their text and summary (that from their text is quoted in the table).

In a longitudinal study of ten of the women (79 - 89 years) and four of the men (79 - 84 years) previously studied by Young and colleagues (1984,1985) no significant reduction in MVF/CSA was found compared to the results from seven years previously though CAT-scanning was used to measure CSA in the follow-up study and the results compared with the previous ultrasound measurements (Greig and Young, 1991).

b) ANKLE PLANTAR-FLEXORS (table 3):

Vandervoort and McComas (1986) reported a decline of about thirty per cent in MVF compared to an ultrasound measurement of CSA in men and women. Davies and colleagues (1986) reported a forty-one per cent decline in supramaximal tetanic force at 50 Hz ($P_0$50)/CSA in elderly men and women compared to a group of young controls. In their study CSA was estimated anthropometrically and allowances were made for muscle pennation and the amount of bone present. There was no decline with age in this estimate of CSA in women. The published decline in force/CSA for their male and female subjects combined, which is quoted in the table is nearly ten per cent larger than the derived values for males and females separately. This is presumably due to some correlation between force and CSA values. Therefore other derived values must be viewed with caution.

c) **BICEPS** (table 3):

The loss of force with ageing has been shown to be more pronounced in leg than arm muscles (McDonagh et al., 1984) but the two studies of biceps MVF/CSA are conflicting one giving one of the highest and the other one of the lowest percentage declines. Moritani and de Vries's study (1980) is another where no significant difference was detected between the CSAs of the young and elderly subjects tested.

d) **SUMMARY**

Apart from Young and colleagues study of female quadriceps (1984) there is reasonable consistency in the decline in force/CSA with age in the various studies quoted. However this conceals a wide variation in the absolute values of force/CSA. So far as percentage change is concerned most of the variation is in the CSA measurements but the variation in absolute force measurements is also wide and it just so happens that in the studies where there is little change in CSA, forces in the elderly subjects were particularly low. Thus although there is direct evidence of a qualitative change in muscle performance with age it is hard to quantify its extent.

POSSIBLE CAUSES OF A REDUCED FORCE/CSA

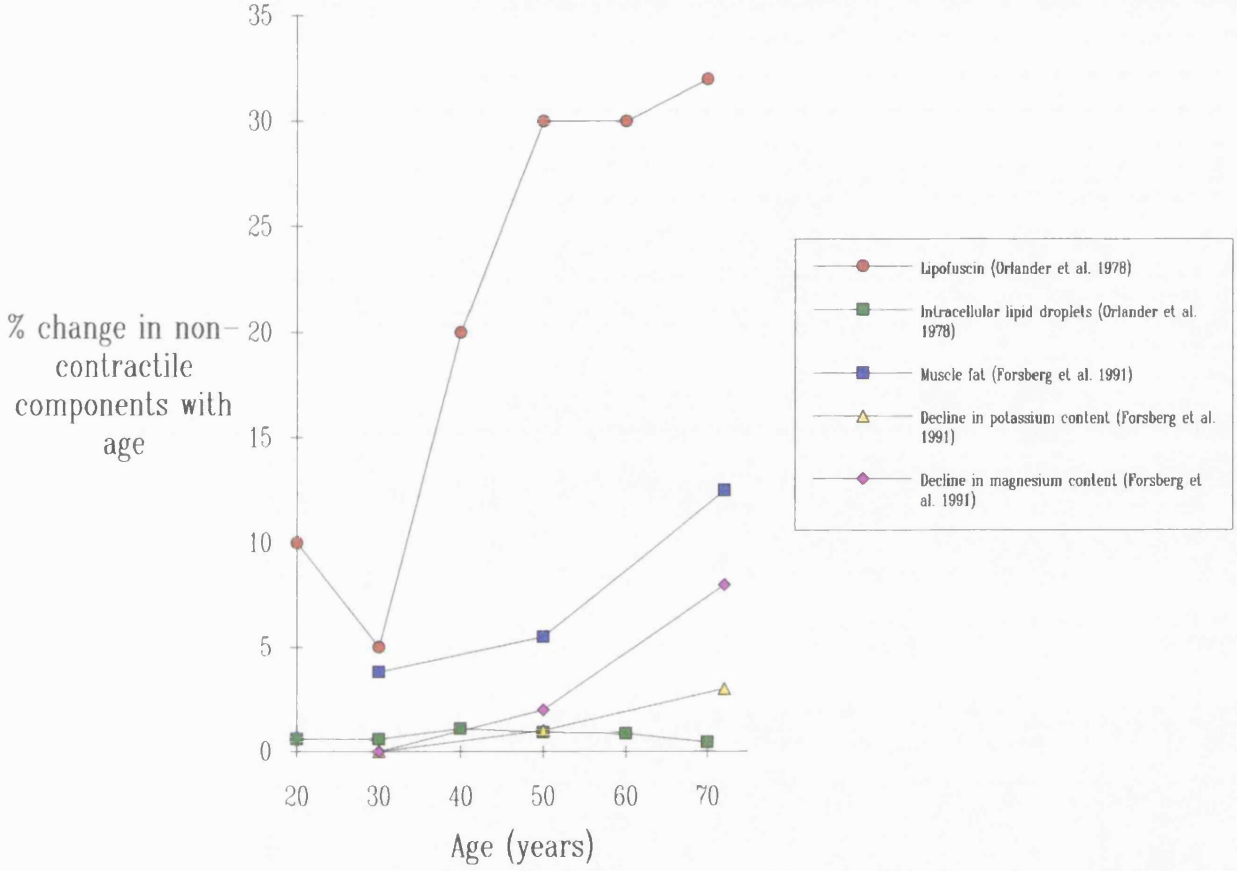
a) REPLACEMENT OF MUSCLE BY NON-CONTRACTILE TISSUE

Earlier studies (reviewed by Rubinstein 1960) tended to emphasise the replacement of muscle by non-contractile tissue, especially connective tissue and fat, together with the deposition of inert material such as lipofuscin, as prominent features of ageing. More recent studies have given widely different results. The most recent, Forsberg et al., 1991 reports an approximately three-fold increase in fat content of needle biopsies from quadriceps. There were also significant declines in potassium and magnesium relative to fat free solid contents from which was inferred an increase in connective tissue with age. These changes summarised in Fig 21 are trivial compared to those reported in a Japanese post-mortem study of the rectus abdominis muscle using light microscopy, it was found that the muscle was of the order of fifty per cent fat and up to twenty per cent connective tissue (by volume) in male and nulliparous female subjects in their eighties compared to an average of less than five per cent fat and seven per cent connective tissue in subjects in their twenties (Inokuchi et al., 1975) (Fig 22).

A light microscopy study of biopsies from vastus lateralis in men (also summarised in Fig 21) found no increase with age in lipid droplets as a percentage of cell volume (Örlander et al., 1978) and a descriptive electron microscopy study of biopsies from gastrocnemius, vastus lateralis, deltoid, gluteus, psoas and external oblique muscles from eight subjects aged 70 to 83 (Shafiq et al., 1978), reported the general architecture of aged muscle to be well preserved, biopsies from only one subject

Fig 21

Replacement of muscle by non-contractile tissue with respect to age

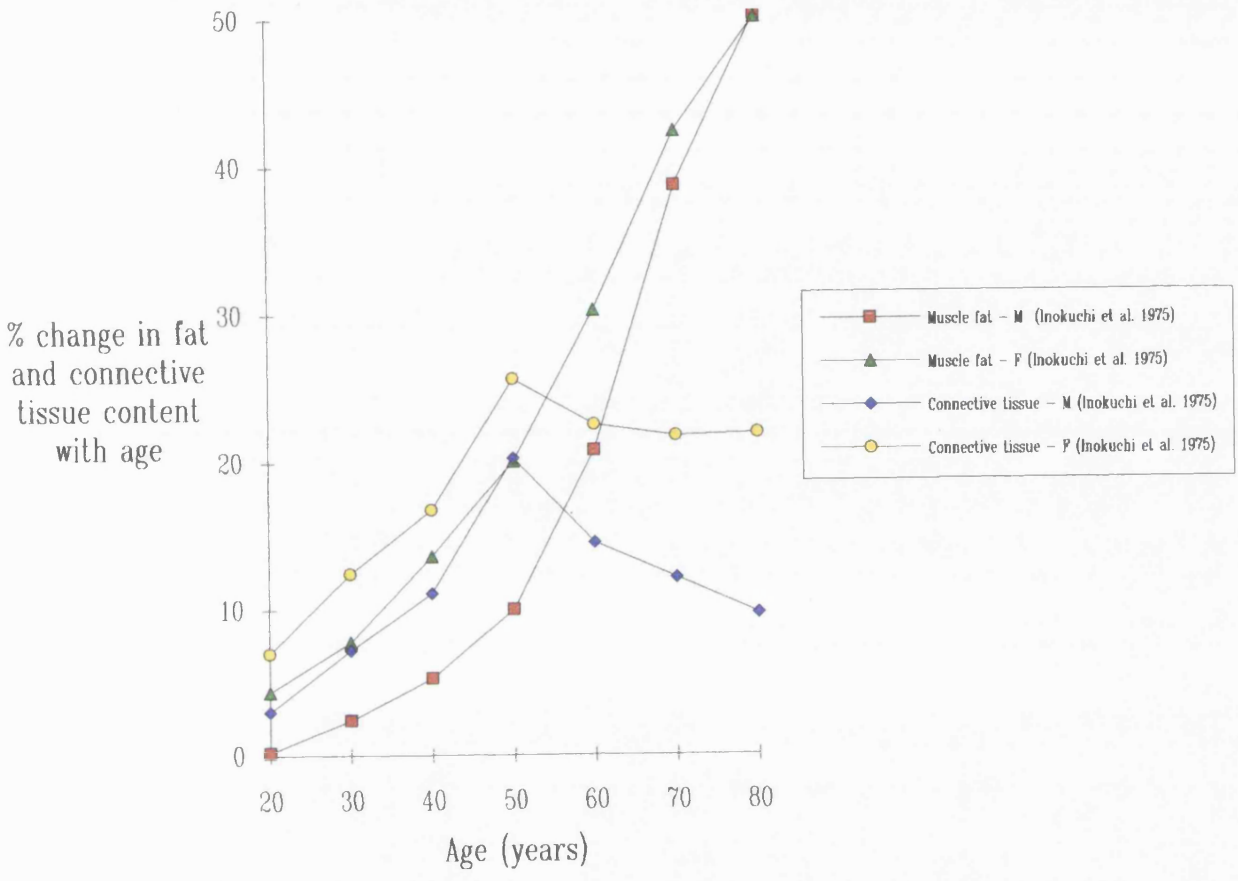


Study	20s	30s	40s	50s	60s	70s	80s
Örlander et al. 1978	5	14	4	6	6	6	-
Forsberg et al. 1991	29		11		10		

Örlander and colleagues subjects were all male. Forsberg and colleagues studied males and females. Their two younger groups combined, contained twenty-three females and their oldest group contained three females.

Fig 22

Replacement of rectus abdominis muscle by fat & connective tissue, with respect to age (Inokuchi et al., 1975)



Study	20s	30s	40s	50s	60s	70s	80s
Inokuchi et al. 1975 (M)	5	5	4	5	5	5	5
Inokuchi et al. 1975 (F)	5	5	5	5	5	5	5

showing a mild increase of fat and connective tissue. Accumulation of lipofuscin was the only characteristic and striking change in Shafiq and colleagues' report. Significant increases in lipofuscin content (expressed as the percentage of the total subsarcolemmal zones examined histologically which contained lipofuscin) were also reported by Örlander and colleagues (1978) (Fig 21). However a subsequent study from the same group found this trend to be reversible in serial biopsies taken before and after training from elderly men (Örlander & Aniansson, 1980).

b) INCOMPLETE ACTIVATION

As noted above (pp 17-18) this is testable in human subjects in two ways:

i) comparing maximal voluntary with maximally stimulated contractions from the same muscle under the same recording conditions

ii) interpolating twitches during a maximal voluntary contraction

i) COMPARING MAXIMAL VOLUNTARY WITH MAXIMAL STIMULATED CONTRACTIONS:

Table 4

Study	Davies & White 1983		McDonagh, White & Davies 1984				Davies, Thomas & White 1986							
Muscle	Triceps surae		Triceps surae		Elbow flexors		Triceps surae							
P_0n	$P_0$20		$P_0$20		$P_0$40		$P_0$20		$P_0$50		$P_0$20		$P_0$50	
sex	M		M				M				F			
young/ old	Y	O	Y	O	Y	O	Y	O	Y	O	Y	O	Y	O
number of subjects	7	13	9	11	9	11	12	20	12	20	8	11	8	11
Age	21	70	26	71	26	71	22	70	22	70	22	69	22	69
P_0n/ MVC	66 %	62 %	75 %	59 %	75 %	73 %	67 %	64 %	84 %	79 %	70 %	62 %	88 %	79 %
$P_0$20/ $P_0$100	76 %	91 %	-	-	-	-	-	-	-	-	-	-	-	-

Table 4 summarises reports of supramaximal tetanic direct muscle stimulation at 20 Hz (P_o20), 40 Hz (P_o40) and 50 Hz ($P_0$50). All the studies quoted from are cross-sectional.

In table 4 results of stimulated contractions have been compared with those of MVF reported in the respective studies. The results are fairly consistent in showing only minor differences with age and suggest that failure of activation is unlikely to be an important cause of reduced force/CSA with age. However it is important to note that in the one study where it is reported (Davies and White, 1983), $P_0 20/P_0 100 = < 1$ in the two subjects, one young and one elderly who accepted supramaximal tetanic stimulation at 100 Hz, supramaximal stimulation above 20 Hz not being tolerated by most subjects. Therefore it has not unequivocally been shown that maximal activation has been achieved by tetanic stimulation in these studies.

ii) INTERPOLATING TWITCHES DURING A MAXIMAL VOLUNTARY CONTRACTION:

No evidence of twitch responses superimposed on the maximal voluntary force of the dorsi-flexor muscles was found in either young or elderly subjects by Vandervoort and McComas (1986) nor in the plantar-flexor muscles of the majority of their subjects. In this study subjects were only tested during maximal contractions. Close to the maximum voluntary force it becomes very difficult to be sure of the presence or absence of small twitches superimposed on the voluntary contraction. However the available evidence again suggests that failure to activate is not a major factor in the decline in force/CSA with age.

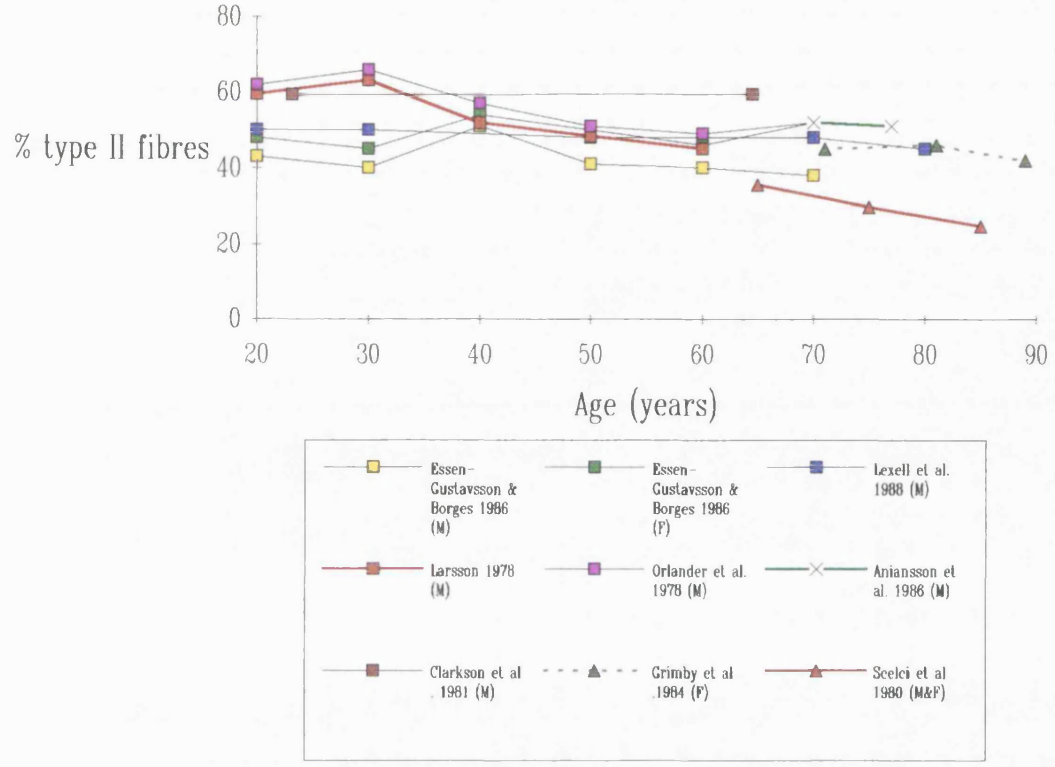
c) A CHANGE IN MYOSIN ISOFORMS

The myosin isoform present in a mammalian fibre is one of the bases of the classification into fibre types. Generally each fibre contains a single myosin isoform. Therefore a change in myosin isoform with age would be indicated by a change in a muscle's relative fibre type composition.

Studies by Larsson and colleagues (e.g. Larsson et al., 1979) found significant and progressive decreases in the proportion of type II (fast twitch) fibres in biopsies from the vastus lateralis muscles of men between their twenties and sixties. Scelci and colleagues (1980) extended the age range into the eighties finding a further progressive significant decline in type II relative to type I fibres. In Larsson and colleagues' studies of human ageing muscle no change was found in the ratio of type IIa fibres to type IIb and no change in the proportion of type IIc (cf. - pp 98-101 - fibre type changes in ageing animals below). Figures for subtypes were not reported by Scelci and colleagues. Results from these studies are plotted with red markers and lines in Fig 23. However other cross-sectional studies plotted with black lines and multicoloured markers have failed to confirm this trend, either in men or women. The one longitudinal study (green line) also showed no change in relative fibre type composition with age. Where changes with age were found they were in fibre area and overall number rather than the relative proportion of type II to type I (cf pp 58-63). Grimby and colleagues (1984) reviewing the various reports of relative muscle fibre composition with age attributed the discrepancies between them to differences in the fitness of the subjects. It seems likely that at least as important a factor is the minute sample size contained in biopsy material relative to the overall number of fibres in

Fig 23

The relative fibre type composition of the quadriceps muscle group with respect to age



Study	20s	30s	40s	50s	60s	70s	80s	90s
Essén-Gustavsson & Borges 1986 (M)	4	6	6	5	5	7	-	-
Essén-Gustavsson & Borges 1986 (F)	5	4	6	6	6	4	-	-
Lexell et al., 1988	9	9	-	8	-	9	8	-
Larsson 1978	11	10	8	12	10	-	-	-
Örlander et al. 1978	11	16	11	8	9	7	-	-
Aniansson et al., 1986	-	-	-	-	41	23	-	-
Clarkson et al., 1981	9	-	-	-	15	-	-	-
Grimby et al., 1984	-	-	-	-	-	13	15	15
Selci et al., 1980	-	-	-	-	20	15	10	-

vastus lateralis muscle (reviewed by Grimby & Saltin, 1983). This makes the post-mortem studies of Lexell and colleagues (e.g. Lexell et al., 1988) in which no significant change in relative fibre type composition with age was found, particularly important to the evaluation of Larsson's findings.

Even if there were a change in relative fibre type composition, how much difference would this make to the force produced per unit cross-sectional area? Human studies examining this in quadriceps muscle have found

1) no effect (Maughan and Nimmo, 1984),

2) a weak positive correlation between percentage CSA of type II fibres and force/CSA (with confidence limits "so wide that the factor relating type I fibre strength to type II fibre strength could be anywhere between zero and infinity") (Young, 1984),

3) the force/CSA of type II fibres is 1.8 that of type I (95% CI: 1.2-3.4) (Grindrod et al., 1987).

Even if type II fibres produced twice the force/CSA of type I fibres and the relative proportion changed from 50% type II to 25% type II, the overall force/CSA would only be reduced by about 15%, ignoring any possible change in relative fibre area. Thus to account for the observed changes in force/CSA with age, changes in fibre type composition much larger than those which have been reported would be required.

SUMMARY

Despite some acceptance of the idea that changes in fibre types can account for the weakness of old age (e.g. Bassey, 1985) it remains controversial whether significant changes in fibre type composition inevitably occur with ageing. Even if such changes do occur it is most unlikely that they could completely account for the observed decline in force/CSA with age.

d) METABOLIC CHANGES

Impaired muscle energy metabolism could result in a raised intracellular inorganic phosphate (Pi). This has been shown to result in lowered isometric force/CSA in animal skeletal (Elzinga et al., 1989) and cardiac muscle (Kentish, 1986) as has increased intracellular hydrogen ion concentration (decreased pH) (Curtin, 1990).

Indirect evidence in favour of a possible increase in Pi with ageing was found in a study of quadriceps muscle biopsies from 14 men and women aged 52-79 years (Möller et al.,1980). Adenine nucleotides and phosphocreatine (PCr) were found to be 5 per cent lower in the older subjects compared with a reference range previously obtained in the same laboratory from young adults aged 18-36 (Harris et al., 1974). There was a concomitant rise in creatine (and by inference Pi) but total creatine (i.e. creatine plus phosphocreatine), and the ATP/ADP ratio were unchanged.

In contrast Taylor and colleagues (1984) who compared ^{31}P nuclear magnetic

resonance spectra from the human arm muscle, flexor digitorum superficialis, in twenty-seven young (20-45 years) and twelve elderly male and female subjects (70-80 years) found no differences in the ratios of adenosine triphosphate (ATP), PCr and Pi to one another at rest. There was also no difference in resting pH. Furthermore aerobic dynamic exercise resulted in similar declines in PCr and similar pH changes with concomitant rises in Pi in young and elderly. Quantifying absolute rather than relative levels of these metabolites is difficult especially using a surface coil, as Taylor and colleagues point out. This is done by measuring the areas under the respective spectral peaks, the critical assumption being that the signal is collected from the same volume of muscle each time. Thus although ^{31}P nuclear magnetic resonance is a better technique than the analysis of biopsy material this study cannot unequivocally answer the question whether intracellular inorganic phosphate concentration is altered in human ageing muscle.

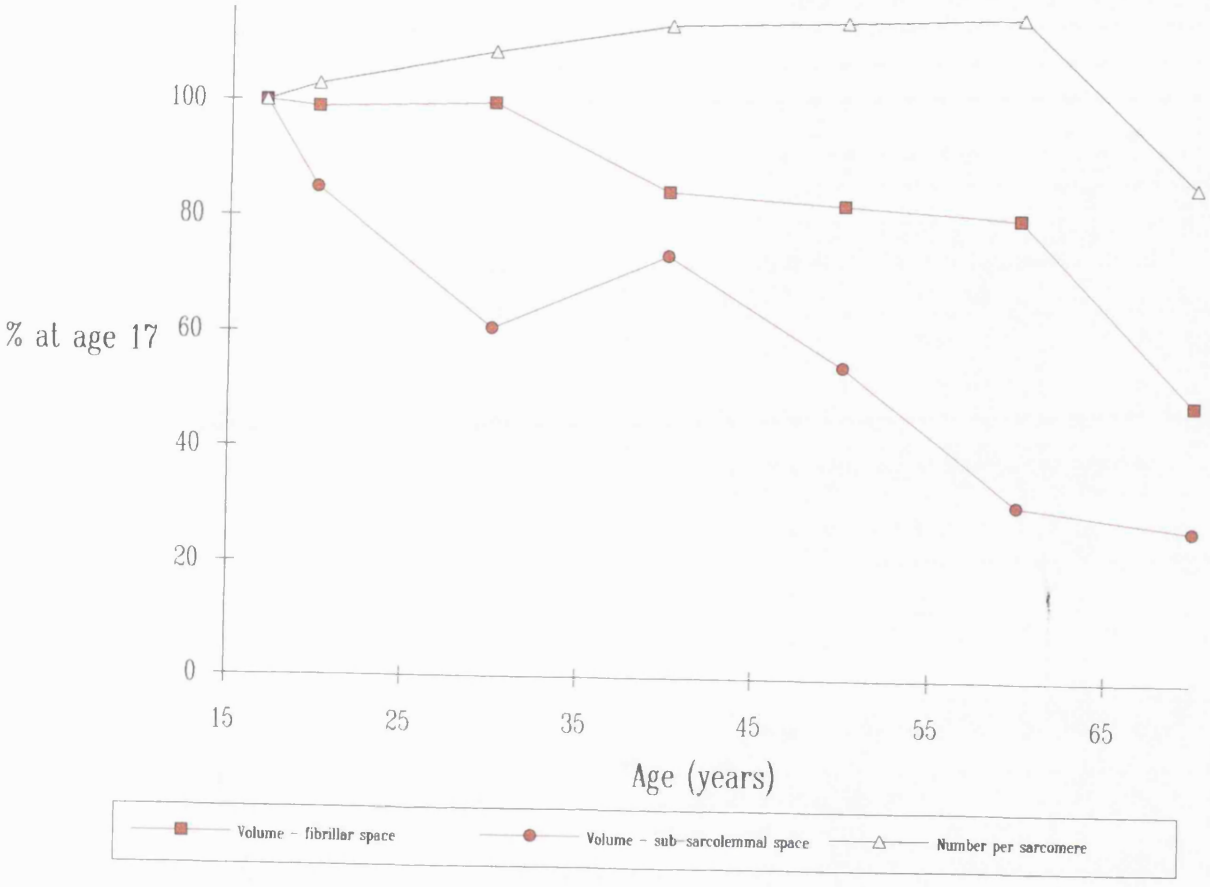
At rest and during light exercise muscle metabolism is normally entirely aerobic, lipid being the predominant fuel, provided plasma free fatty acid levels are adequate and muscle blood flow increases normally during exercise (Layzer, 1991). So far as muscle blood flow is concerned, no differences between the capillaries in biopsies from vastus lateralis and biceps brachii were found during a longitudinal study of four men (mean age 77 at the end of the study) (Aniansson et al., 1986). Biopsies of both these muscles were examined from twelve men and twelve women aged 78-81 years and no sex difference in capillary density found (Grimby et al., 1982).

Örlander and colleagues (1978) found no change with age in the number of mitochondria per sarcomere but mitochondrial volume fraction declined with age in

both fibrillar and subsarcolemmal spaces in quadriceps biopsies from male subjects aged 66-76 years, though a group of subjects aged 16-18 years had to be included with those aged 20-65 years before the declines were statistically significant (Fig 24). The activities of mitochondrial enzymes with respect to age have been studied in muscle homogenates obtained from biopsies of vastus lateralis muscle and expressed as mol/min/g wet weight. The results have been conflicting. For example, Örlander and colleagues (1978) found no age-associated decline in the activity of citrate synthase, the first enzyme of the citric acid cycle, in fifty-six men aged 22-65 years. Essén-Gustavsson and Borges (1986) reported a significant decline ($p < 0.05$) in the activity of this enzyme in thirty-four men aged 20-70 years but not in 31 women of similar age-range. Örlander and colleagues (1978) also found no change in the activity of the electron transfer chain enzyme, cytochrome *c* oxidase. However Trounce and colleagues (1989) have reported highly significant declines ($P < 0.001$) in the activities of this and another electron transfer chain enzyme, succinate- cytochrome *c* reductase, in twenty-nine male and female subjects (orthopaedic patients and subjects with chronic fatigue syndrome) aged 16-92 years, contrasting these declines with the absence of any age-associated change in the activity of monoamine oxidase, an outer mitochondrial membrane enzyme (Fig 26a). A post-mortem study of forty ileopsoas muscle specimens and fifty-eight diaphragms from men and women aged 28-86 years also found a highly significant decline in cytochrome *c* oxidase with age, using an apparently more subjective histo-chemical technique (Müller-Höcker, 1990). Trounce and colleagues (1989) also reported significant age-related declines in state III (activated) mitochondrial respiration rates expressed as ng oxygen atoms per min per mg mitochondrial protein, for three substrates in vastus lateralis biopsies (Fig 26b).

Fig 24

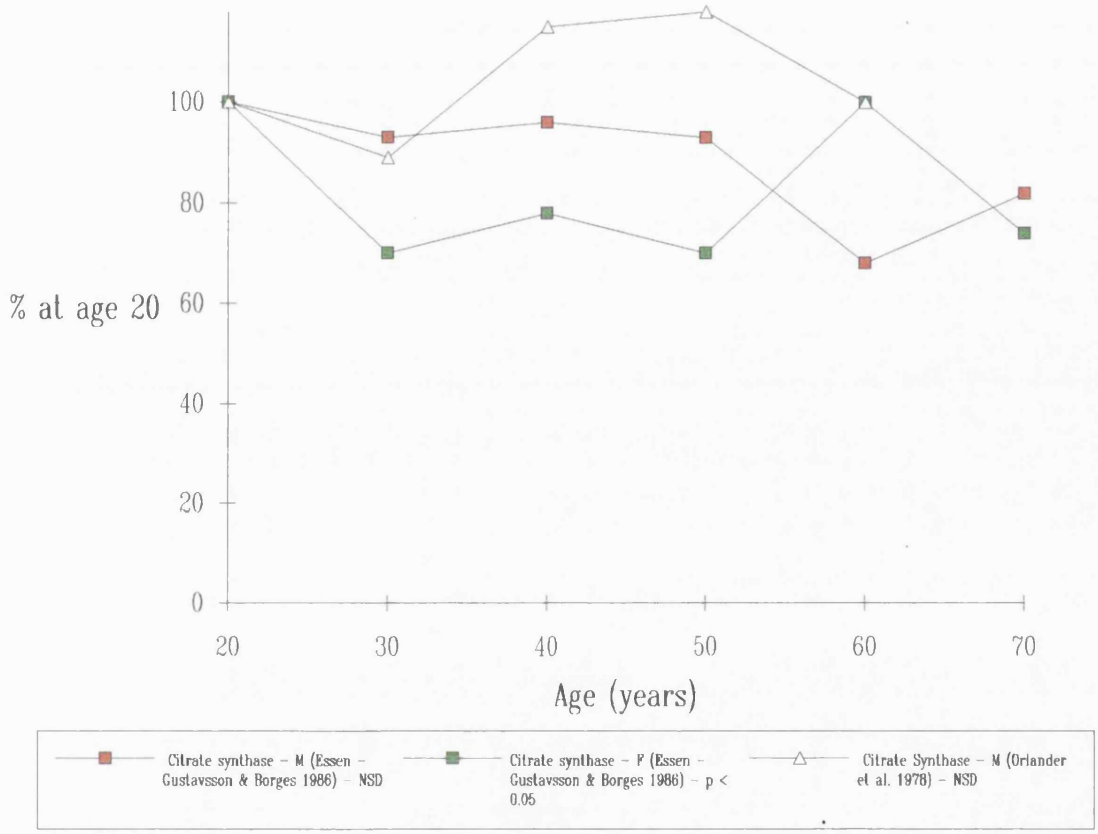
Mitochondrial morphology in males with respect to age
(Orlander et al. 1978)



Study	16-18	20s	30s	40s	50s	60s	70s
Örlander et al. 1978 - volume - fibrillar space	6	5	14	4	6	6	7
Örlander et al. 1978 - volume - sub-sarcolemmal space	3	4	14	4	6	6	6
Örlander et al. 1978 - number per sarcomere	6	5	14	4	6	6	7

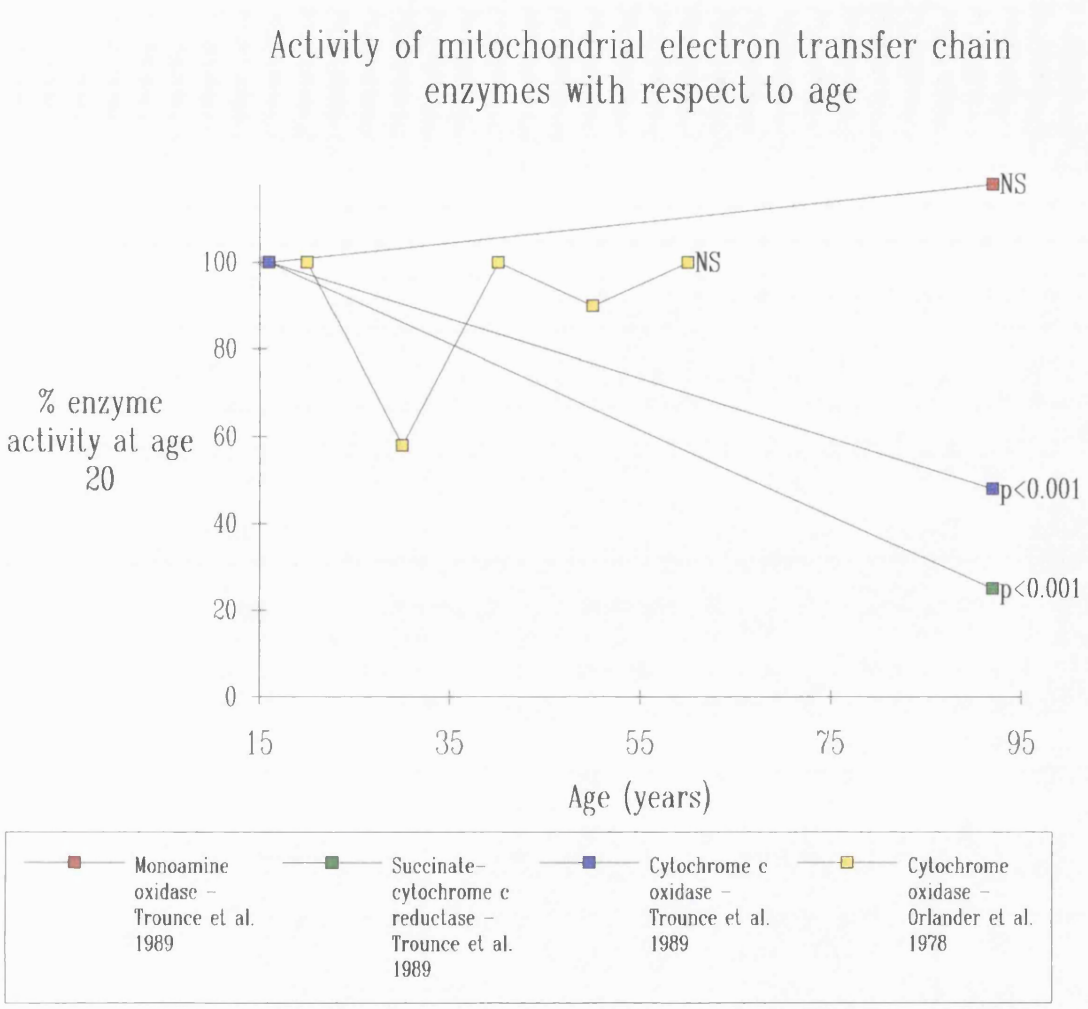
Fig 25

Changes in citrate synthase activity (umol/min/g. wet weight) with respect to age



Study	sex	20s	30s	40s	50s	60s	70s
Essén-Gustavsson & Borges, 1986	M	4	6	6	5	5	7
Essén-Gustavsson & Borges, 1986	F	5	4	6	6	6	4
Örlander et al., 1978	M	11	16	11	9	9	-

Fig 26a



Study	sex	20s	30s	40s	50s	60s
Örlander et al., 1978	M	11	16	11	9	9
Trounce et al., 1989	M & F	29 subjects aged 16-92 years - plotted values measured from published regression lines.				

State III (activated) mitochondrial respiration rates for three different substrates with respect to age in 29 male and female subjects aged 16 – 92 years (Trounce et al., 1989)

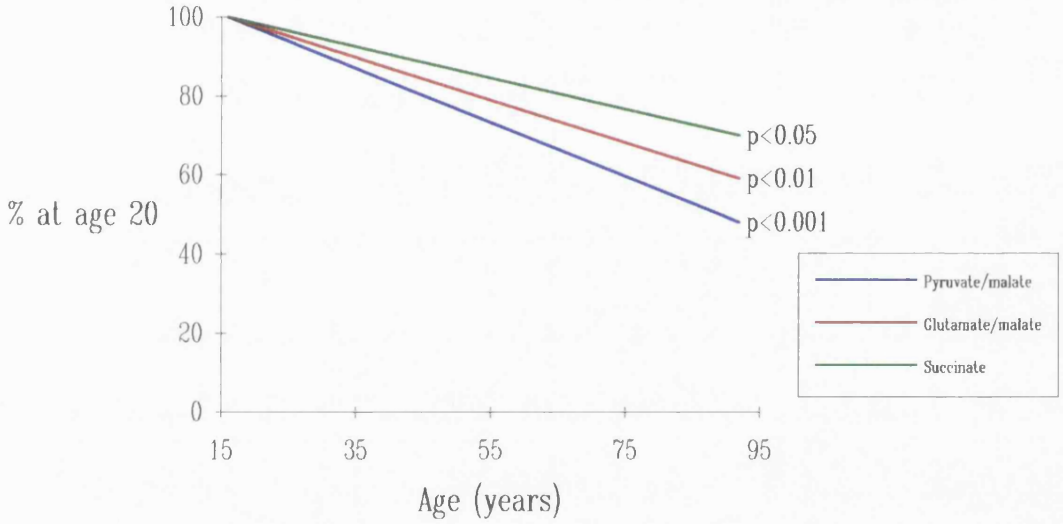
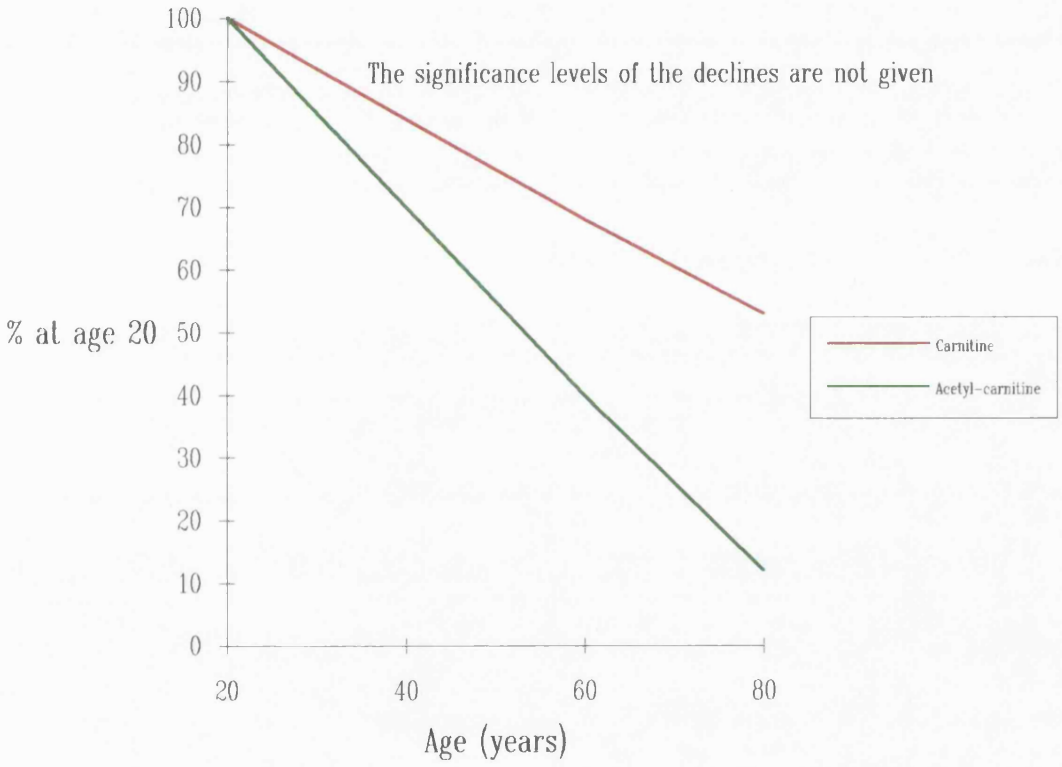


Fig 27 shows declines in muscle carnitine and acetyl carnitine with age in quadriceps muscle biopsies from twenty-five orthopaedic patients aged <20 - >80 years (Costell et al., 1989). Carnitine is an essential co-factor for the transport of long-chain fatty acids into mitochondria (Newsholme & Leech, 1984). This reaction is catalysed by the enzyme carnitine palmitoyl transferase, hereditary deficiency of which is a well recognised cause of myopathy characterised by weakness precipitated by either fasting or prolonged exercise, situations in which muscle glycogen, on which sufferers depend for their muscles' energy metabolism, becomes exhausted (Layzer, 1991).

Thus it would seem quite possible that declines in energy metabolism sufficient to result in an increase in intracellular phosphate (see pp184-185) could occur in ageing muscle. In skinned rabbit psoas muscle the reduction in absolute force/CSA due to raised intracellular phosphate is restored by rapid stretch of the muscle during an isometric contraction (Elzinga et al., 1989). Thus if the decline in force/CSA associated with ageing is due to the kind of metabolic changes outlined above applying stretch during an isometric contraction should result in increasing the force. A suggestion that this might be the case comes from a study by Vandervoort and colleagues (1990). This was a study of dynamic rather than isometric contractions in groups of twenty-six young and elderly female subjects (aged 20-29 and 66-89 years). Flexion and extension of the knee joint were studied firstly under conditions of iso-velocity shortening and then with the subject trying to resist as a motor rotated the lever arm about the knee-joint. The latter experimental condition is closely analogous to applying stretch during an isometric contraction and interestingly the declines in peak torque in the elderly subjects were 10-20 per cent less than under conditions of iso-velocity shortening, for both extension and flexion for two angular velocities of knee-joint rotation.

Changes in muscle carnitine and acetyl-carnitine with respect to age in 25 male and female subjects aged <20 - >80 years (Costell et al. 1989)



OTHER CONTRACTILE PROPERTIES OF STIMULATED MUSCLE

Twitch contraction time, time to peak twitch tension and half-relaxation time were increased in old compared to young subjects when twitches were elicited by stimulation of the motor nerve of adductor pollicis muscle (Botelho et al., 1954) and extensor digitorum brevis (EDB) (Campbell et al., 1973) and with direct stimulation of triceps surae muscle (Davies and White, 1983, McDonagh et al., 1984, Davies et al., 1986) and FDI (Newton and Yemm, 1986). Similar changes were also reported from direct stimulation of biceps brachii (McDonagh et al., 1984) though these were not statistically significant. Results of these studies are summarised in Tables 5 and 6.

Table 5

Study	Davies & White 1983					McDonagh, White & Davies 1984				Davies, Thomas & White 1986					
Muscle	Triceps surae					Triceps surae				Triceps surae					
sex	M					M				F					
Numbers of subjects (young)	7					4				8					
Numbers of subjects (old)	1					4				11					
age -young	21					26				22					
age - old	70					71				69					
parameter	P_o20	TPT	½RT	Pt	FI	P_o20	TPT	Pt	FI	P_o20	P_o50	TPT	½RT	Pt	FI
% change	38	31	27	23	32	50	24	37	19	36	35	8	29	22	40
increase/ decrease	d	i	i	d	d	d	i	d	d	d	d	i	i	d	d
sig/non-sig	s	s	s	ns	s	s	s	s	s	s	s	s	s	ns	s

Abbreviations: P_o20/40/50 - supramaximal tetanic force from direct muscle stimulation at 20,40 and 50 Hz. TPT - time to peak twitch tension. ½RT - half relaxation time of twitch. Pt - peak twitch tension. FI - fatigue index. CT - twitch contraction time. d - decrease, i - increase. s - difference between age-groups is significant, ns - no significant difference.

Table 6

Study	Botelho et al. 1954	Campbell et al. 1973		McDonagh, White & Davies 1984					Newton & Yemm 1986	
Muscle	Adductor pollicis	EDB		Biceps brachii					FDI	
sex	F	M&F		M					M	
number of subjects (young)	11	66		4		9			6	
number of subjects (old)	13	28		4		11			6	
age -young	18-24	16-58		26					20-29	
age - old	45-61	60-90		71					70-79	
parameter	CT	CT	½RT	$P_0$40	FI	TPT	½RT	Pt	CT	½RT
% change	51	45	105	33	11	7	10	23	50	2
increase/ decrease	i	i	i	d	i	i	i	d	i	i
sig/non-sig	s	s	s	s	ns	ns	ns	ns	s	ns

Abbreviations: $P_0$20/40/50 - supramaximal tetanic force from direct muscle stimulation at 20,40 and 50 Hz. TPT - time to peak twitch tension. ½RT - half relaxation time of twitch. Pt - peak twitch tension. FI - fatigue index. CT - twitch contraction time. d - decrease, i - increase. s - difference between age-groups is significant, ns - no significant difference.

A difference due to age in the relationship between the length of the muscle and twitch tension was found with extensor hallucis brevis (EHB), the most medial subdivision of EDB. In young subjects the maximal twitch tension did not appear to be attained even when the muscle was maximally stretched by plantar-flexion of the great toe. In the elderly however, an appreciable portion of the maximum tension was achieved at resting length (Sica and McComas, 1971).

From the point of view of elucidating the mechanism(s) of the weakness, changes in twitch contraction time and time to peak twitch tension are non-specific. They could be accounted for by changes in fibre types (pp 78-81) and/or changes in the sizes of the motor units (p 63-66). Relaxation rate is discussed in the section on muscle function and subnutrition (p 32).

STUDIES OF AGEING IN ANIMAL MUSCLE

a) WASTING

i) FIBRE NUMBER AND SIZE

As in humans both decline in total number of muscle fibres and in fibre size have been reported in aged animals but there is less consistency between studies. Declines in fibre number of around thirty per cent have been reported in rat (Caccia et al., 1979, Gutman & Hanzlíková, 1966) and dog (Ihemelandu, 1980) and of up to twenty per cent in mice (Hopper, 1981).

A more recent study of twenty-five female Wistar rats aged 6-24 months found atrophy to be common after twelve months of age in both soleus and EDL muscles but that it was entirely attributable to decline in fibre size there being no loss of total fibre numbers in either muscle (Brown, 1987). The animals in Brown's study were divided into seven age groups the number of muscles reported on in each age group is thus small (n = 1 - 4). Larsson and Edström (1986) comparing the same muscles in male Wistar rats in two groups aged six and twenty-four months (n = 10 - 13 in each group) found a decline in both total number and fibre size in soleus but not EDL. In Q-strain mice Hopper (1981) found a decline in fibre number in sternomastoid, biceps brachii and tibialis anterior (TA) muscles from twelve 70-week old animals compared with those from fifteen 26-week old animals the decline being most marked in TA. Mean fibre length and sarcomere number also declined in all three muscles but sarcomere length was unchanged and mean fibre diameter was actually found to

increase with age. There had also been earlier reports (reviewed by Larsson, 1982) suggesting an increase in fibre diameter with age in rat muscle.

ii) MOTOR UNITS

A rearrangement of motor unit fibres to occupy a larger territory and display an increased innervation ratio, indicating a denervation-reinnevation process, has been reported in three rat muscles:

1) Soleus - male Wistar rats aged 3-6 months (n = 7) and 20-24 months (n = 6) (Edström & Larsson, 1987)

2) Gastrocnemeus - specific pathogen free male Fischer rats (F344/DuCrj) aged 10 - 14 months (n = 7) and 26 - 30 months (n = 6) (Kanda & Hashizume, 1989)

3) Tibialis anterior - male Wistar rats aged 3-6 months (n = 13) and 20-24 months (n = 16) (Larsson et al., 1991).

These changes are similar to those discussed above from studies on motor units in ageing humans.

b) FORCE/CSA

The results of five published studies of force/CSA related to age in mouse and rat muscle are summarised in tables 7 and 8.

Table 7

Study	Brooks & Faulkner 1988		Larsson & Edström 1986		Klitgaard et al. 1989	
Species	C57BL/6 mouse		Wistar rat		Wistar rat	
Sex	M		M		M	
Muscle	Sol	EDL	Sol	TA	Sol	Plant
Number of animals (Young)	14	15	30		5	
Number of animals (Old)	14	18	21		5	
Age (Young) - months	9-10		6		9	
Age (Old) - months	26-27		20-24		29	
Force N (Young)	259±11mN (±SEM)	411±13 mN	2.99±0.49N (±SD)	13.5±0.8N	2.74±0.37N (±SD)	6.26±0.55N
Force N (Old)	202±9mN	299±14mN	2.43±0.47N	13.3±1.7N	1.5±0.18N	3.79±0.36N
Force/CSA (Young)	22.1±0.65 N/cm^2	23.8±0.67 N/cm^2	11.7±1.0 N/mg	11.4±1.1 N/mg	14.5±1.3 N/cm^2	25.9±2.1 N/cm^2
Force/CSA (Old)	18.7±1.05 N/cm^2	18.6±0.86 N/cm^2	10.4±0.8 N/mg	9.9±1.4 N/mg	10.7±1.1 N/cm^2	21.4±3.0 N/cm^2
% decline (Force/CSA)	15 (nsd)	22	12	13	26	17

Abbreviations: Sol = soleus, EDL = extensor digitorum longus, TA = tibialis anterior, Plant = plantarus, nsd = no significant difference.

Table 8

Study	Fitts et al. 1984			Eddinger et al. 1986			
Species	Long Evans rat			Fisher 344 rat			
Sex	?			M			
Muscle	Sol	EDL	SVL	Sol	EDL	Sol	EDL
				fibre bundles		skinned fibres	
Number of animals (Young)	8			34			
Number of animals (Old)	8			35			
Age (Young) - months	9			9			
Age (Old) - months	28			29			
Force N (Young)	-	-	-	-	-	-	-
Force N (Old)	-	-	-	-	-	-	-
Force/CSA (Young)	(15.6) N/cm^2	(26.4) N/cm^2	(11.2) N/cm^2	5.9±2.0 N/cm^2	11.4±4.0 N/cm^2	8.7±0.8 N/cm^2	9.8±3.0 N/cm^2
Force/CSA (Old)	(15.9) N/cm^2	(28.9) N/cm^2	(12.0) N/cm^2	8.5±1.8 N/cm^2	8.9±3.5 N/cm^2	12.2±2.0 N/cm^2	12.3±2.2 N/cm^2
% INCREASE (Force/CSA)	2 (nsd)	10 (nsd)	7 (nsd)	44	22% decline (nsd)	40	26 (nsd)

Abbreviations: Sol = soleus, EDL = extensor digitorum longus, SVL = superficial vastus lateralis, nsd = no significant difference.

The studies summarised in table 7 reported significant declines in force/CSA with age. Those in table 8 reported a tendency for force/CSA to increase wih age. However the absolute values of force/CSA show great variability in the two studies summarised in table 8, and the percentage changes are mostly not statistically significant. The low force/CSA recorded from young soleus muscle in Eddinger and colleagues' study (1986) is particularly puzzling. It is difficult to dissect fibre bundles from soleus and it maybe that this result reflects a relatively high proportion of damaged fibres.

POSSIBLE CAUSES OF REDUCED FORCE/CSA

a) REPLACEMENT OF MUSCLE WITH NON-CONTRACTILE TISSUE

Descriptive studies have shown an age-related increase in connective tissue and fat in rat muscle (Rubinstein, 1960). A more recent quantitative study, also of rat, reported a thirty-six per cent increase in connective tissue in EDL muscles of male CFY Sprague-Dawley rats aged between 84 and 716 days (Alnqueeb et al., 1984). However as connective tissue only contributes about two per cent of total CSA changes of this magnitude would have little effect on force/CSA (Faulkner et al., 1991). Brooks and Faulkner (1988) found no change with age in the dry mass to wet mass ratio which also suggests that changes in extracellular constituents are unlikely to be a major factor in their observed changes in force/CSA with age (Faulkner et al., 1991).

However Alnqueeb and colleagues (1984) did find a significant increase in resting muscle stiffness associated with the reported increase in connective tissue. This would increase parallel elasticity and thus increase force with stretch (cf. p 185).

b) INCOMPLETE ACTIVATION

This is excluded by the use of supramaximal stimulation of isolated muscle preparations in the animal experiments.

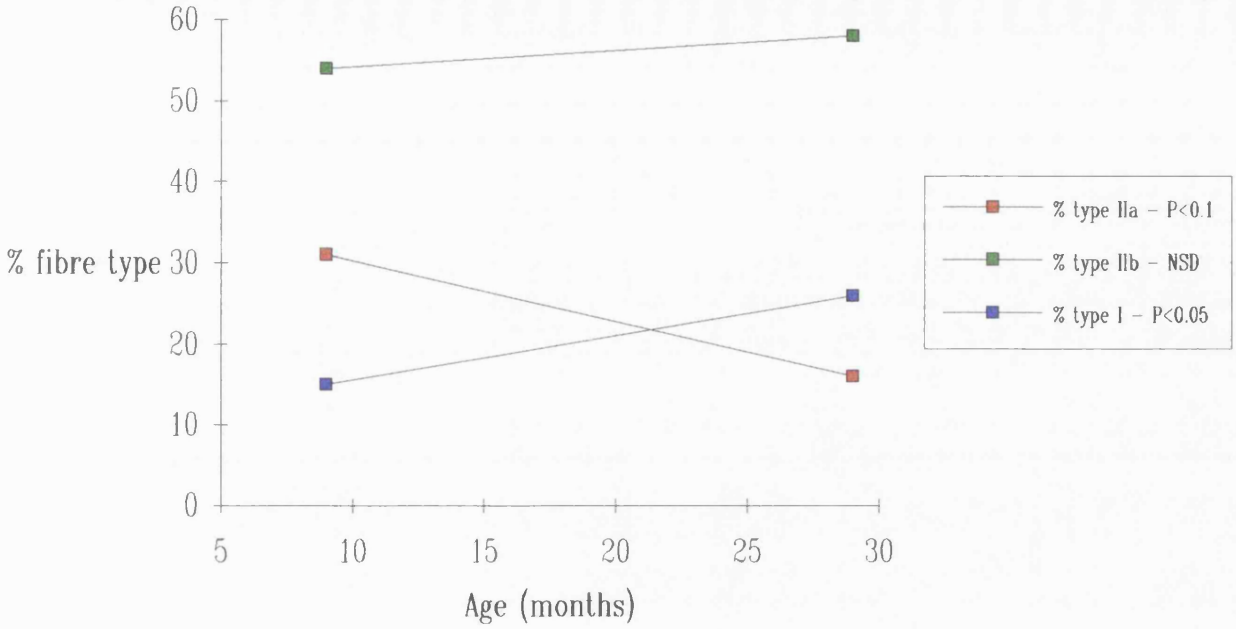
c) A CHANGE IN MYOSIN ISOFORMS

As in humans there is controversy over whether type II fibres are affected more than type I fibres in animal models of ageing muscle. Larsson and Edström (1986) comparing muscles from male Wistar rats aged six months (n = 30) and 20-24 months (n = 21) found fibre loss and decline in fibre size to be most pronounced in type II (especially IIa) fibres in soleus. No changes were found with EDL or Tibialis anterior. This is perhaps surprising as both have a much higher proportion of type II fibres than soleus and one might therefore expect to see such changes more easily if they were of general significance in the process of muscle ageing. Florini and Ewton (1989) found no change in fibre types with age in either the soleus or EDL muscles of male Fischer 344 rats or C57B1/NNia mice between the ages of eight and twenty-four months. In their discussion Florini and Ewton attributed any changes in fibre types to environmental factors rather than ageing. They pointed out that in studies where barrier protected specific-pathogen-free animals had been used, these being "generally regarded as the most appropriate models for gerontological research", no changes were found in muscle fibre composition with age. However they simplify the results of Brooks and Faulkner's (1988) study, quoted in Table 7, in support of their case, and a more recent study (Holloszy et al., 1991) using specific pathogen free Long-Evans rats which is reviewed more fully in the next section, did find a decline in the proportion of type IIa fibres and in the CSA of type IIb fibres of plantaris, a muscle with a high proportion of type II fibres (Fig 28).

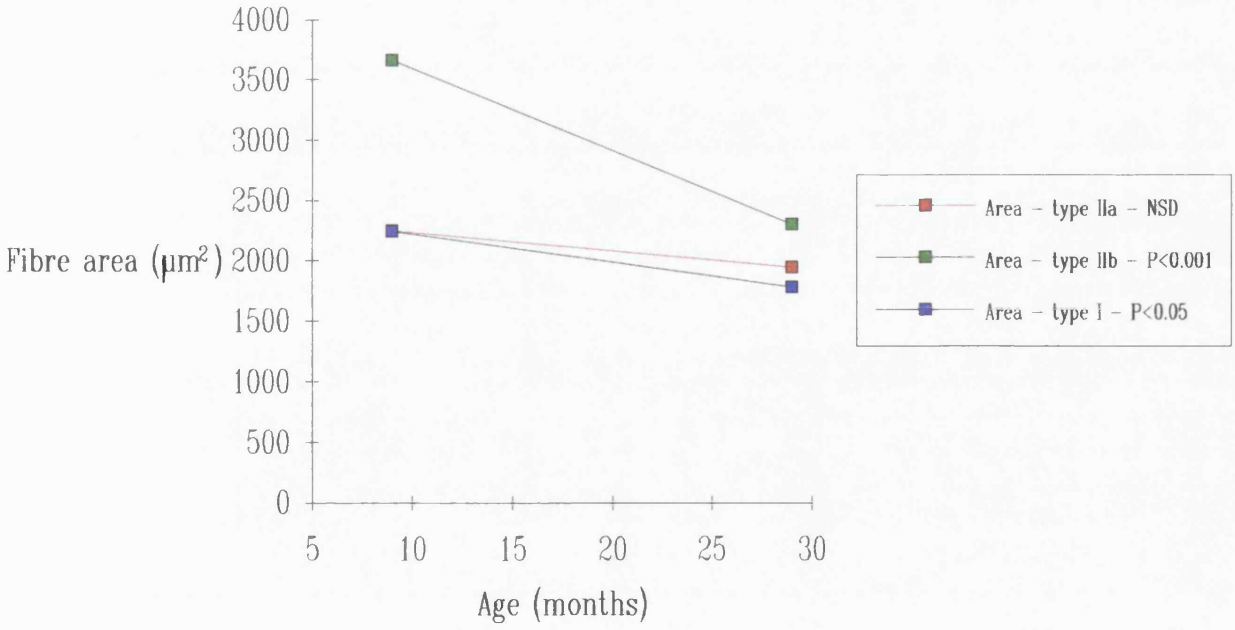
Isometric force/CSA has been compared in skinned type I and type II fibres from rat diaphragm (Eddinger & Moss, 1987), rabbit plantaris (Greaser et al., 1988) and rat

Fig 28

a) Effect of age on relative fibre type composition of rat plantaris muscle (Holloszy et al., 1991)



b) Effect of age on fibre area in rat plantaris muscle (Holloszy et al., 1991)



Age	9 months	28-30 months
Numbers in groups	6	14

soleus, EDL and plantaris muscles (Bottinelli et al., 1991). No difference was found between type I and type II fibres from rabbit plantaris but both the studies of rat muscles found isometric force/CSA of type I fibres to be lower than that of type II. In the study of rat EDL, soleus and plantaris (Bottinelli et al., 1991) isometric force/CSA of the type I fibres was about thirty per cent lower than that of the type II in all three muscles studied. There was no difference in CSA between fibre types, in contrast to the other two studies, and force/CSA did not differ between the type II subtypes; (in rat diaphragm force/CSA was found to be lower in type IIa than type IIb (Eddinger & Moss, 1987)).

Larsson and Edström (1986) give fibre numbers and cross-sectional areas for rat soleus muscle in which they found type I, IIa and IIc fibres. Applying Bottinelli and colleagues' (1991) values for force/CSA of type I and type IIa fibres to Larsson and Edström's data for rat soleus, gives tetanic forces of 2.6 N for six-month old rats and 1.6 N for those 20-24 month old, ignoring pennation angle of the fibres which is unknown and assuming that there is no change in force/CSA with age of the individual fibre types. These are plausible, though underestimates compared with the observed values (2.99 and 2.43 N respectively). (Type IIa fibres were 10% of the total in the young animals and $<1\%$ in the old animals. There are so few IIc fibres in both age groups that ignoring them makes no difference to the calculation.) From this calculation force/CSA is 23 $N.cm^{-2}$ for the young animals and 21 $N.cm^{-2}$ for the old animals, plausibly similar to the values observed by Brooks and Faulkner (1988) for mouse soleus (Table 7) a calculated decline of about eight per cent. The observed decline in force/CSA for soleus in Larsson and Edström's study was twelve per cent and thus cannot be wholly accounted for by a change in fibre types even though the

underestimate of total force in the above calculation was greater in the old than the young muscles which would have exaggerated any effect of such a change.

SUMMARY

Published values for differences in force/CSA between fibre types cannot account for all the observed changes in overall muscle force/CSA in ageing animals although in some muscles the factor may make a significant contribution.

d) METABOLIC CHANGES

A number of earlier studies of rat muscle reviewed by Ermini (1976) reported cellular respiration to decline with age in agreement with studies of human muscle reviewed above. Observed changes in the relative proportions of the constituents of the Lohmann reaction with increases in ADP and creatine and decreases in ATP and phosphocreatine were felt to result from the limited aerobic capacity of ageing muscle to produce ATP, though this has been reported to be reversible with aerobic training (Beyer et al., 1984, Cartee & Farrar, 1987). Anaerobic ATP production has been shown to decline in white gastrocnemeus muscle of male Fischer 344 rats (aged 10 and 24 months, n = 7 in each group). This appeared to be due to reduced energy demand rather than a decline in ATP provision and there were no such changes in the other muscles studied - soleus, plantaris and red gastrocnemeus. White gastrocnemeus muscle has a high proportion of type IIb fibres though the question as to whether the reported result was due to changes within these fibres or to the relative fibre type

composition was unanswered by the study (Campbell et al., 1991). An ambitious recent study (Holloszy et al., 1991) sets forth to relate fibre atrophy, relative fibre type proportions and biochemical analyses of mitochondrial and glycolytic enzymes in weight-bearing and non-weight-bearing muscles from the upper and lower limbs of two groups of specific pathogen free male Long-Evans rats aged 9-10 months (n = 12-16) and 27-28 months (n = 9-12). The interesting and wide-ranging conclusions of Holloszy and colleagues' discussion are that atrophy occurs in weight-bearing rather than non-weight-bearing muscles, that this relates specifically, to atrophy of type IIb fibres, and that in muscles where atrophy is associated with ageing, there is a decrease in respiratory capacity of type I fibres and a decrease in the glycolytic capacity of type II fibres. Unfortunately it would appear that the rather complex design developed during the course of the study rather than being inherent in the dialectic. Muscle wet weights are reported from six muscles (or muscle groups): quadriceps, gastrocnemeus, plantaris, soleus (all showing significant declines), adductor longus and epitrochlearis (neither of which showed any significant decine with age). Protein content ($mg.g^{-1}$) is reported from quadriceps, plantaris and soleus (no significant differences) but data on fibre types is only reported from one muscle - plantaris (fig 28).

No enzyme studies are reported from the two muscles that did not show atrophy (making that distinction in the discussion of the paper puzzling) or from gastrocnemeus. From the other three muscles the most consistent finding is that the activities of the two terminal enzymes of glycolysis, pyruvate kinase and lactate dehydrogenase, significantly decline with age in all three. Tri-carboxylic acid cycle enzyme activity declined in plantaris (predominantly fast) and soleus (predominantly

slow) but not in quadriceps (predominantly fast). The activity of 3-hydroxyacyl-CoA dehydrogenase (fatty acid oxidation) declined in soleus but not in quadriceps or plantaris. However even this is hard to evaluate since, in plantaris, which was studied in more detail, though the activities of this enzyme and carnitine palmitoyl transferase (cf. p 88) do not decline significantly, ^{14}C-palmitate oxidation, measured directly, does. This was not measured in the other muscles.

SUMMARY

Measurable declines in energy metabolism do appear to be found in ageing animal skeletal muscle, as in humans, but their exact significance remains elusive.

CONCLUDING INTRODUCTORY REMARKS

I have quoted Holloszy and colleagues' study (1991) in such detail above because it seems to me to exemplify, albeit in an extreme form, problems that afflict a number of the studies quoted in this section. These problems lead to a general lack of clarity particularly when one attempts to use the results to elucidate the possible mechanisms underlying the observed changes. Faulkner and White sum up the problem with a certain acerbity in a letter to the editor of the Journal of Gerontology (J. Gerontol. 1988; 43: B3-4). Commenting on a paper by McCarter and McGee (1987) in which a "striking absence of functional change with age and diet" was revealed, in soleus and lateral omohyoideus muscles from specific pathogen free Fischer 344 rats, they complain of: "1) unsubstantiated basic premises 2) flawed experimental design 3) a complex design with inadequate statistical treatment of the data, and 4) unwarranted interpretations and conclusions." In a number of the studies quoted it would seem that data have been collected first and subsequently the attempt made to conjure hypotheses out of them rather than that the study had been designed to test any particular idea.

Our hypotheses are

1) the weakness of old age has two components

2) there is atrophy caused at least in part by loss of motor units

3) there is also a decline in force/CSA the cause of which is more obscure

We were concerned to test hypothesis 3) since, at the onset of our study there was controversy as to the existence of a decline in force/CSA with age and only rather uninteresting speculation as to its possible mechanism (replacement of muscle with non-contractile tissue). We felt that one reason for the controversy was that decline in

force/CSA is hard to measure when a large but variable amount of atrophy is also occurring. Atrophy may be more pronounced in human lower limb muscles (McDonagh et al., 1984) and perhaps in the weight-bearing muscles of animals (Holloszy et al., 1991). Bassey and colleagues (1988) showed that decline in muscle strength in ankle plantar flexors is correlated with customary walking activity. Thus we predicted that an upper limb muscle would be a better model for measuring decline in force/CSA than those lower limb muscles previously studied - quadriceps (Young et al., 1984 & 1985) and Triceps surae (Davies et al., 1986 and Vandervoort & McComas, 1986). Published studies of the effects of ageing on distal upper limb muscles (adductor pollicis - Botelho et al., 1954, Narici et al., 1991 and first dorsal interosseous - Newton and Yemm, 1986, Newton et al., 1988) have not addressed this problem. Studies of force/CSA in biceps have been difficult to evaluate because in one the CSA measurement gave a bizarre result (Moritani & de Vries, 1986) and in the other it was difficult to see how the values of force/CSA were arrived at (Klitgaard et al., 1990).

We have measured MVF and CSA of adductor pollicis in fit young and elderly male and female subjects. Having found a decline in force/CSA in the elderly we have used the method of interpolation of stimulated twitches (Merton, 1954) to test for full activation in the weak subjects. We then plotted the time-course of the decline in force/CSA of this muscle in men and women and have tested the further hypothesis that the decline in women is hormone-related. These studies have been published (Bruce et al., 1992b, Phillips et al., 1992, Phillips et al., 1993a).

METHODS

1. FORCE MEASUREMENT

Merton's apparatus for measuring maximal contractions of adductor pollicis is described in his 1954 paper. He went to considerable lengths to minimise the contributions to the recorded force of opponens pollicis and flexor hallucis longus. The contribution of opponens pollicis was minimised by the action of a large ball-bearing which moved when the thumb was opposed but not when it was adducted. Fixing the ball-bearing so that opponens pollicis did contribute, increased the recorded force by about thirty per cent. The contribution of flexor hallucis longus was minimised by an adjustable compensatory mechanism consisting of an inverted steel "U" whose limbs diverged with flexion of the thumb. The degree of divergence was measured by the tension transducer and in the absence of this compensatory mechanism the force recorded by the transducer was "greatly augmented by flexing the thumb". The other muscle which can potentially contribute to the recorded force is first dorsal interosseous. The design of Merton's hand splint also minimised this but he made the point that any small contribution that remained from this muscle, was of little importance as it is usually supplied by the ulnar nerve, as is adductor pollicis. Therefore it will contribute equally to voluntary and stimulated contractions. Although the illustration in Merton's paper shows the apparatus being used in a clinical setting, with the patient reclining in bed, it does appear rather cumbersome.

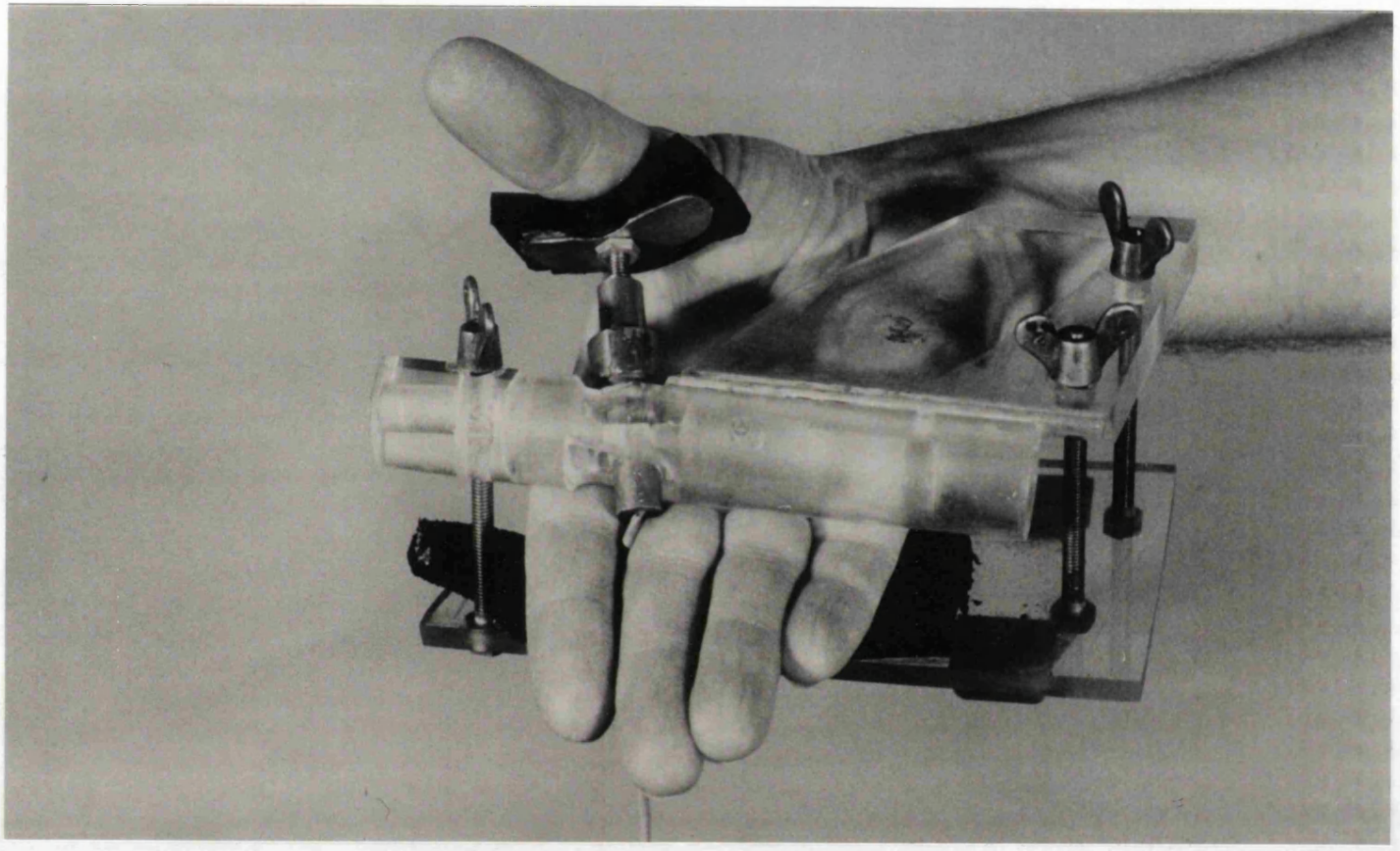
The apparatus was greatly simplified by Edwards and colleagues (1977). In their apparatus the hand is secured with the forearm supine and the fingers slightly flexed.

The thumb is abducted with the metacarpo-phalangeal and inter-phalangeal joints maximally extended. The strain gauge is linked by a chain to a loop around the inter-phalangeal joint of the thumb. However as they point out this simplification was at the expense of accepting augmentation to the recorded force from the long flexors of the thumb (Edwards et al., 1977). We felt that it would be impossible to eliminate this with the point of attachment of the transducer being at the level of the inter-phalangeal joint. Placing the transducer there also introduces a variable length lever into the system (the length of the proximal phalanx of the thumb).

We therefore further modified the method as shown in Fig 29. MVC's of the adductor pollicis were measured using a strain gauge bridge circuit. In our preliminary study (Bruce et al., 1986b) results were obtained using a transducer which had two strain gauges mounted either side of a ring so that sideways force on one gauge was cancelled out by an equal and opposite force on the other (Bruce et al., 1986a). It was found that this system was not entirely stable and for the nutrition study, and an initial study of ageing (Bruce et al., 1989b), the strain gauge was mounted in the centre of a small brass plate seated in a brass cylinder. A rod opposed thumb adduction at the base of the proximal phalanx, running down inside the cylinder and depressing the plate when force was applied. This system was insensitive to sideways forces applied to the cylinder thus eliminating any contribution from opponens pollicis. The other end of the cylinder was applied to a ball-bearing mounted in a perspex hand splint so as to lie between the index and middle fingers. The splint inhibited flexion of the fingers about the metacarpo-phalangeal joints. Contribution to the recorded force from the flexor muscles of the fingers was thereby reduced though not completely eliminated. The point at which the transducer opposed adduction of the thumb was chosen because

Fig 29

Apparatus used to measure maximum voluntary force of adductor pollicis muscle for the nutrition study



it is close to the attachment of the adductor pollicis muscle, thus eliminating the lever. It is also proximal to the attachments of the flexor muscles of the thumb whose action is approximately at right angles to the movement at this point. The force measured was therefore largely due to activity of adductor pollicis with a contribution from first dorsal interosseous.

The apparatus for measuring force was subsequently further modified in order to eliminate, as far as possible, the contribution from the long flexors of the fingers - Figs 30 and 30a. Using this apparatus subjects are requested to hold their thumb flat in the plane of the palm of the hand. The force transducer which is mounted on an angled metal bar is wedged in between the bases of the proximal carpel bone of the thumb and the metacarpal bone of the index finger. The fingers and inter-phalangeal joint of the thumb are kept maximally extended throughout the measurements eliminating any contribution from the flexors of the thumb. The subjects are requested to squeeze the bar as hard as possible against the metacarpal of the index finger. This apparatus was used in all the studies reported here except the nutrition study.

Results from the various transducers were comparable after appropriate calibration.

In all studies each subject's hand and forearm were warmed in hot water (40°C) for five minutes. They were then asked to perform nine, 2 s maximum voluntary contractions, within a period of about three minutes.

In the nutrition study, twenty of the control subjects and nine of the sub-nourished also performed a MVC sustained for 30 s.

Fig 30

Apparatus used to measure maximum voluntary force of adductor pollicis muscle for all except the nutrition study

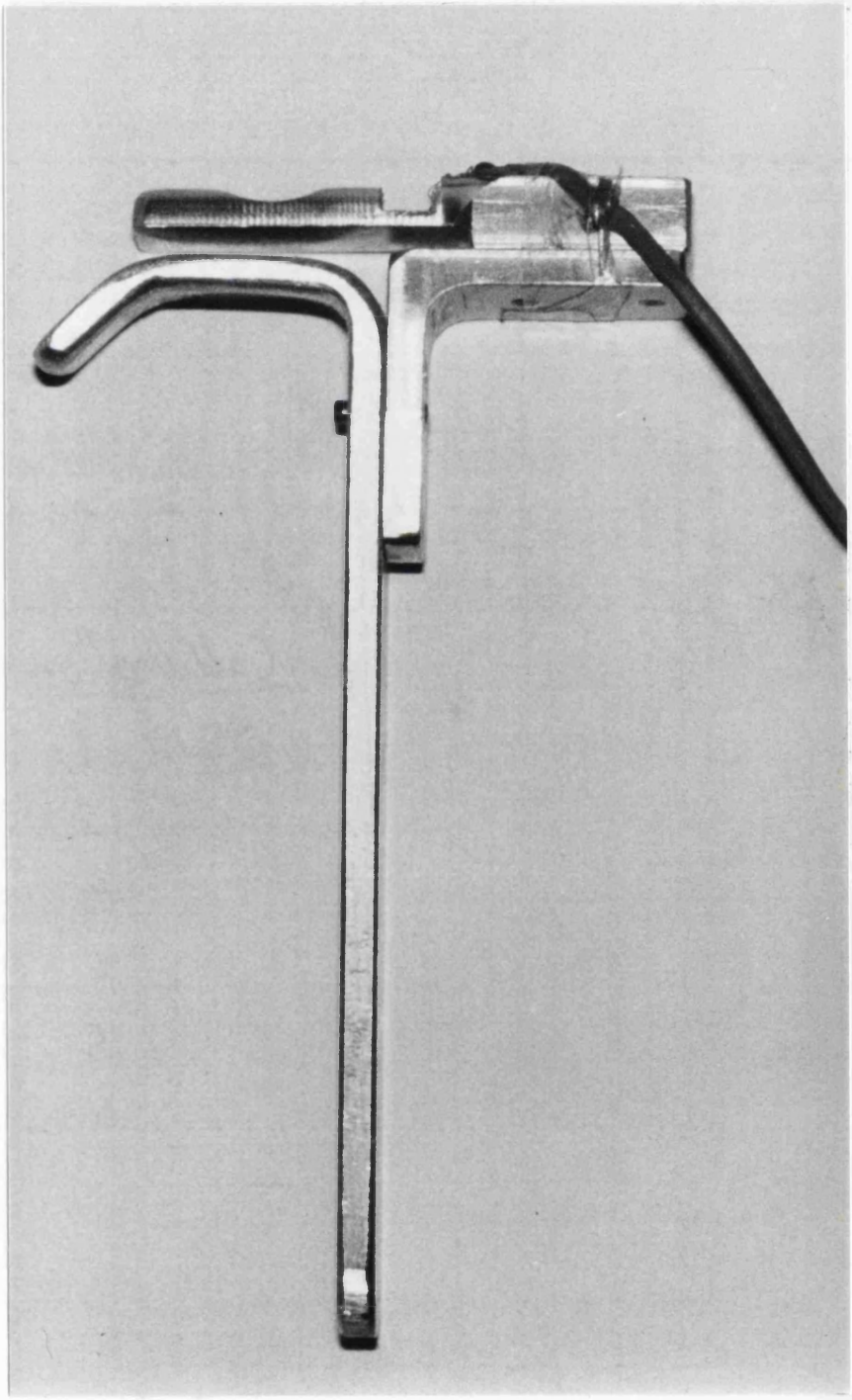
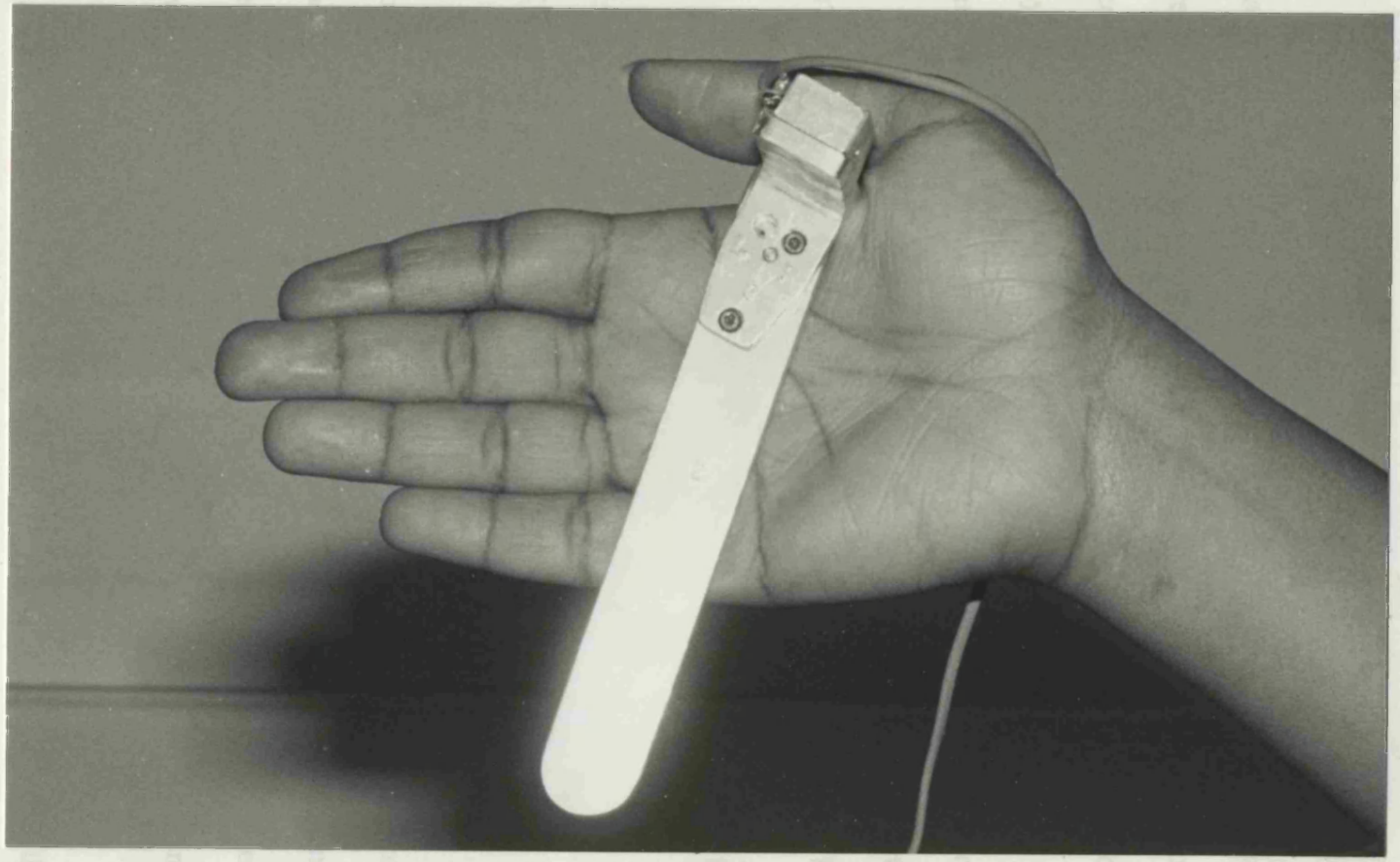


Fig 30a

Hand positioned for the measurement of maximum voluntary force of adductor pollicis muscle using the apparatus shown in Fig 30



The subjects were allowed to watch the screen of the Nicolet 3091 portable oscilloscope or Compaq personal computer on which data was collected. They were also encouraged verbally.

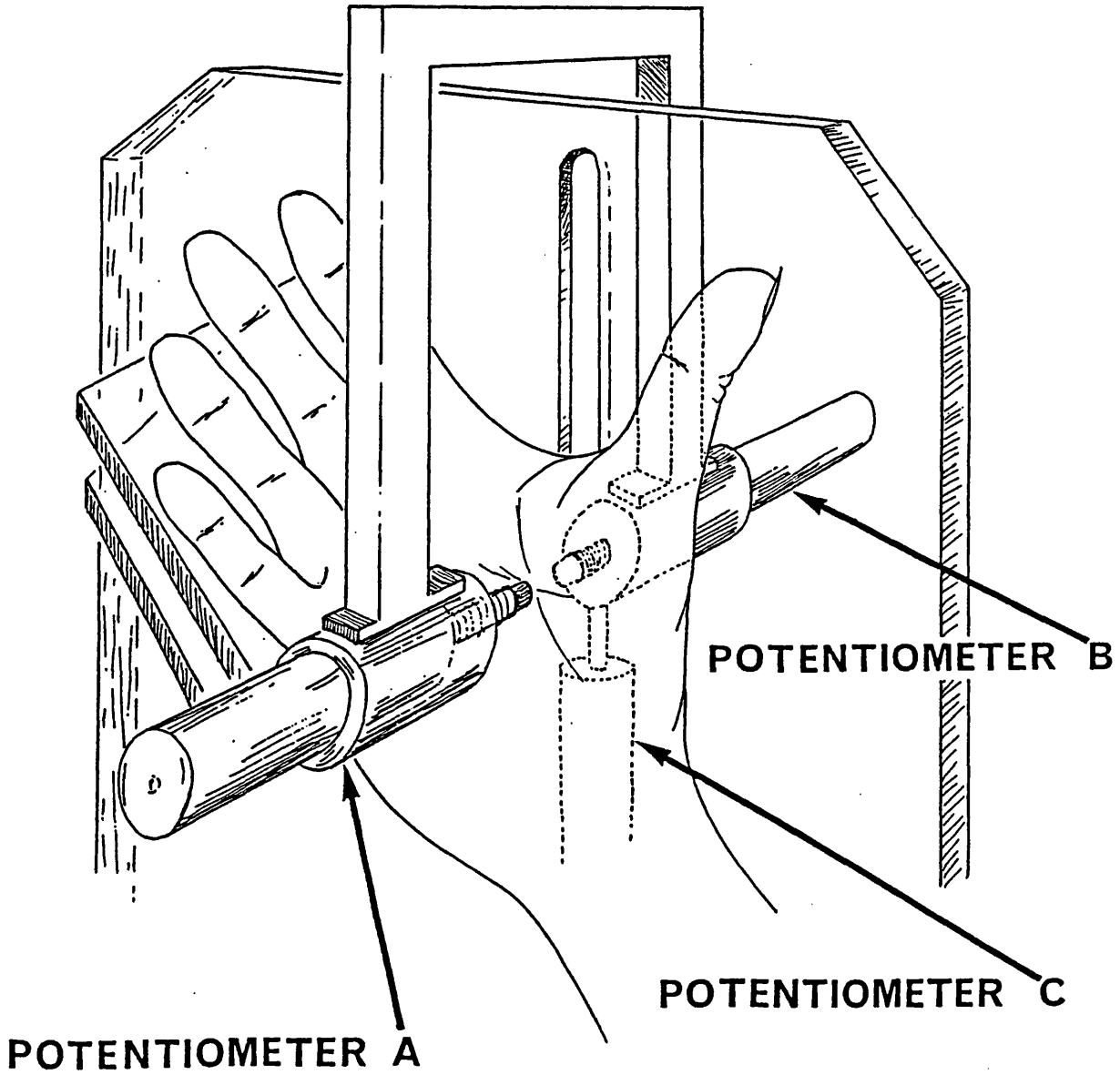
Measurements for the sub-nourished patients were made at the bedside but data could also be transferred for analysis on to a Nicolet 4094 oscilloscope or on to the personal computer. The computer was used to store and analyse data from the elderly subjects except when they were tested for full muscle activation. Maximal relaxation rate (MRR) was measured using a differentiating programme available on this oscilloscope or Nicolet PC31 computer programme and normalised by the maximum force exerted (Wiles et al., 1979). MRR has the units s^{-1} (equivalent to percentage force loss in 10 ms).

2. CROSS-SECTIONAL AREA MEASUREMENT

The apparatus for estimating CSA of adductor pollicis is shown in Fig 31. The profile of the hand is measured with the thumb fully abducted. The plane of the measurement bisects the angle between the metacarpal bones of the thumb and index finger up to the reference point which is between the bases of these bones. The thickness of the hand along this plane is measured by the difference in the outputs of two linear potentiometers (A & B in Fig 31). The shafts of these are held by springs against the two surfaces of the hand. The potentiometers are held in a light frame which can be moved over the hand while its position is monitored by a third potentiometer (C).

Fig 31

Apparatus for estimating the cross-sectional area of adductor pollicis muscle

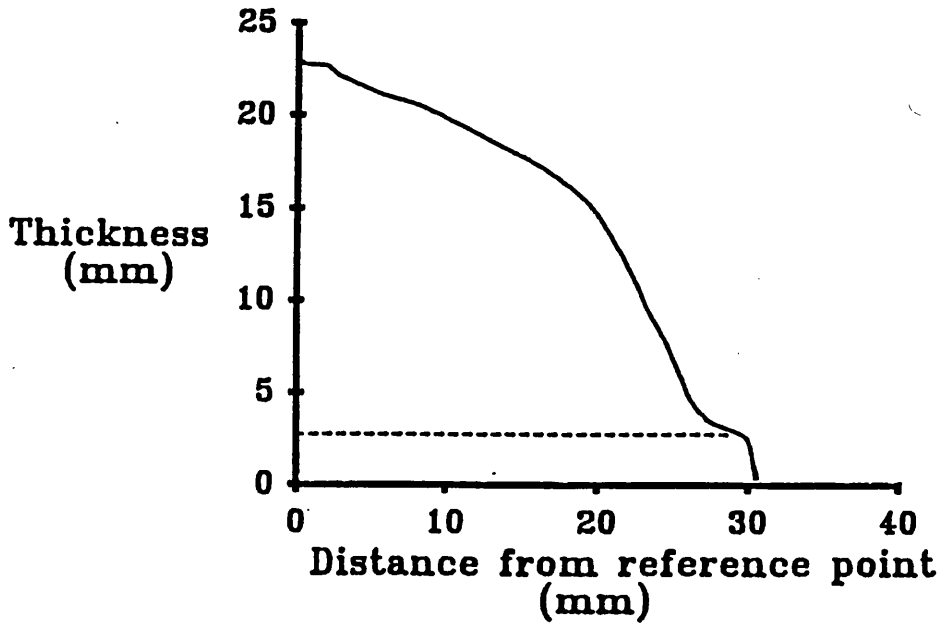


An X-Y plot of thickness against distance moved thus represents a profile of the hand (Fig 32). Three profiles are obtained for each subject, the subject being asked to remove the hand from the apparatus between each measurement. These profiles are integrated after allowing for skin thickness. That this profile does approximate to the cross-sectional areas of adductor pollicis together with part of the first dorsal interosseous was confirmed in two ways. Firstly an anatomical dissection of a cadaver hand was made through this plane (Fig 33a-d). Secondly we obtained images of the hand using computer assisted tomography (CAT, n = 4) and magnetic resonance imaging (MRI, n = 12). An example is shown in Fig 34. We found a good correlation (r = 0.937) between the area measured using our callipers and measurements of muscle CSA obtained from the CAT and MRI images through the same plane (Fig 35). The estimated CSA obtained from our hand profiles appears to underestimate actual muscle CSA by approximately forty per cent. This is partly because some of the muscle is proximal to the bases of the metacarpal bones and is therefore not included in our CSA estimates. There is also a small compressing effect of the springs holding the potentiometers against the two surfaces of the hand. This underestimate does not affect the conclusions which are based on comparing relationships between force and CSA and not the absolute value of their ratio.

The area measurement could be made at the bedside using Gaussian quadrature integration but specimen records were kept for transfer either to the Nicolet 4094, which has an integration programme or to a personal computer. Areas could be measured on a computer using an extended Nicolet PC31 programme.

Fig 32

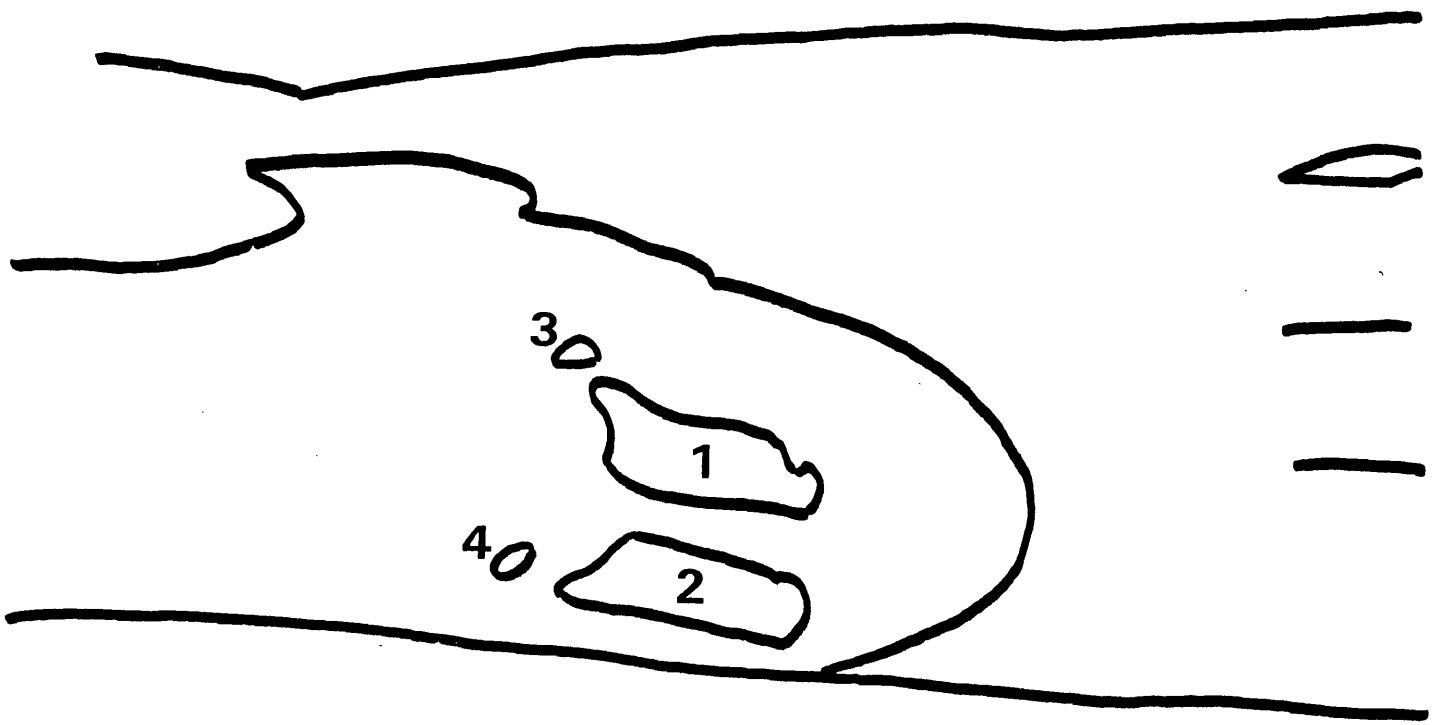
A profile of the hand obtained using the apparatus shown in Fig 31.



Hand thickness was measured by the difference between the outputs of the potentiometers A and B and the distance from the reference point (see text) by the output of potentiometer C. The area above the broken line on the resulting X - Y plot shown, is taken to represent the CSA of adductor pollicis. The area below the line represents skin and subcutaneous fat.

Fig 33a

A key to the important structures shown in Fig 33b that are related to the hand profile measured.



1. Adductor pollicis; 2. First dorsal interosseous; 3. Tendon of flexor pollicis longus; 4. Radial artery.

Fig 33b

Anatomical dissection through the plane measured by the apparatus shown in Fig 31 (medial surface). A key to the important structures that are related to the hand profile measured, is shown opposite.

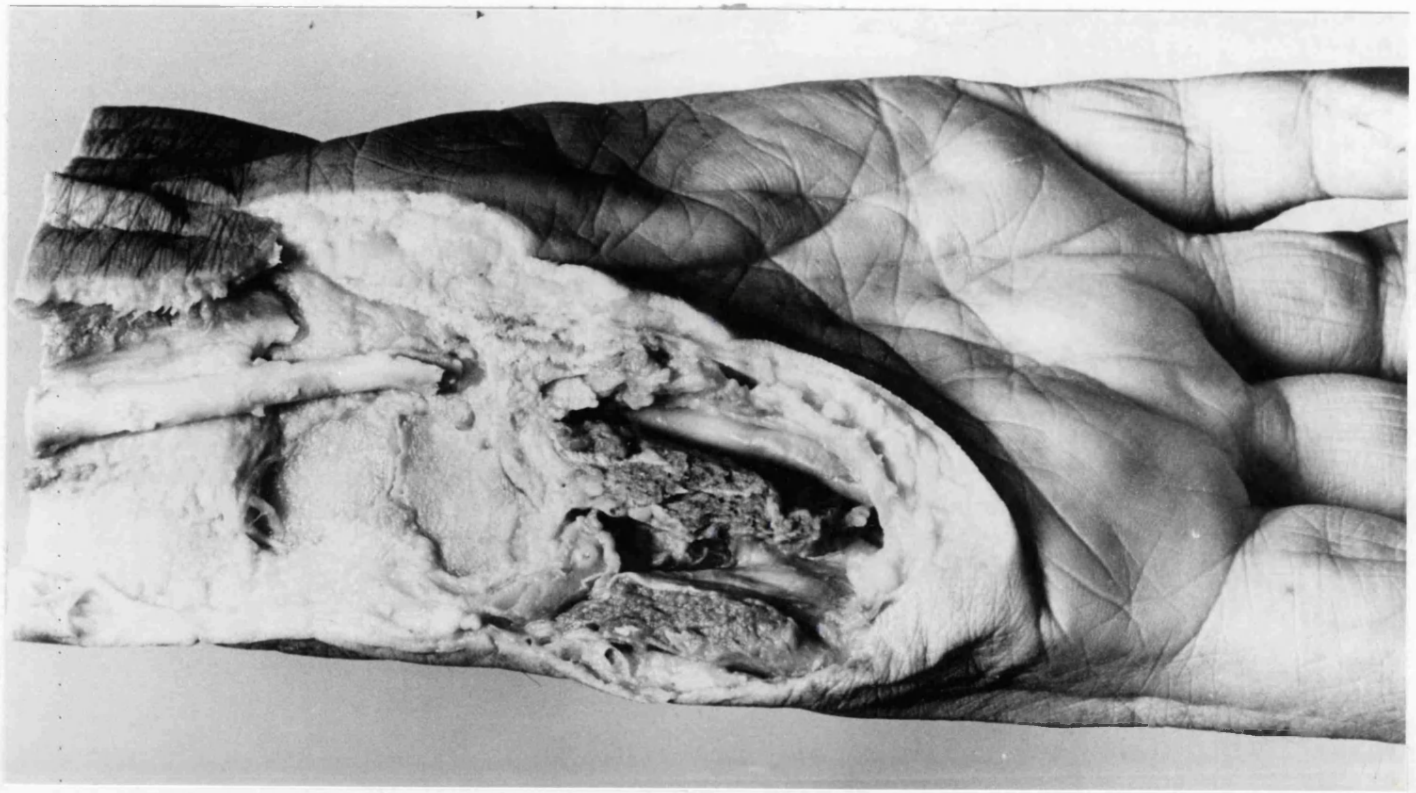
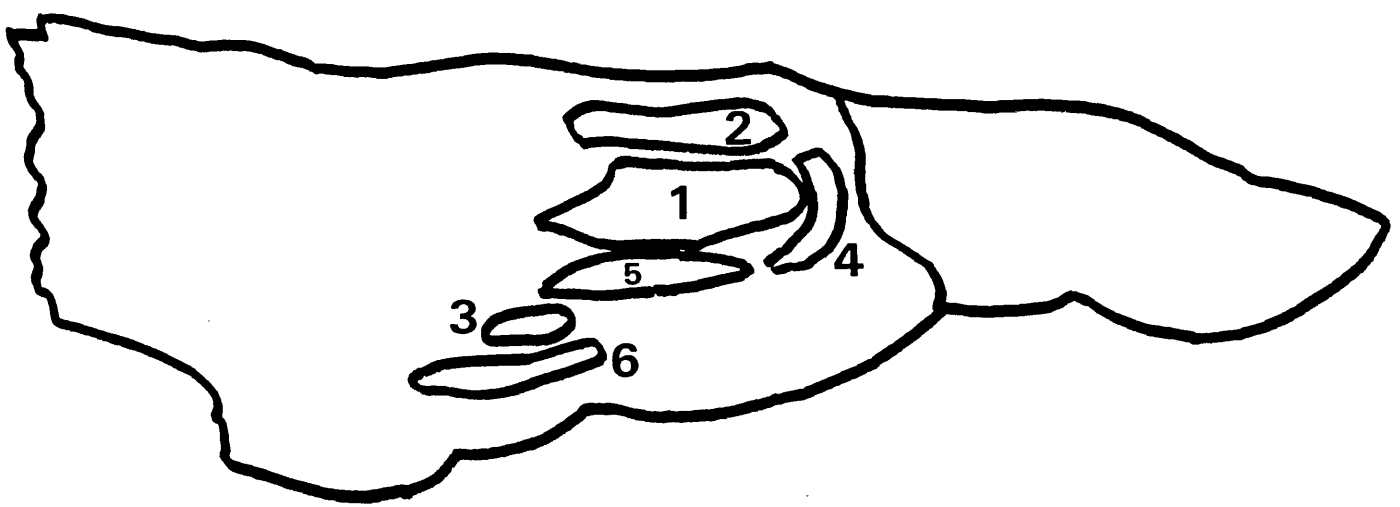


Fig 33c

A key to the important structures shown in Fig 33d that are related to the hand profile measured.



1. Adductor pollicis; 2. First dorsal interosseous; 3. Tendon of flexor pollicis longus; 4. Radial artery; 5. Opponens pollicis; 6. Flexor pollicis longus and abductor pollicis brevis

Fig 33d

Anatomical dissection through the plane measured by the apparatus shown in Fig 31 (lateral surface). A key to the important structures that are related to the hand profile measured, is shown opposite.

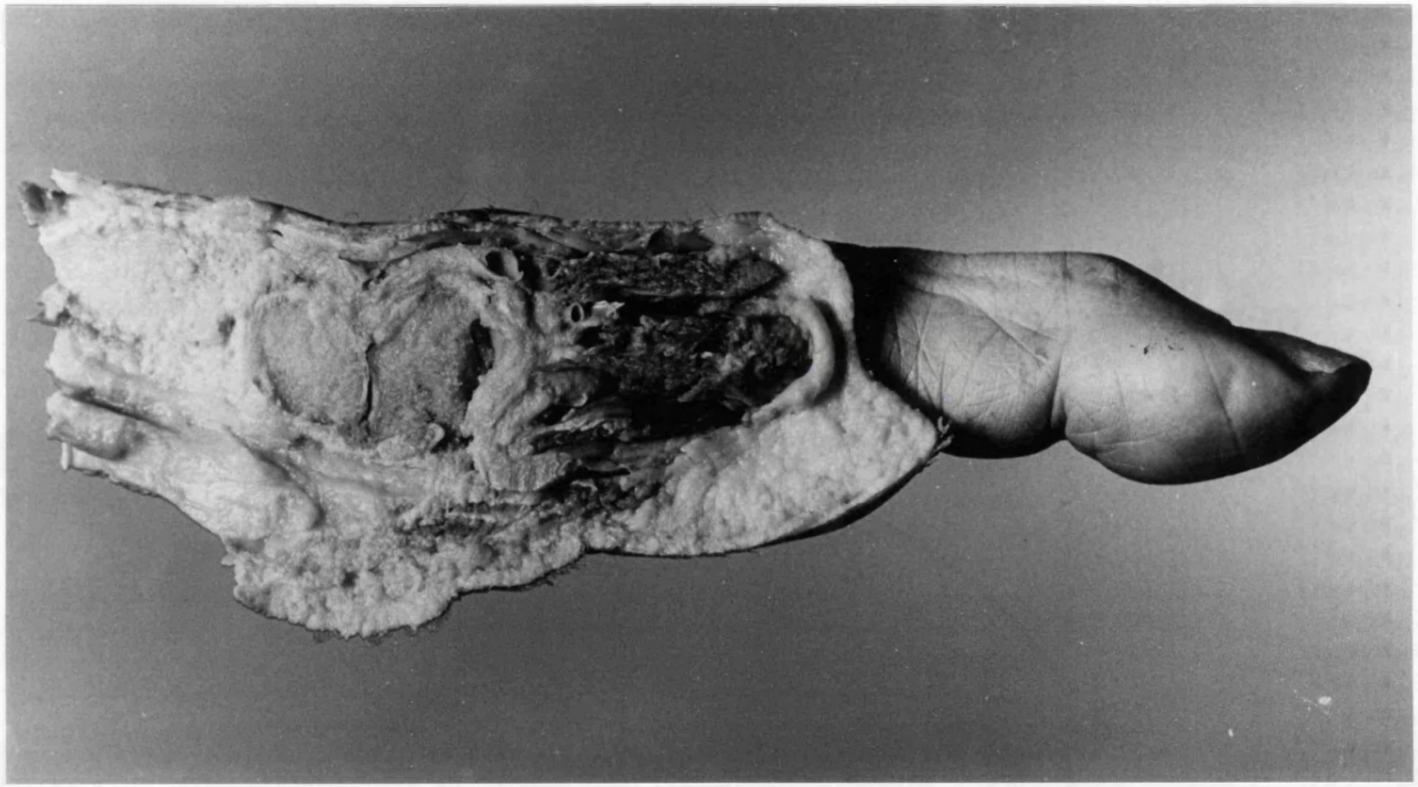


Fig 34

N.M.R. image through the plane of measurement shown in Fig 31.

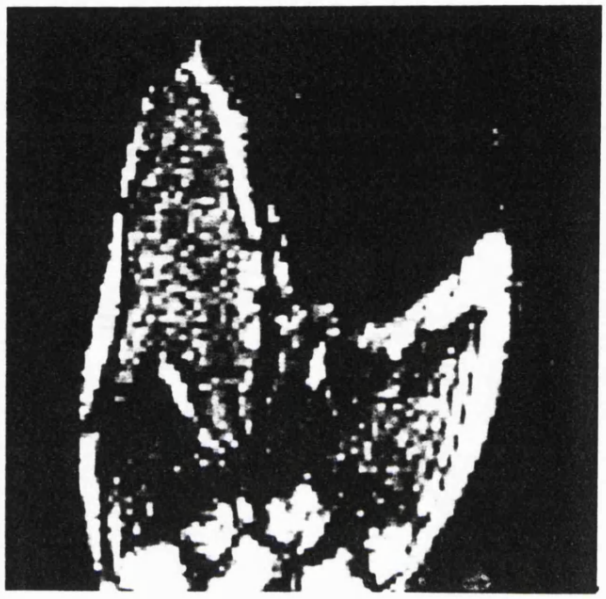
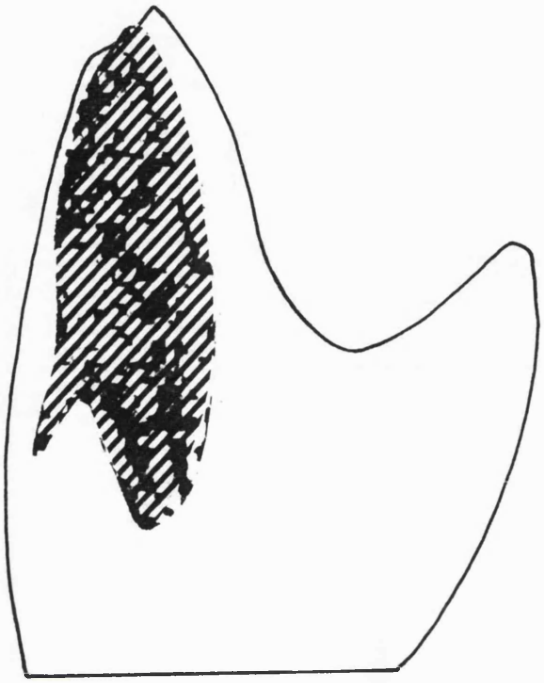
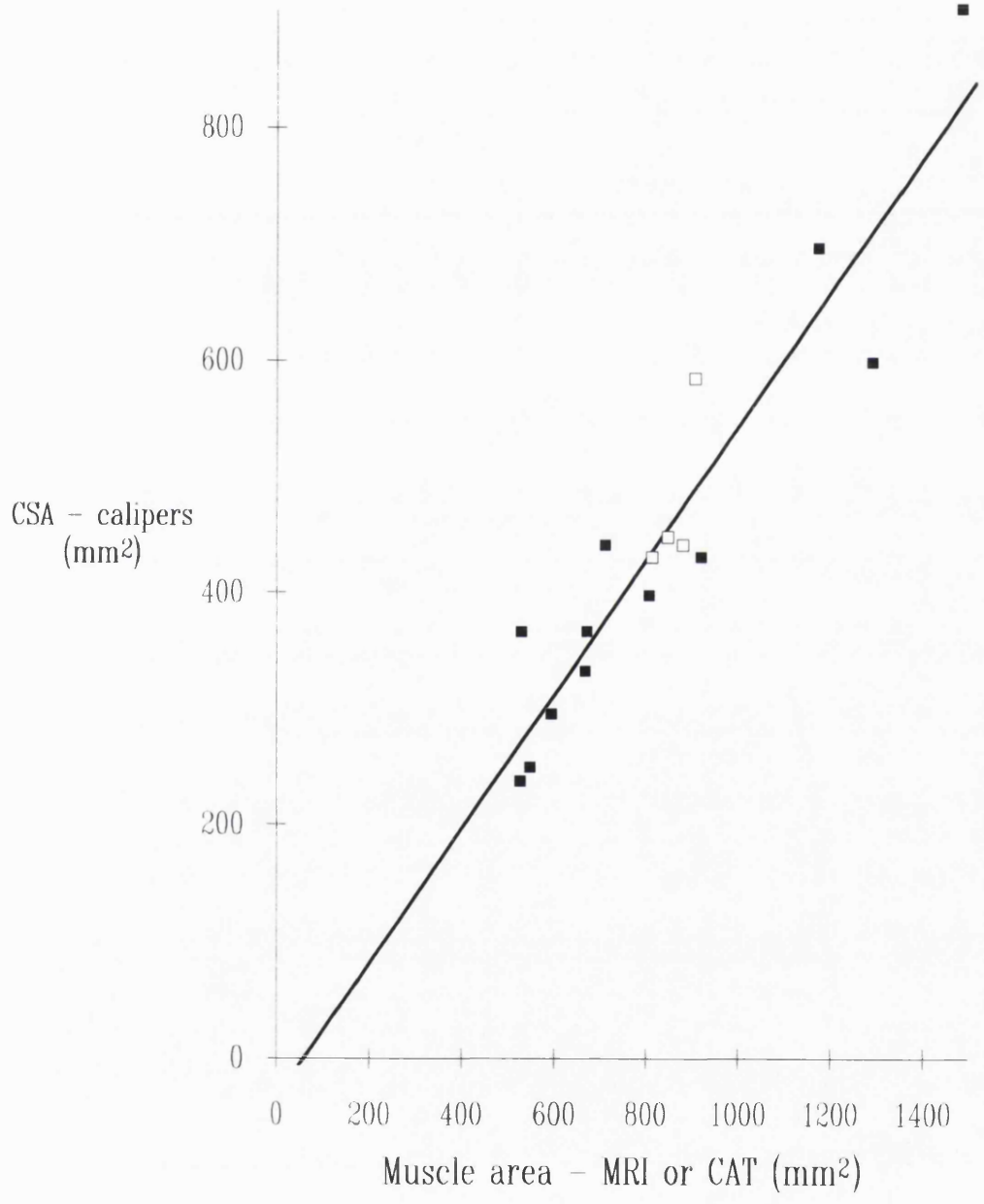


Fig 34a

The part of the N.M.R. image shown in Fig 34 which was used to compare with the estimate of muscle CSA measured using the apparatus in Fig 31



Relationship between muscle area measured by MRI or CAT scanning and CSA as measured by method described in text



□ **CAT scan:** ■ **MRI scan**

The unbroken line is the regression line y = 0.58x - 35

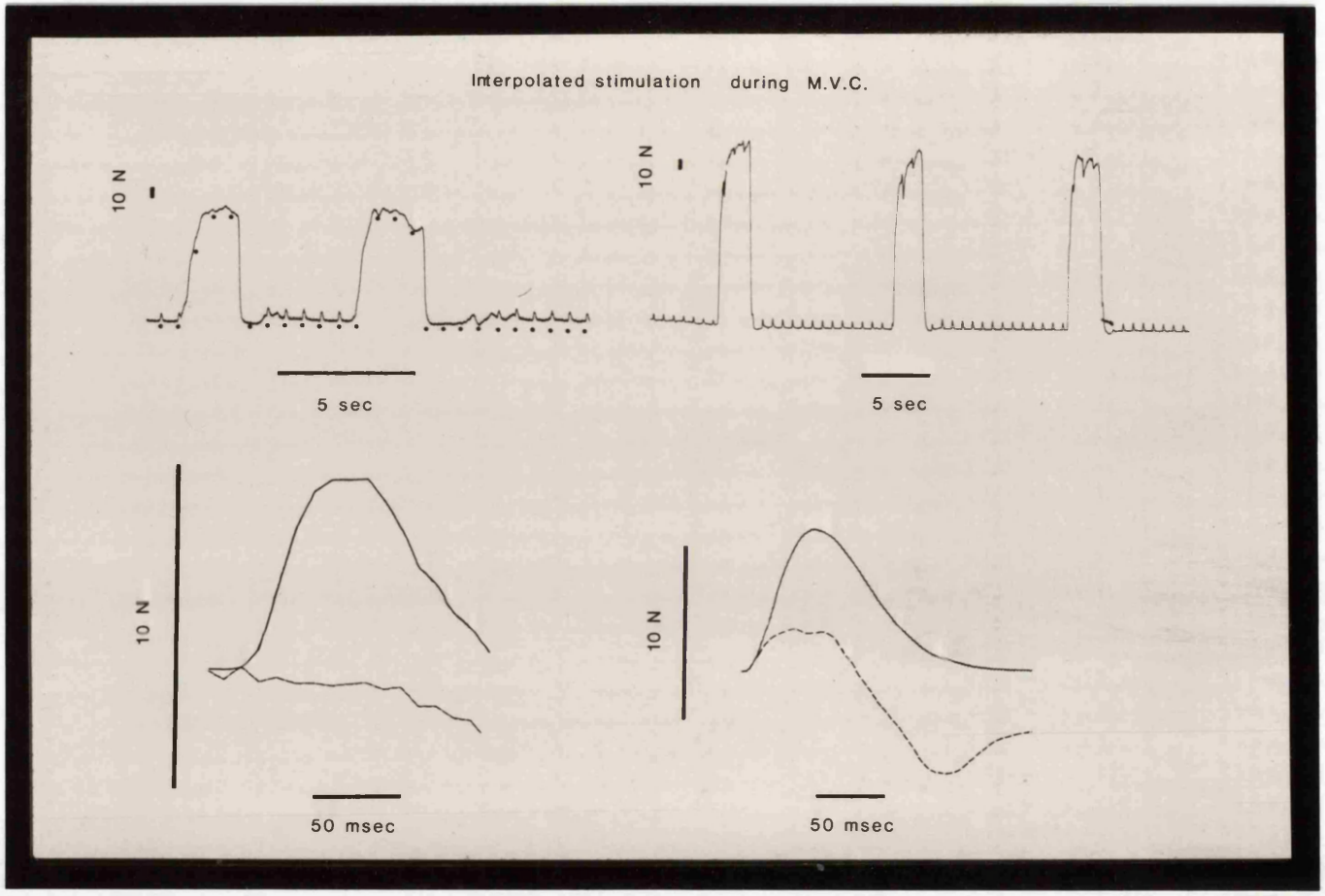
3. TESTING FOR FULL ACTIVATION

As well as MVF and CSA measurements, 8 young (5 male) and 4 elderly (2 male) subjects were also tested for full muscle activation. As stated in our published report of this experiment (Phillips et al., 1992), we did not feel that it was ethically justified to recruit more elderly subjects since the results obtained from this small sample were significant and the test involves some discomfort.

Interpolation of stimulated twitches during voluntary contractions, as described on p 18 was used to test for full activation (Merton 1954).

Some previous studies, both clinical (McComas et al., 1983) and with ageing muscle (Vandervoort & McComas, 1986) have only attempted to interpolate stimulated twitches during maximal voluntary contractions (MVCs). If full activation is achieved by the subject then no twitch will be recorded. However, there is an interpretative problem with relying on this single measurement, in that the absence of a twitch is much more difficult to be certain about than its presence. Fig 36 illustrates this problem. Two examples of apparent MVCs are shown. Twitches can be seen clearly on the baseline prior to each MVC and they appear to be absent during the MVC. However, the plateau of the voluntary contraction forms a relatively wandersome baseline and the presence or absence of small residual twitches is difficult to assess with certainty. In the second pair of records averaging has demonstrated the presence of residual twitches during the MVC and full activation was therefore not achieved by this subject on this occasion.

Fig 36. Interpolated twitches during maximal voluntary contractions



The upper two traces show maximal voluntary contractions with interpolated twitches, obtained using our apparatus. The lower two traces show averaged records of the baseline twitches and of the times during the maximal voluntary contractions when the ulnar nerve was stimulated. In the second pair of records a residual twitch is evident in the averaged record.

This source of error can be excluded by plotting twitch height against the percentage of maximum force and showing that the line of best fit joining the points crosses the x-axis at 100% activation (Merton 1954). This is therefore the technique we have employed. For this study data was stored and analysed on the Nicolet 4094.

4. MEASUREMENTS OF FORCE AT DIFFERENT VELOCITIES OF *STRETCH DURING A MAXIMAL VOLUNTARY CONTRACTION*

For the application of stretch during a maximal voluntary contraction of adductor pollicis the force transducer shown in Fig 30 was further modified as shown in Figs 37a and 37b. In this apparatus the metal bar on which the force transducer is mounted can be raised by a gas operated piston, the extent of the movement being limited by a stop. The distance moved is adjustable and measured by the output of a linear potentiometer. The velocity of stretch is controlled by the gas pressure acting through a fast-acting high pressure solenoid valve. Length and force were recorded on a Nicolet 3091 oscilloscope.

During a MVC the solenoid valve was opened and the bar raised 8 mm, a sufficient distance for a plateau to be observed in the force records. A typical record obtained using this apparatus is shown in Fig 37c and 37d. The force produced towards the end of the stretch was compared with the voluntary force just prior to the stretch. Passive force was measured with the thumb just resting on the transducer and stretched without a voluntary contraction. Passive force was deducted from the active force before calculating the ratio of the stretch force to the maximum voluntary force.

Fig 37a

Apparatus used for the application of stretch during a maximal voluntary contraction of adductor pollicis muscle

a) before the application of stretch

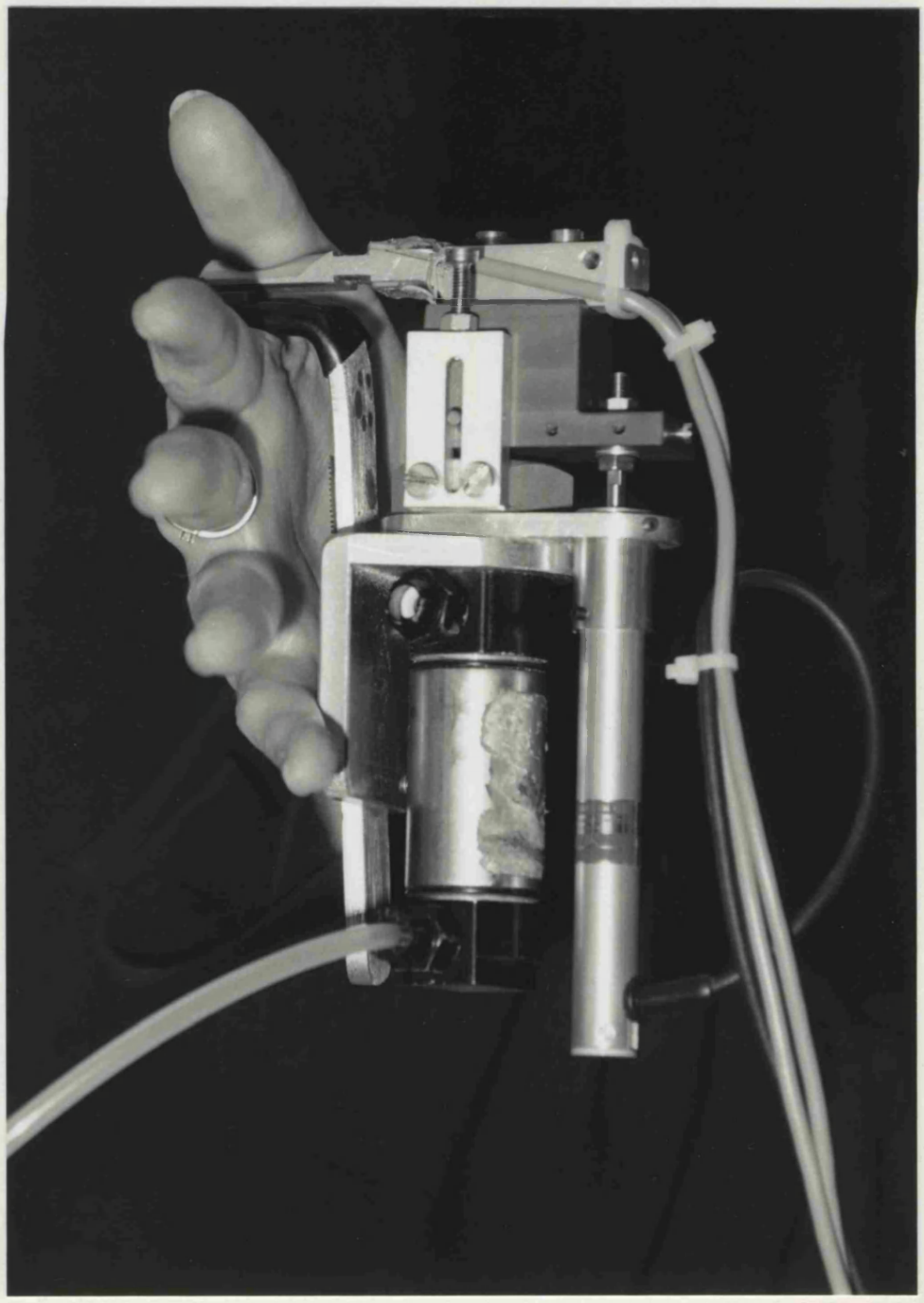


Fig 37b

Apparatus used for the application of stretch during a maximal voluntary contraction of adductor pollicis muscle

b) after a stretch of 8 mm has been applied

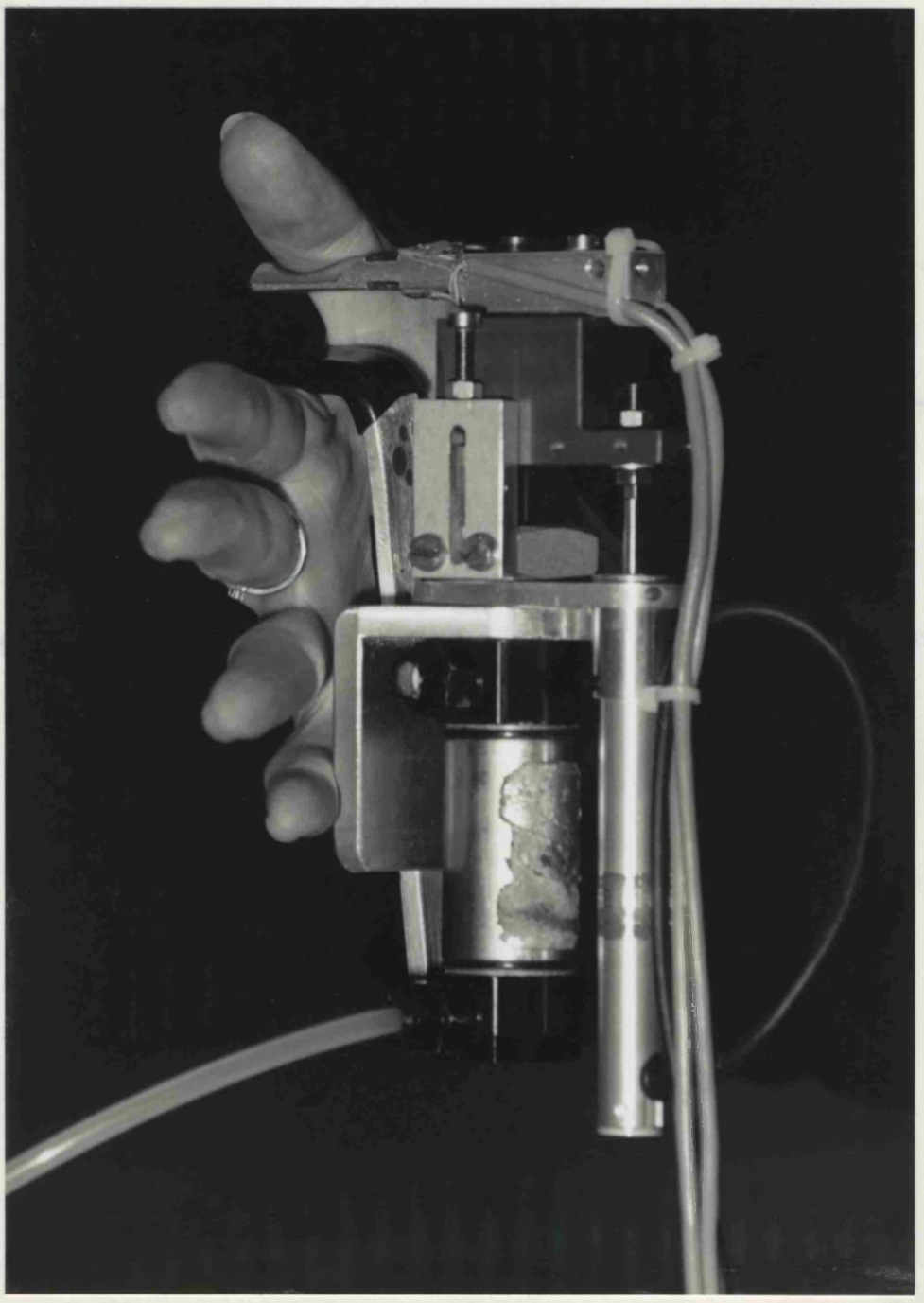


Fig 37c

Typical record of force and length obtained using the apparatus shown in Figs 37a & 37b.

Initially force is isometric. The rapid stretch of 8 mm is applied at ↑.

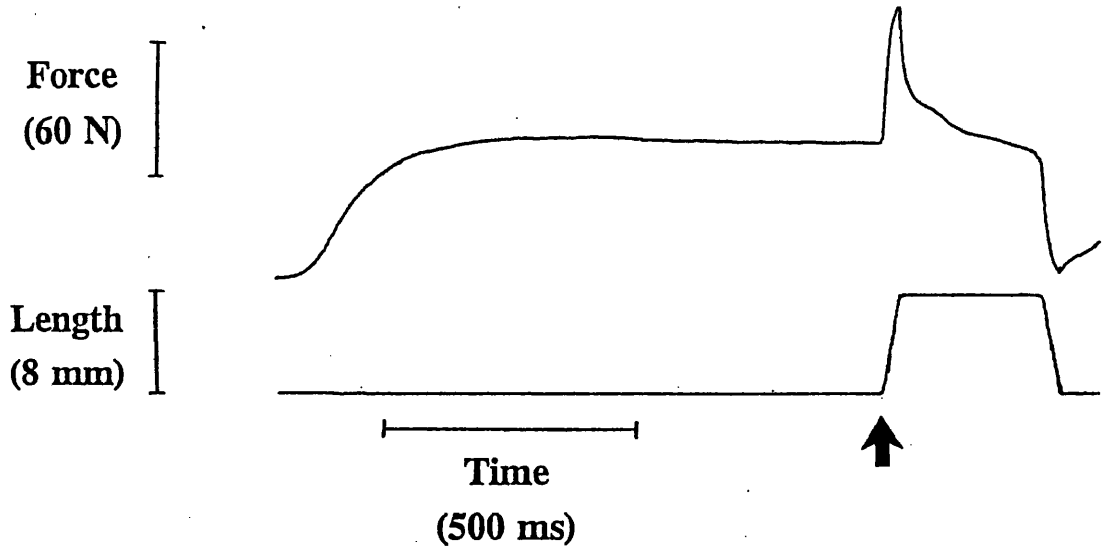
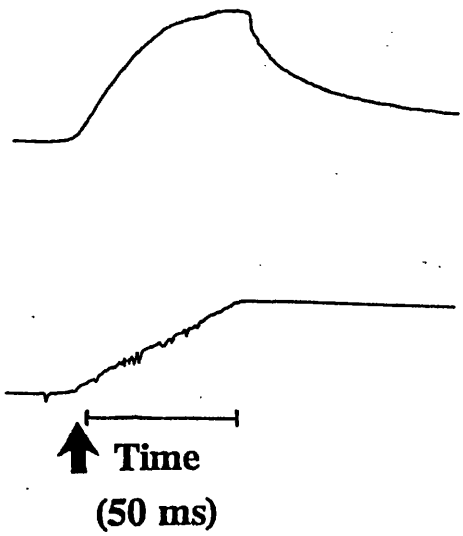


Fig 37d. The time axis of the record shown in Fig 37c has been expanded to show force and length only during stretch



5. STATISTICS

Regression lines were calculated by the least squares method. The confidence limits are for the population means in all except the nutrition study where confidence limits are plotted for individual observations. The formulae are as follows (Snedecor & Cochran, 1976):

population means: estimated standard error of $\hat{y}$ is

$$S\hat{y} = Sy.x\sqrt{1/n+x^2/\Sigma x^2}$$

individual values of y: estimated standard error is

$$S\hat{y} = Sy.x\sqrt{1+1/n+x^2/\Sigma x^2}$$

Regression lines were compared using analysis of co-variance (Snedecor & Cochran, 1976). Ratio standards were compared using two-tailed Student's t-test for unpaired data.

The potential pitfalls in interpreting regression analyses and the relative merits of ratio standards are discussed on pages 167-170.

SUBJECTS

Details of the subjects are given with the results of the individual studies. There is some overlap, particularly of young subjects, between the various studies. In all studies subjects were excluded if they had: 1) pain or stiffness of movements of the thumb, 2) specific wasting of the hand muscles, 3) cardiovascular or generalized neuromuscular disease, 4) osteomalacia or thyroid disease, 5) were taking regular medication likely to affect muscle function or motivation.

All subjects gave informed consent. Approval was given by the ethical committees at University College London, University College Hospital, Guy's Hospital and Hastings Health Authority.

RESULTS

1. FORCE AND CROSS-SECTIONAL AREA MEASUREMENTS IN YOUNG MALES AND FEMALES

Twenty-three males (19-53 years) and twenty eight females (22-42 years) were selected from staff and students at University College London to give as wide as possible a range for height and frame size

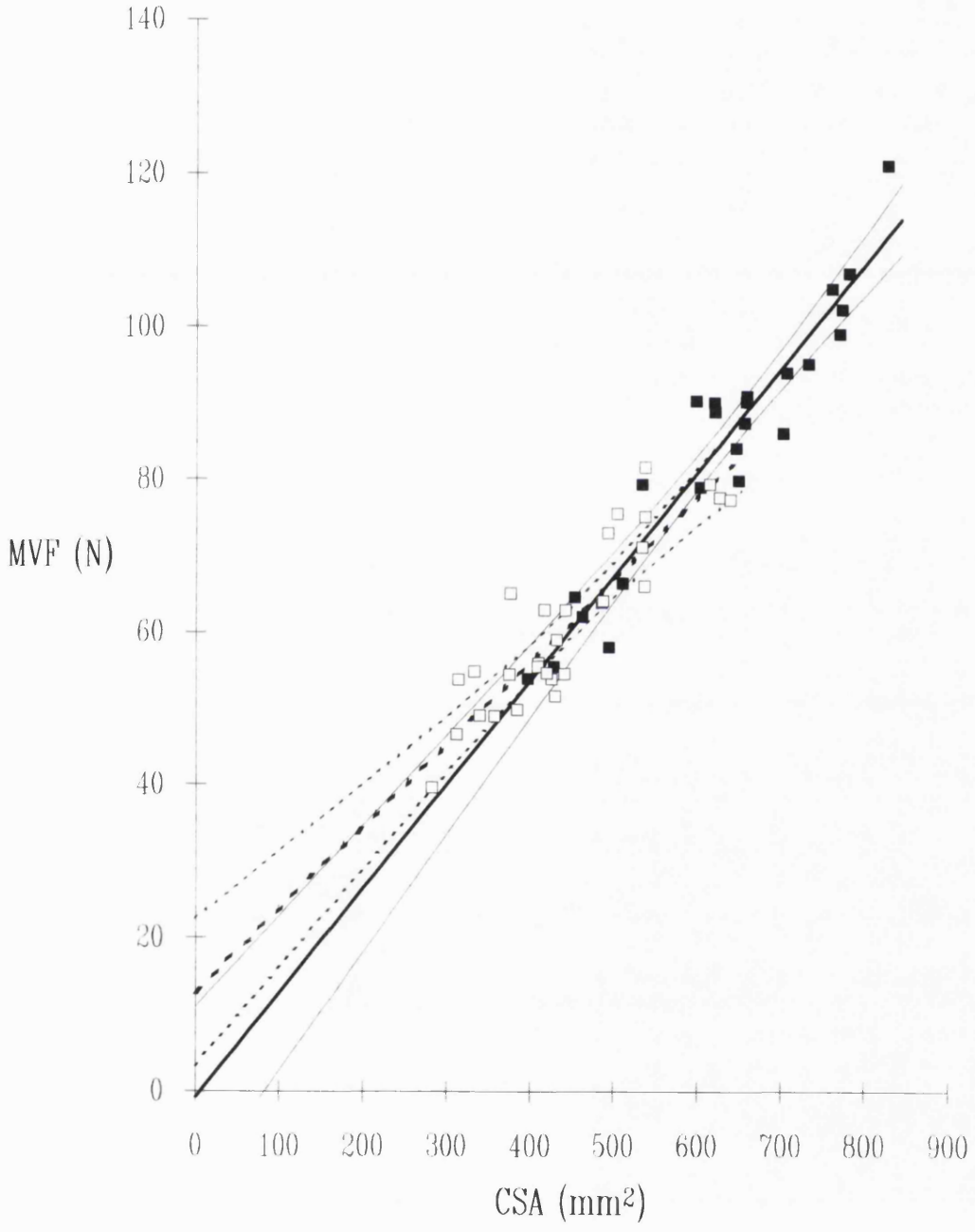
Results of force and CSA of adductor pollicis muscle in male (■) and female (□) subjects are shown in Fig 38. Regression lines and 95% confidence limits are shown (male - continuous lines, female - dotted lines). There is a strong correlation between force and CSA in both groups ($r = 0.96$, $p < 0.001$ - male, $r = 0.89$, $p < 0.001$ - female). Mean MVF/CSA for the female subjects was 0.139 ± 0.003 $N.mm^{-2}$ (mean $\pm$ SEM) and for the twenty-three male subjects was 0.134 ± 0.002 $N.mm^{-2}$.

There is no difference between the male and female subjects neither comparing these ratio standards ($p > 0.1$) nor the regression lines, the equations for which are:

$$\text{males: } y = 0.14x - 0.9$$

$$\text{females: } y = 0.11x + 12$$

Relationship between MVF and CSA of adductor pollicis of fit young male and female subjects



□ and broken lines - female
■ and unbroken lines - male
Regression lines and 95% confidence limits are shown

2. NUTRITION STUDY

Forty normally nourished healthy subjects (age range 17-53 years, mean 28 years, 21 male,19 female) were selected from staff and students at University College London to give as wide a range as possible for height and frame size.

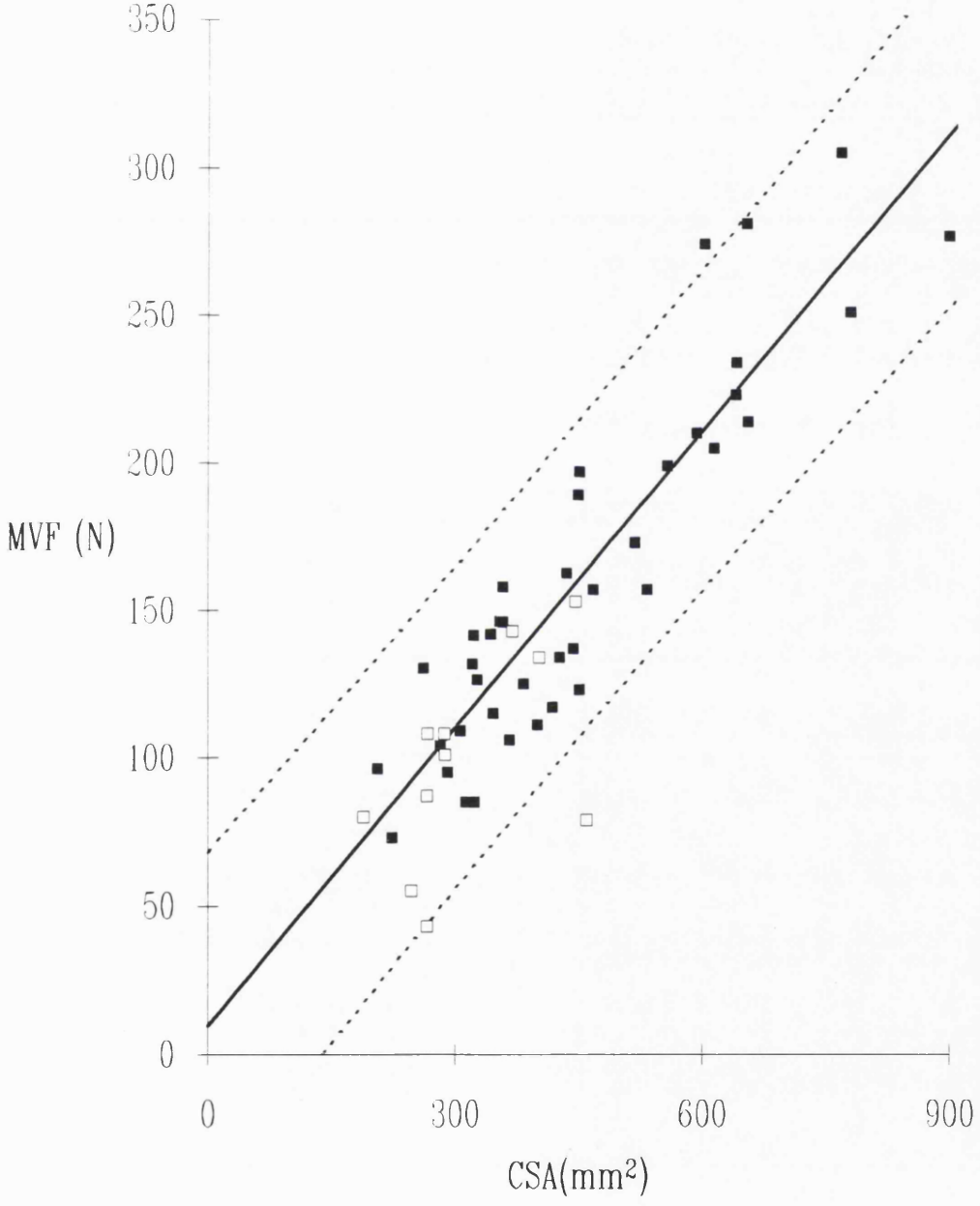
Eleven patients who were known to be chronically less than ninety per cent of ideal body weight for height and frame size were tested (age range 19-54 years, mean 29 years, six males, five females). Eight of these had Crohn's disease, one had ulcerative colitis, one short-bowel syndrome and one pulmonary tuberculosis. At the time of testing their percentage ideal body weights ranged from 76.4 to 89% (mean 83.5%). Two of these patients were on steroids at the time they were tested.

a) MVF/CSA

The coefficient of variation for the force measurements on each subject was five per cent or less for the control group and for all but one of the subnourished group. The mean co-efficient of variation for the area measurements on any one subject was 5.1% in both groups.

The results of MVF and CSA measurements for the forty normal subjects and the eleven subnourished patients are shown in Fig 39. The regression line and 95% confidence limits for the observations from normally nourished subjects are shown ($r = 0.907$, $p < 0.001$). The regression line passes through the origin within the confidence limits and it can be seen that all but two of the observations from the

Relationship between force and CSA of adductor pollicis of normal and subnourished subjects



□ - subnourished
■ - normally nourished
The regression line (y = 0.34x + 9) and 95% confidence limits for the observations from normally nourished subjects are shown

subnourished patients are evenly scattered about it. These two observations are discussed on pages 171-172.

b) MVF/HEIGHT

Fig 40 shows MVF plotted against height for twenty of the controls (with the regression line for these observations) and the eleven subnourished patients. It can be seen that the subnourished patients are generally weaker relative to their height than the controls. The significant correlation between force and height seen in the control group ($r=0.73$, $p < 0.001$) is absent in the subnourished group. This is partly because of the smaller range of heights, but is probably mostly because of the variable degree of subnutrition in this group.

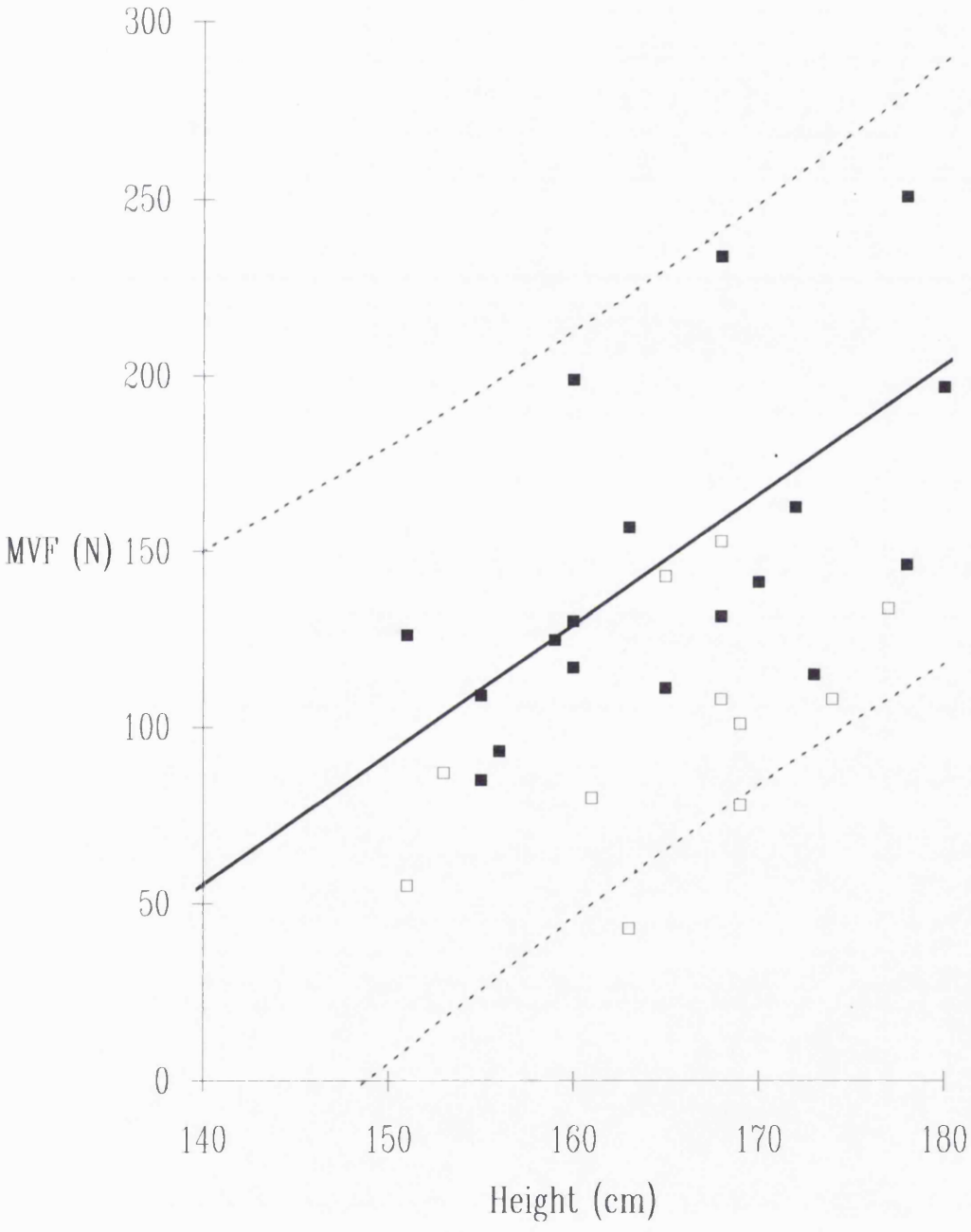
c) MAXIMAL HAND-GRIP/ARM MUSCLE AREA

Fig 41 shows maximal hand grip plotted against arm muscle area (AMA), measured in twenty of the normally nourished and ten of the subnourished patients. Maximal hand grip was measured using a commercially available dynamometer. AMA was measured using the conventional formula (Burr & Phillips, 1984):

$$AMA = (\text{arm circumference} - \pi(\text{triceps skinfold thickness}))^2/4\pi$$

The regression line and 95% confidence limits for the individual control observations are shown ($r = 0.852$, $p < 0.001$). As for MVF/CSA the regression line passes through the origin within the confidence limits and all but two of the observations from the subnourished patients fall within the confidence limits for the control observations.

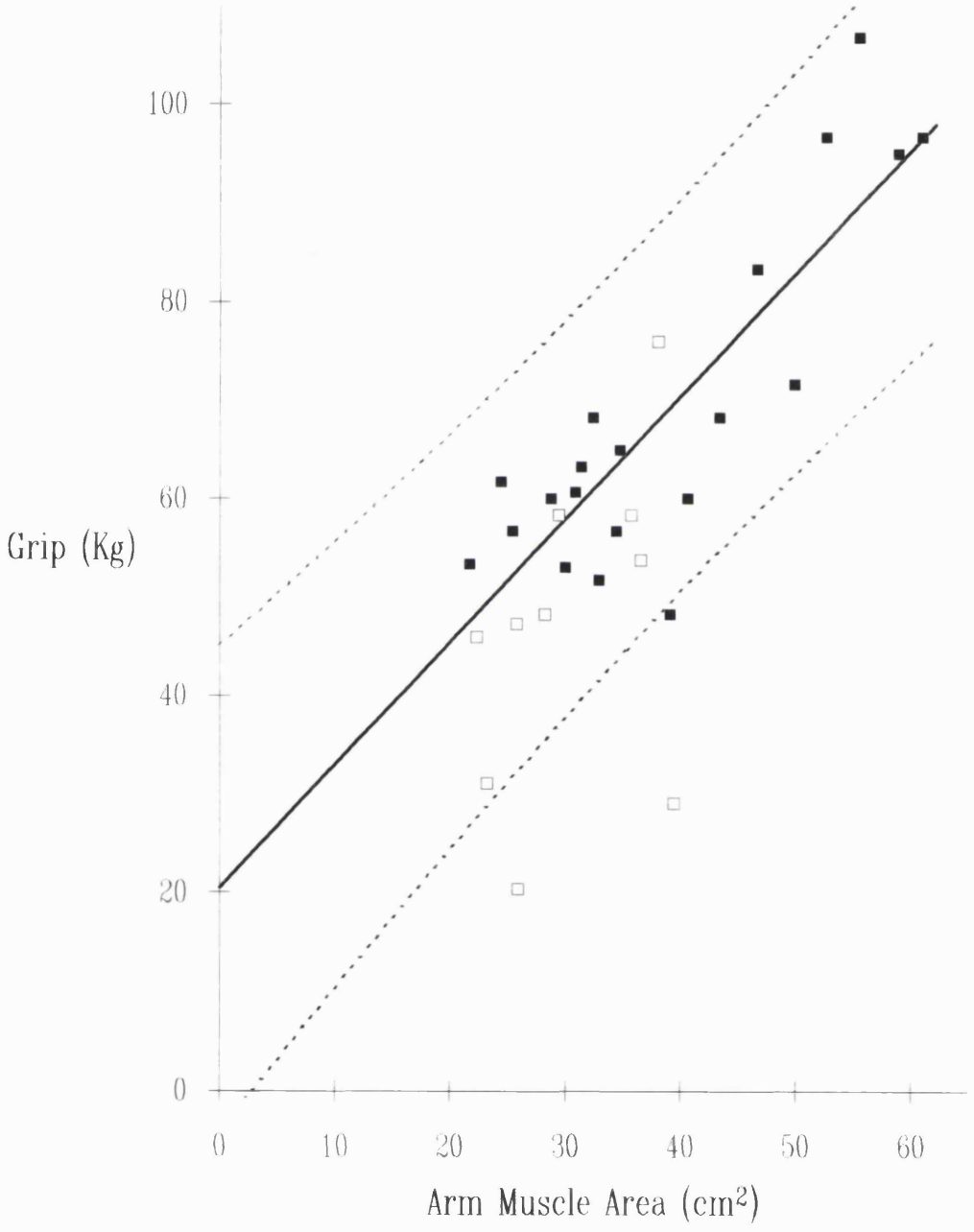
Relationship between force and height of normal and subnourished subjects



□ - subnourished
■ - normally nourished

The regression line (y = 3.7x - 463) and 95% confidence limits for the observations from the normally nourished subjects are shown

Relationship between grip and arm muscle area of normal and subnourished subjects



□ - subnourished
■ - normally nourished

The regression line (y = 1.2x + 20) and 95% confidence limits for the observations from normally nourished subjects are shown

These are from the same two patients discussed on pages 171-172.

d) MAXIMAL RELAXATION RATE

Maximal relaxation rate (MRR) was measured for 28 of the control group and eight of the subnourished patients. The mean coefficient of variation for measurements of relaxation rate on control and subnourished subjects was 13.7%. The normalized MRR in the control group was 6.8 $\pm$ 0.216 s^{-1} (mean $\pm$ SEM, range 4.9 - 9.4 s^{-1}). In the subnourished patients the value was 5.2 $\pm$ 0.336 s^{-1} (range 4.0 - 6.7 s^{-1}). Thus relaxation was significantly slower in this group ($P < 0.001$).

e) FATIGUE

There was no significant difference between the twenty control subjects and nine subnourished patients. The mean fall of force for all subjects and patients was 25% $\pm$ 12% (mean $\pm$ SEM).

3. COMPARING FORCE AND CROSS-SECTIONAL AREA BETWEEN YOUNG AND VERY ELDERLY SUBJECTS

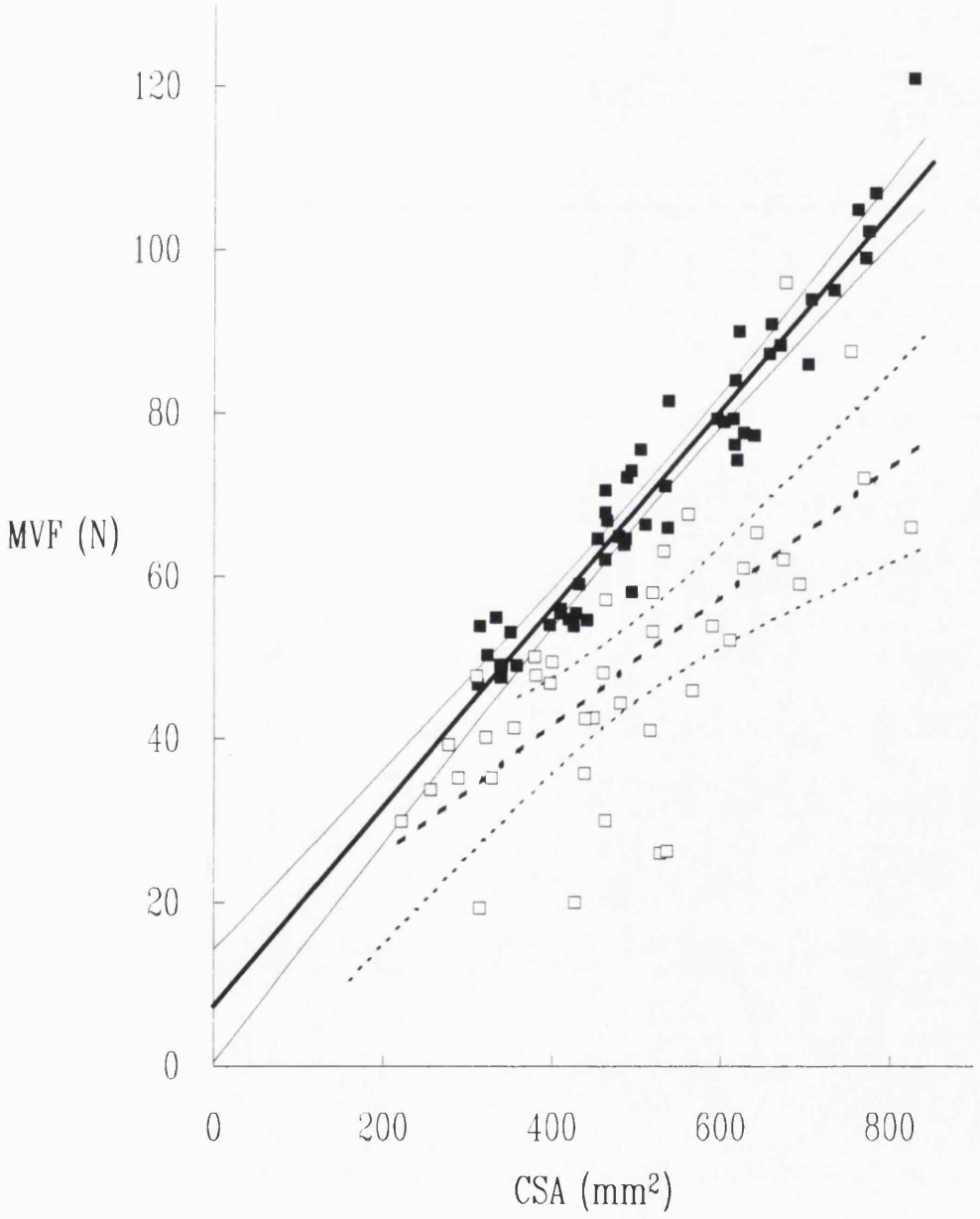
Fifty-three young subjects between 19 and 55 years (mean age 28 ± 1.1 years, 26 male & 27 female) were recruited from staff and students of University College London. The average height for young male subjects was 1.72 ± 0.02 m and they weighed 72.7 ± 2.4 kg, while the females were 1.60 ± 0.01 m tall and weighed 57.9 ± 1.7 kg (mean ± sem).

Elderly subjects were recruited from three sources. Firstly, from retired staff of University College London (still active in their respective fields) and their relatives, secondly from a fitness club in London, and thirdly from a bowling club in Hastings. Altogether we studied thirty-nine healthy elderly subjects (22 male and 17 female) between 74 and 90 years of age (mean age 80 ± 0.7). The height of the elderly male subjects was 1.71 ± 0.02 m and they weighed 64.1 ± 3.4 kg, while the females were 1.57 ± 0.02 m and weighed 58.1 ± 1.5 kg. A questionnaire modified from a Department of Health & Social Security questionnaire was used to assess health and physical activity.

MVF is shown plotted against CSA for these subjects in Fig 42. Measurements were made by three different investigators. Observer variation was not found to be a problem with the measurement of MVF which was highly reproducible (coefficient of variation < 5% for up to nine observations for each subject). The measurements were made by three different investigators. However systematic differences were found between the investigators in the measurement of CSA. Scaling factors were

Fig 42

Relationship between force and CSA of adductor pollicis of young and very elderly subjects



□ - very elderly
■ - young

The regression lines - young: (y = 0.12x + 8), elderly: (y = 0.08x + 10), - and 99% confidence limits of the population regression line for each group are shown

obtained by comparing measurements of CSA made on the same subjects by different investigators and the results adjusted to those of a single observer as standard. The correlation coefficient was higher for the young subjects ($r = 0.96$, $p < 0.001$) than for the elderly subjects ($r = 0.71$, $p < 0.001$). The regression line for the elderly is significantly different from that for the young subjects ($p < 0.01$).

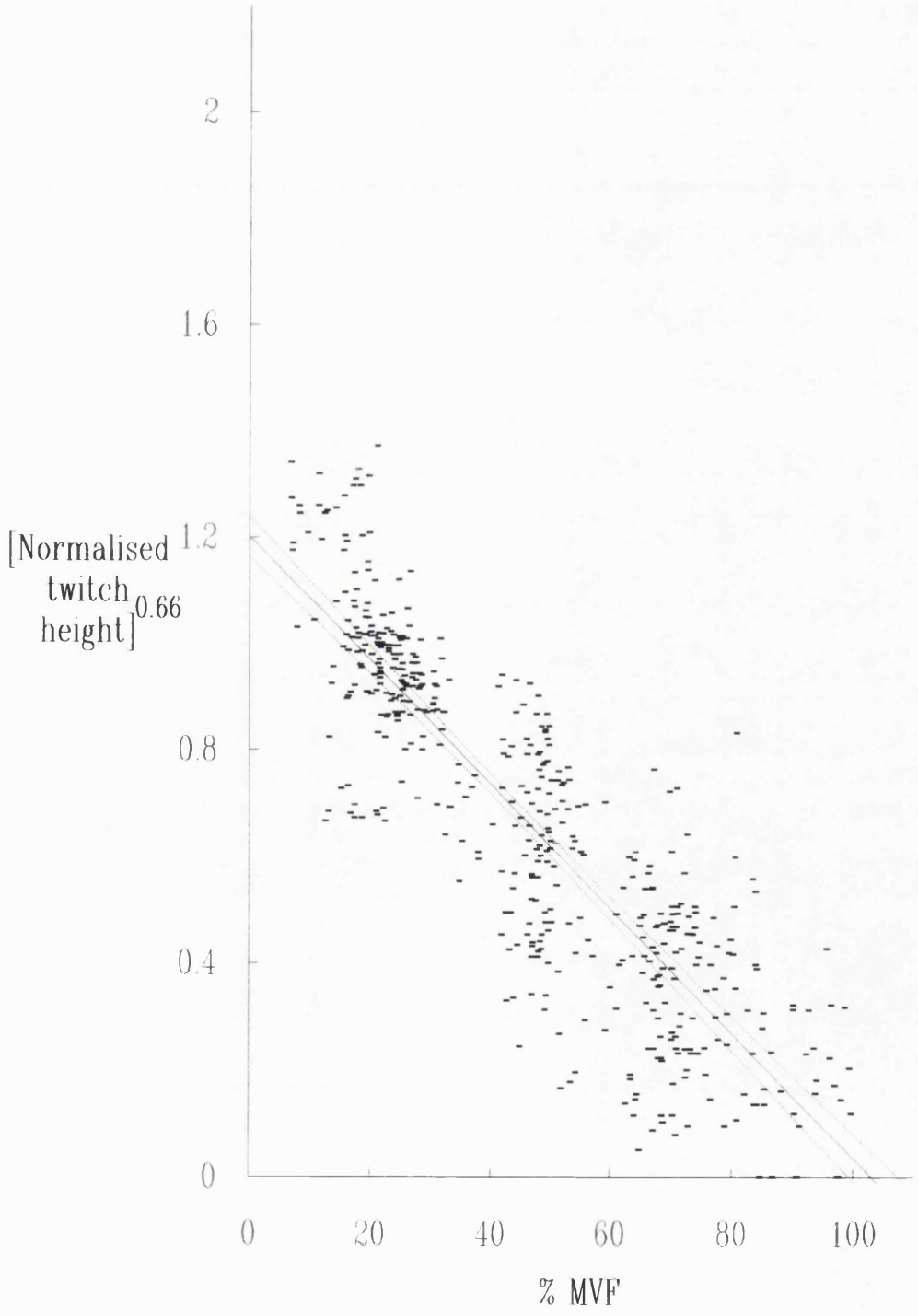
4. ACTIVATION STUDY OF WEAK VERY ELDERLY SUBJECTS

To position the thumb correctly on our force transducer a small baseline deflection is produced. Therefore it was not always possible to reliably record the height of the interpolated twitch at 0% of MVF. For this reason twitch height for each subject is presented as a proportion of the twitch height at 20% of MVF ("normalised twitch height"). Normalised twitch height is plotted against the degree of concomitant activation expressed as percentage of MVF. In the young subjects the relation between twitch height and voluntary force was found to be curvilinear. A curvilinear relationship has also been described for the quadriceps muscle group (Rutherford et al., 1986). The data from our subjects has been transformed to a linear scale by plotting (normalised twitch height)$^{0.66}$ against percentage MVF.

a) YOUNG SUBJECTS

The results from the twitch interpolation experiments on eight young subjects are shown in Fig 43. It can be seen that the regression line passes through zero at 100% MVF within the 99% confidence limits showing, in agreement with Merton (1954), that young subjects can fully activate their adductor pollicis muscle.

Relationship between linearised normalised twitch height and percentage of measured MVF in young subjects



The regression line and 99% confidence limits of the population regression line are shown

b) ELDERLY SUBJECTS

The data plotted is from three of the four elderly subjects who were tested. MVF/CSA for the fourth subject (an 83 - year old woman) was indistinguishable from those recorded from the young subjects and twitch interpolation showed her to be able to fully activate. Therefore her results could not contribute to answering the question whether or not the weakness of elderly subjects whose MVF/CSA measurements are low, is due to failure of activation. The results for the three elderly subjects whose MVF/CSA measurements were low compared with those from the young subjects, are shown in Figs 44 & 45. They have been plotted in two ways corresponding to the two opposing hypotheses:

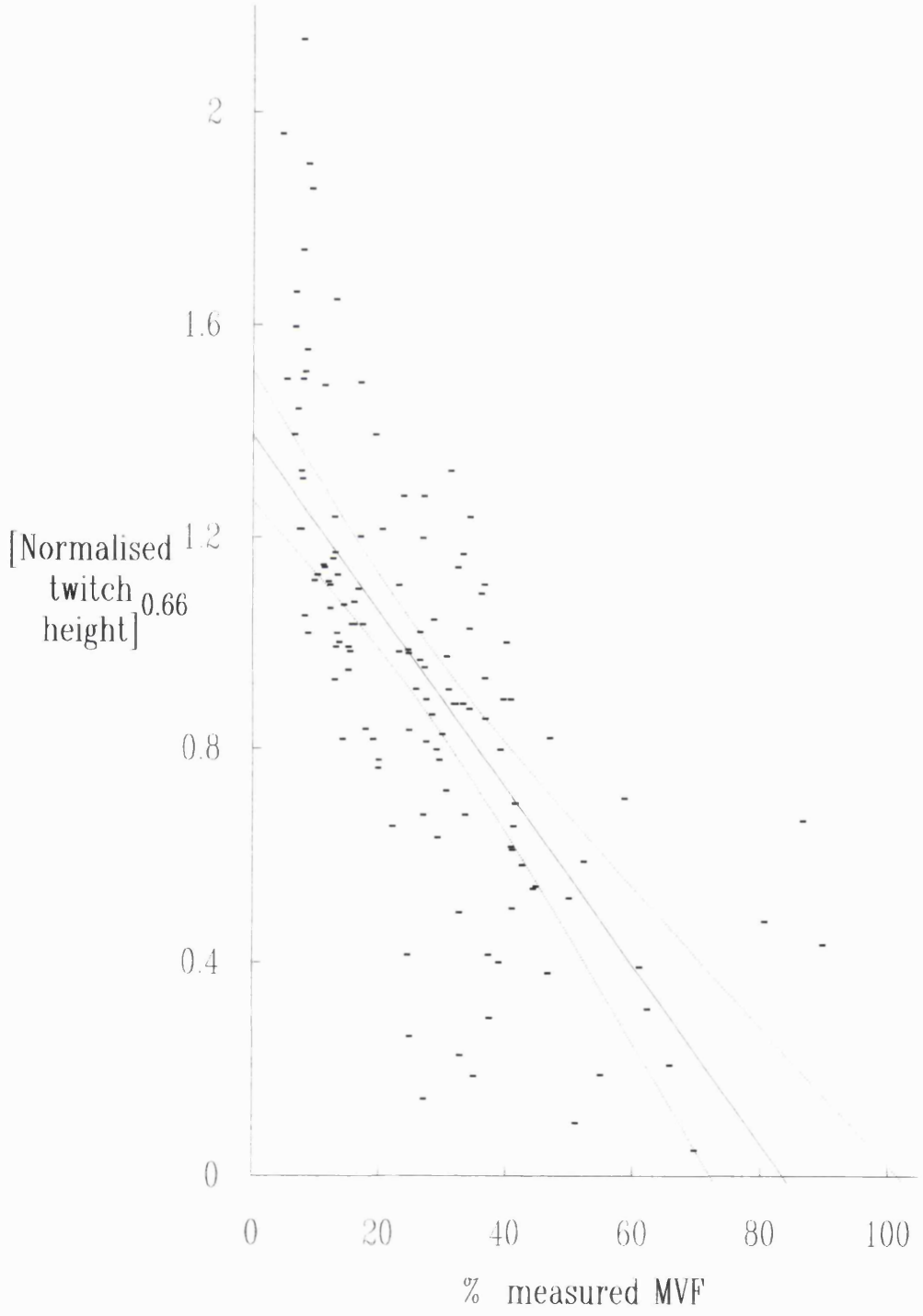
(i) that elderly subjects can fully activate their muscles

(ii) that the reduction in MVF/CSA in elderly subjects is due to their inability to fully activate.

Hypothesis (i) is tested by plotting the linearised results in the same way as for the young subjects, i.e. (normalised twitch height)$^{0.66}$ is plotted against the degree of concomitant activation expressed as percentage of MVF (Fig 44). As for the young subjects the regression line passes through zero at 100% MVF within the 99% confidence limits. Therefore this hypothesis, that despite being weak these elderly subjects were fully activating their muscles, is compatible with our results.

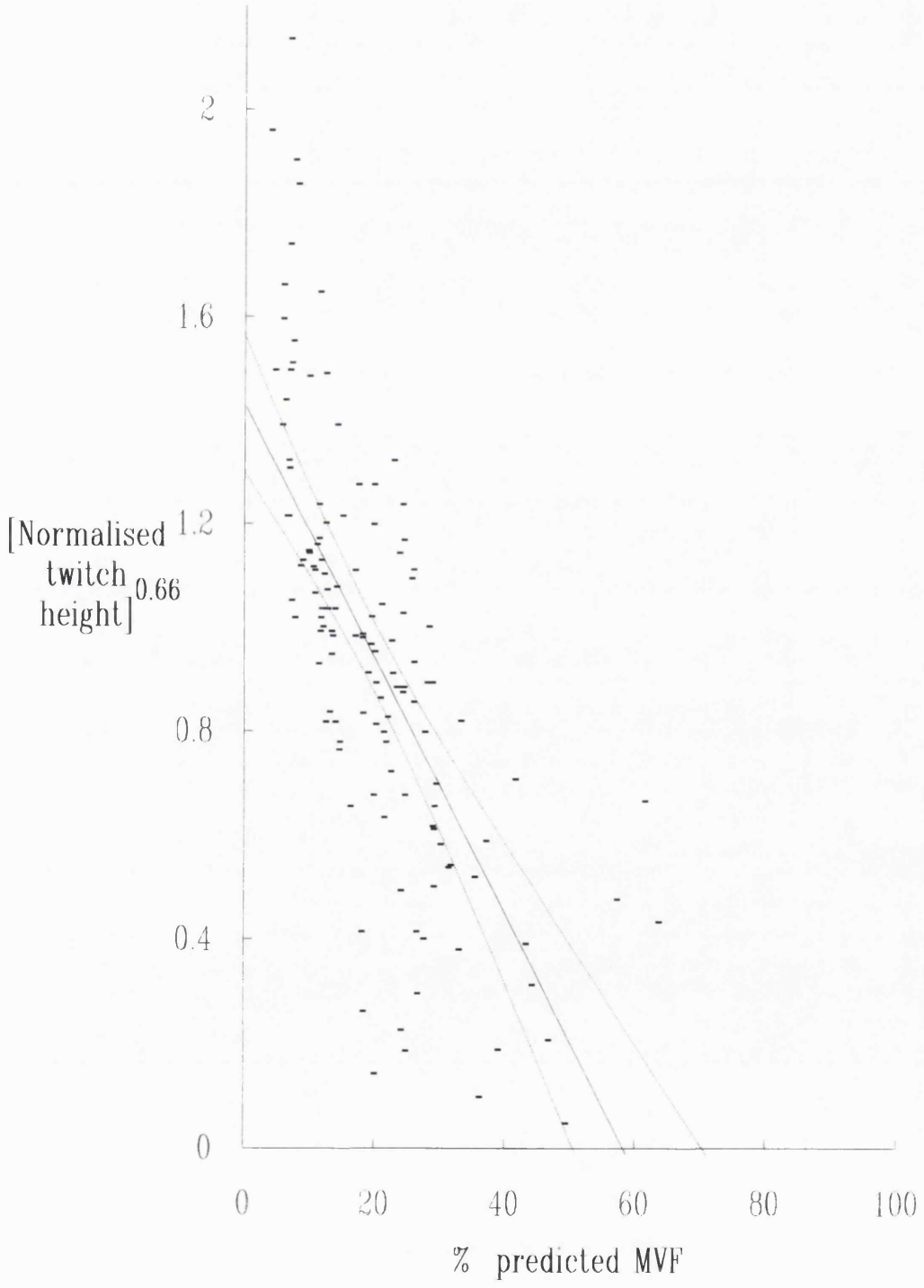
Hypothesis (ii) is tested by replacing the actual measured MVF from the weak elderly subjects by one predicted for "full activation". The predicted MVF was obtained from the regression line of the young subjects for the respective CSA's of the weak elderly

Relationship between linearised normalised twitch height and percentage of measured MVF in elderly subjects



The regression line and 99% confidence limits of the population regression line are shown

Relationship between linearised normalised twitch height and percentage of predicted MVF in elderly subjects



The regression line and 99% confidence limits of the population regression line are shown

subjects, i.e. it is the force that these elderly subjects would have produced from fully activated muscles if hypothesis (ii) were correct.

When the experimental points are plotted in this way (Fig 45) they are clearly different from those for the young subjects, the regression line crossing zero at approximately 60%, not 100%. Thus hypothesis (ii) is not compatible with our results and because it predicts full activation at 60% MVF it strengthens the interpretation that these elderly subjects were fully activating their adductor pollicis muscles.

5. FORCE AND CROSS-SECTIONAL AREA IN VERY ELDERLY HIP FRACTURE PATIENTS

Twenty-three hip fracture patients (18 female) were recruited post-operatively from the orthopaedic and geriatric orthopaedic wards in Hastings. Their results were compared with those from the fifty-three young subjects and thirty-nine fit elderly subjects described in section four. The results are summarised in table form (Table 10) and shown in Fig 46.

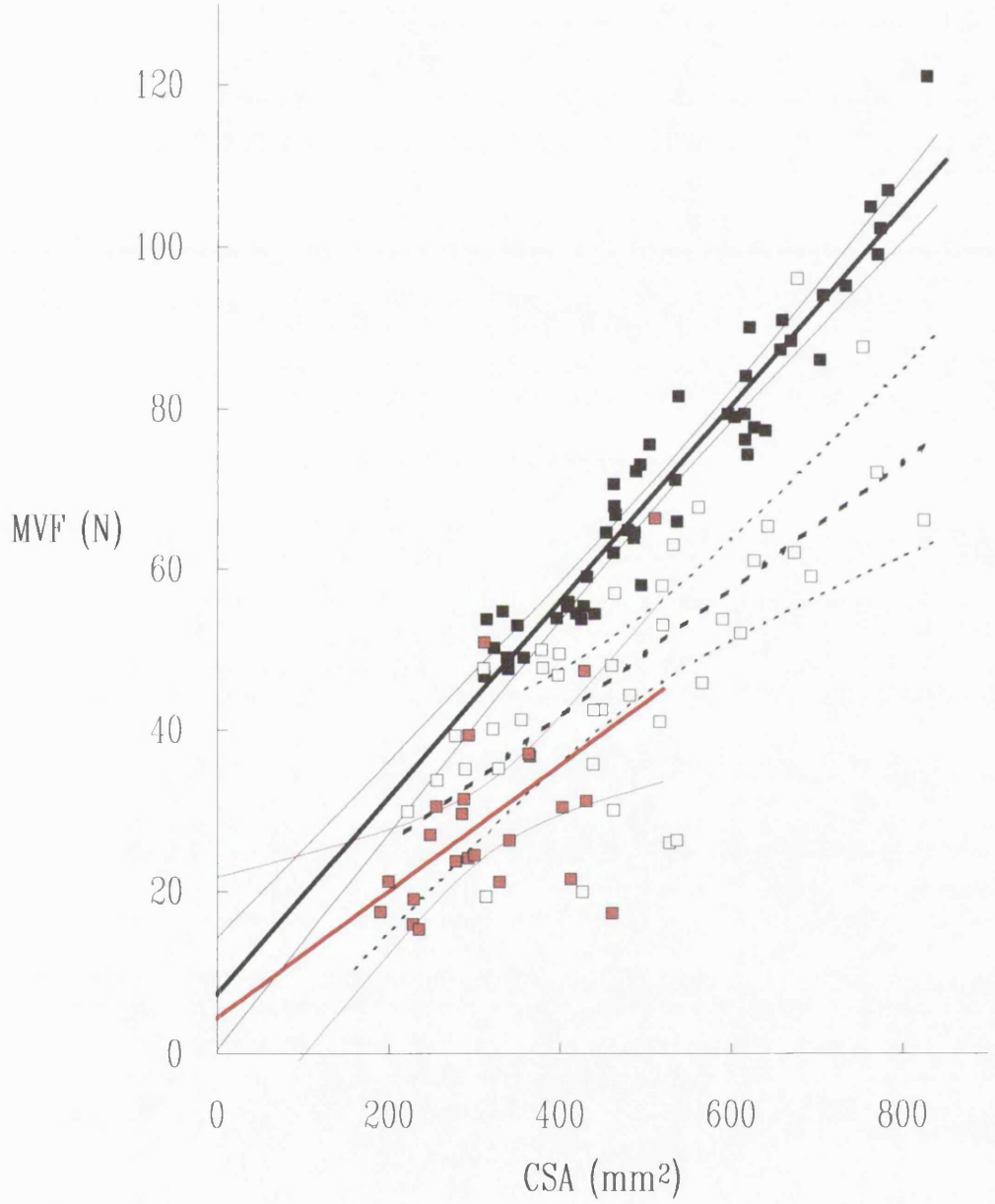
Table 10

	sex	number of subjects	age (years)	force (N)	CSA (mm^2)	height (m)	% loss of force
young	F	27	27±1	61±2	440±1	1.59±0.02	-1±2
	M	26	30±2	82±3	613±2	1.71±0.02	0±1
fit elderly	F	17	81±1	40±3	401±2	1.57±0.03	26±5
	M	22	80±1	55±4	556±3	1.74±0.02	27±3
elderly hip fracture	F	18	83±1	27±2	299±1	1.60±0.01	39±5
	M	5	76±1	32±2	357±2	1.67±0.03	36±4

The regression line for the young subjects shown in Fig 46 was used to predict the expected MVF for the measured CSA of each of the elderly subjects and hip fracture patients, and thereby to calculate the percentage loss of force as shown in the last column of table 10. The percentage loss of force between the elderly and young subjects was highly significant ($p < 0.001$) and there was an additional significant percentage loss of force in the hip fracture patients ($p < 0.02$). There is also evidence of greater atrophy of adductor pollicis in the hip fracture group, their mean CSA being the lowest despite there being no difference in the mean heights of the groups.

Fig 46

Relationship between force and CSA of adductor pollicis of young and very elderly subjects and very elderly hip fracture patients



□ - very elderly; ■ - young; red markers and lines - very elderly hip fracture. The regression lines - young: (y = 0.12x + 8), elderly: (y = 0.08x+ 10), hip fracture (y = 0.08x + 4) - and 99% confidence limits of the population regression line for each group are shown

6. THE TIME-COURSE OF THE DECLINE IN FORCE/CSA IN MEN AND WOMEN

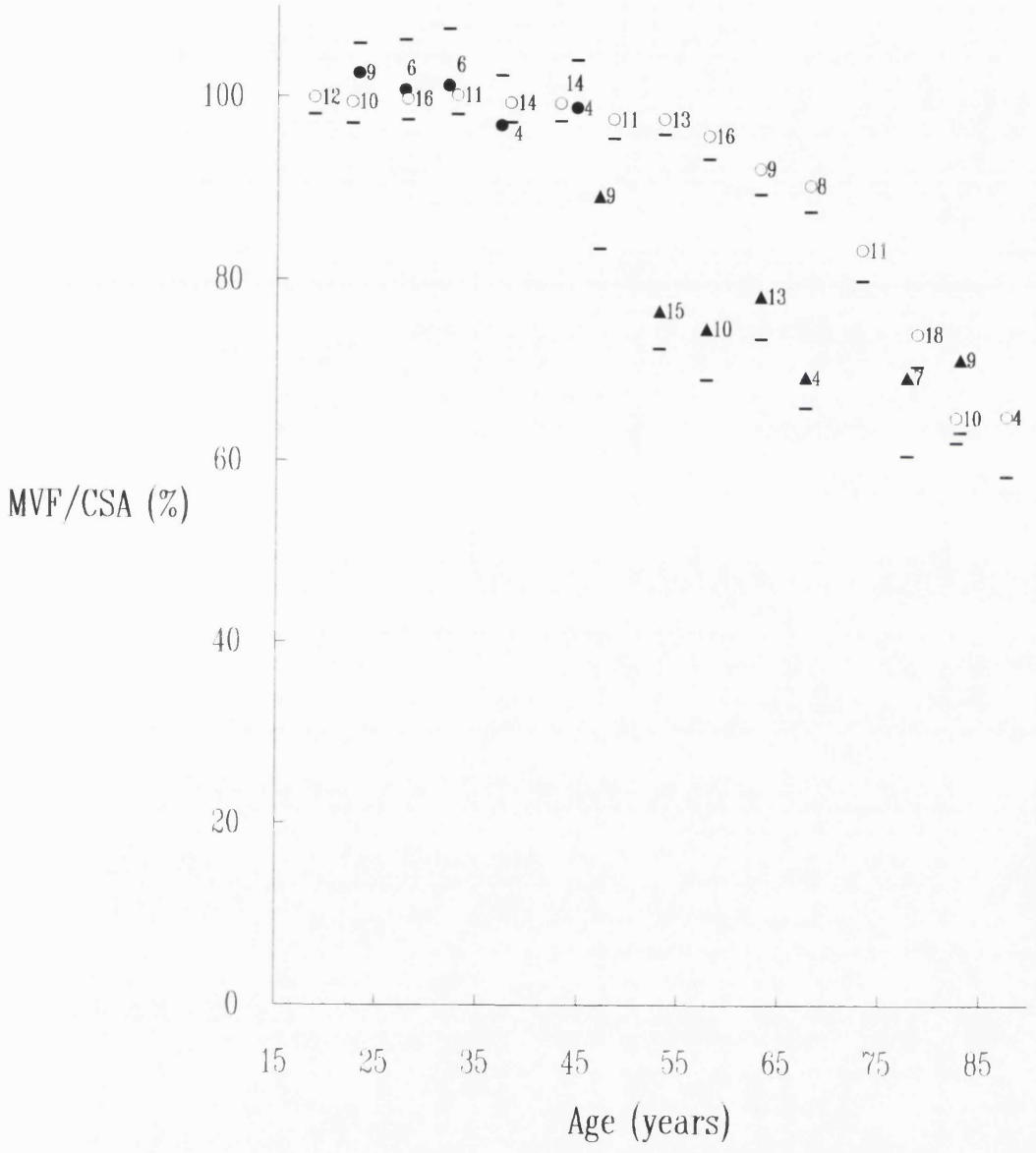
Subjects were recruited from students, current and retired staff of University College London, pensioners of the Chelsea Royal Hospital, a sports centre in London, a bowling club in Hastings, and the menopause clinic at the Elizabeth Garrett Anderson Hospital. Altogether 273 subjects between the ages of 17 and 90 years were tested (176 men, 30 pre-menopausal and 67 peri- or post-menopausal women who were not receiving hormone replacement therapy).

In this study mean coefficients of variation for measurements on each subject were 3.5% for MVF and 7.5% for CSA. MVF and CSA were strongly correlated in 148 men aged 17 - 60 years ($r = 0.83$, $p < 0.001$) and thirty pre-menopausal women aged 22 - 45 years ($r = 0.79$, $p < 0.001$). As in the young adults described in study one, neither the regression lines nor the mean MVF/CSA were significantly different in these young male and female subjects.

In order to find the time course of the decline in adductor pollicis MVF/CSA in men and women mean MVF/CSA for all our subjects has been plotted in age-groups of five years (Fig 47). The justification for the use of ratio standards in this way is discussed on page 69. The absence of a difference between men and women up to the menopause is again emphasised by plotting the data in this way. However after the menopause there is a dramatic decline in MVF/CSA in women. In the first five years post-menopause the decline in MVF/CSA is 23%. This is significantly different from MVF/CSA in the young women ($p < 0.01$). A plateau at about a 30% decline in

Fig 47

Relationship between mean MVF/CSA of adductor pollicis and age in men and women



MVF/CSA is expressed as a percentage of the mean value of MVF/CSA for male and female subjects, under 45 years, combined.
The points shown are means and SEMs for men and women separately, in age groups of five years. The numbers adjacent to the points are the number in each group.

MVF/CSA appears to be reached after about ten years. In men the decline starts later in life and is more gradual reaching the same level as post-menopausal women only after the age of about 75 years.

7. THE EFFECT OF HORMONE REPLACEMENT THERAPY ON FORCE/CSA IN WOMEN

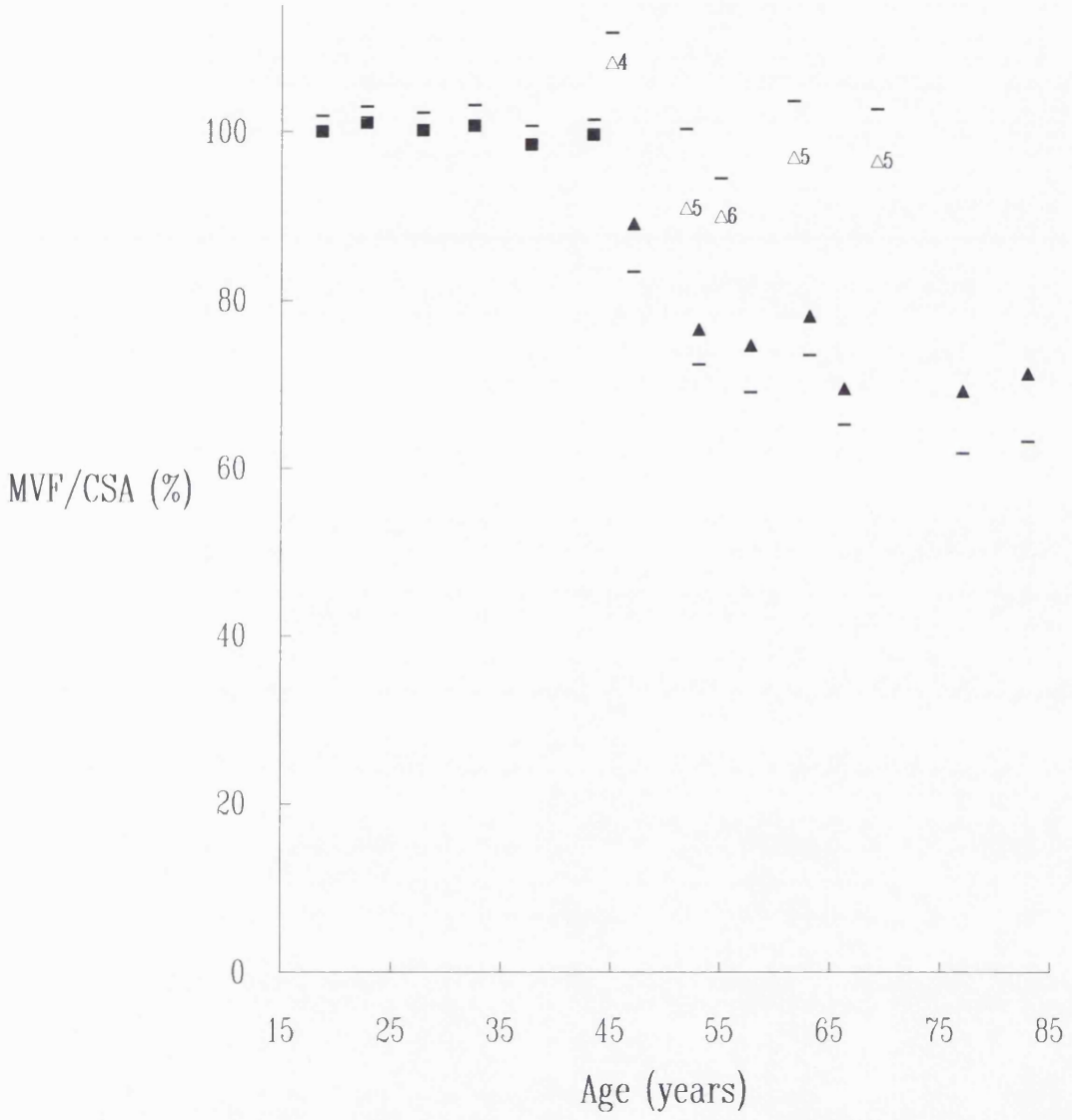
A further twenty-five women aged 42 - 72 who were receiving hormone replacement therapy (HRT) were recruited from the menopause clinic at the Elizabeth Garrett Anderson Hospital. Mean MVF/CSA from these subjects is compared with those in study six.

The women on HRT (combined sequential conjugated oestrogen/progestin, or conjugated oestrogen alone in the five women who had had a hysterectomy) had started therapy peri-menopausally except for two. One of these was sixteen years post-menopausal, the other seven years and they had received HRT for nine and five years respectively.

Fig 48 shows the effect of HRT. MVF/CSA is plotted in age-groups of five years as in Fig 47. In order to simplify the presentation, data from young men and pre-menopausal women has been pooled, there being no significant difference in MVF/CSA between them. In contrast to the post-menopausal women not on HRT those on HRT show no loss of MVF/CSA over the age range studied.

Fig 48

Effect of hormone replacement therapy on mean MVF/CSA of adductor pollicis in post-menopausal women



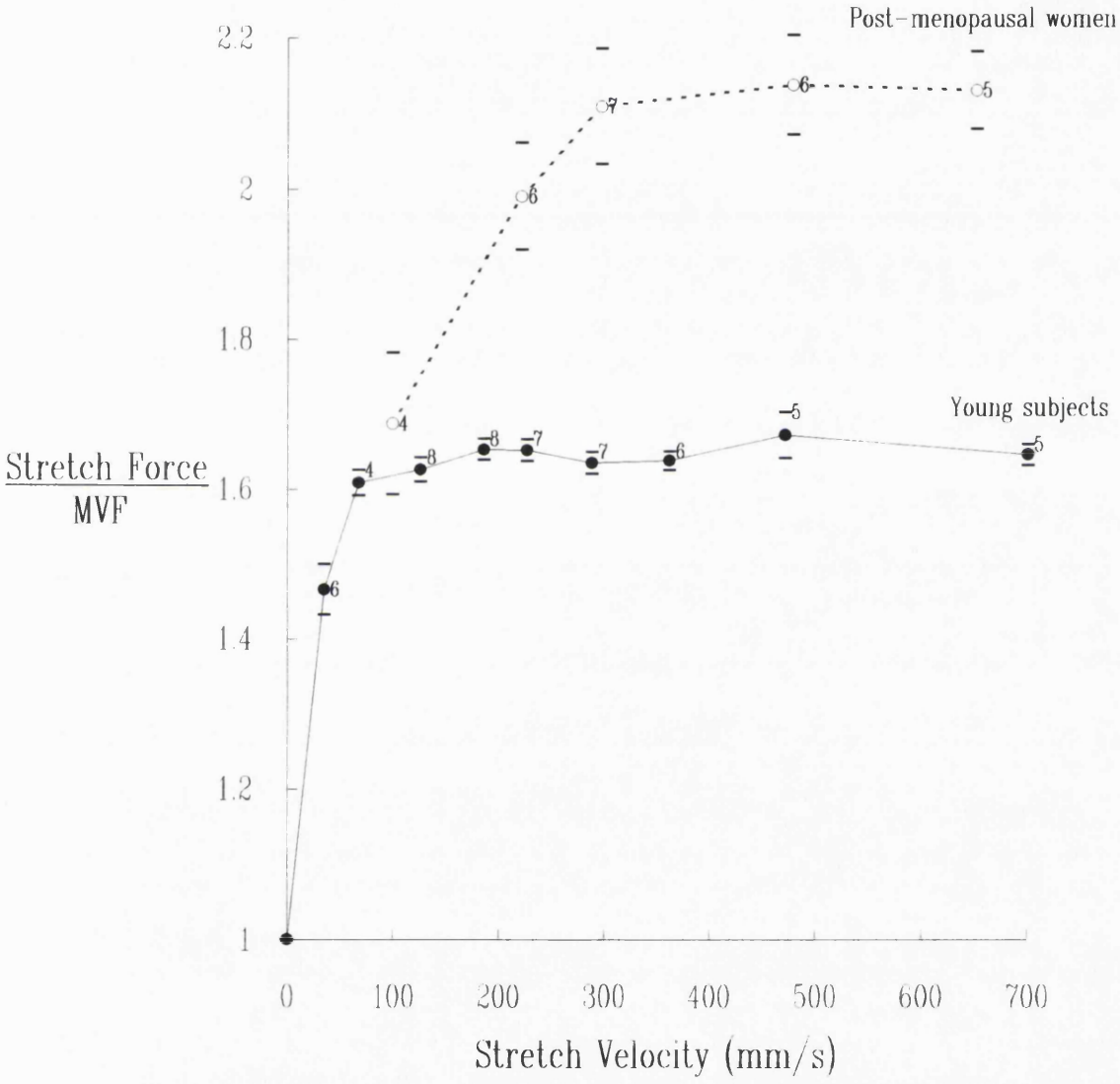
MVF/CSA is expressed as a percentage of the mean value of MVF/CSA for male and female subjects, under 45 years, combined. For clarity and because there was no difference in MVF/CSA between the men and women under 45 years, observations from these groups have been combined (■) in Fig 48, rather than shown separately as in Fig 47. The points (▲) are means with SEMs for post-menopausal women not on HRT, in age groups of five years as in Fig 47. The points (△) are means and SEMs for post-menopausal women on HRT, in age groups of five years. The numbers adjacent to these points are the number of subjects in each age group.

8. THE EFFECT OF APPLYING RAPID STRETCH DURING A MAXIMAL VOLUNTARY CONTRACTION IN WEAK POST-MENOPAUSAL WOMEN

Nine post-menopausal women aged 44 - 75 (62.1 ± 3.8 mean ± SEM) years who were not receiving HRT, were recruited from staff of University College London and the menopause clinic at the Elizabeth Garrett Anderson Hospital. Eight young male and female subjects aged 21 - 30 (23.9 ± 1.0) years were recruited from staff and students of University College London.

MVF/CSA from eight of the post-menopausal group was 0.113 ± 0.011 $N.mm^{-2}$ (mean ± SEM). MVF/CSA was not measured in the eight young subjects in this study but comparison with previous groups gives a thirty to forty per cent decline in MVF/CSA in this post-menopausal group. The ratio of the force observed during rapid stretch to the MVF is plotted against velocity of stretch in Fig 49. This ratio is greater in the weak post-menopausal than in the young subjects ($p < 0.001$)

The ratio of stretch force to MVF at different velocities of stretch for nine post-menopausal women compared to that for eight young male & female subjects



The points plotted are means ± SEM for observations at similar velocities of stretch. The numbers adjacent to the points are the number of observations in each group.

DISCUSSION

FORCE/CROSS-SECTIONAL AREA MEASUREMENTS IN NORMALLY NOURISHED YOUNG ADULTS

In normally nourished young adults we have shown that there is no sex difference in the force produced for a given cross-sectional area of adductor pollicis muscle. Women tend to produce lower forces but this is because they have smaller muscles.

Although measurement of isometric force from the adductor pollicis muscle is a well established research and clinical technique (Merton, 1954, Edwards et al., 1977) we believe this is the first attempt to correlate force measurements from this muscle with its cross-sectional area. This information is essential to compare voluntary activity in a muscle between individual subjects. Previous studies with the quadriceps muscle group have generally not produced as good correlations between MVF and CSA (Maughan et al., 1983, Chapman et al., 1984, Young et al., 1984 & 1985) as ours for adductor pollicis.

We have investigated the possible reasons for residual variance about regressions of MVF and CSA in two ways: firstly with an anatomical model and secondly with simulated data.

a) ANATOMICAL MODEL

Two fixed cadaver hands were dissected. (Preliminary results from one of these were

presented at the Third Vienna Muscle Symposium (Bruce et al., 1992a)). The adductor pollicis and first dorsal interosseous muscles were divided into bundles, as far as possible following natural lines of cleavage. Both our specimens of adductor pollicis had clearly divisible oblique and transverse heads. The numbers of bundles dissected are shown in table 11. A diagrammatic two-dimensional reconstruction of the dissection of the large hand is shown in Fig 50.

Table 11

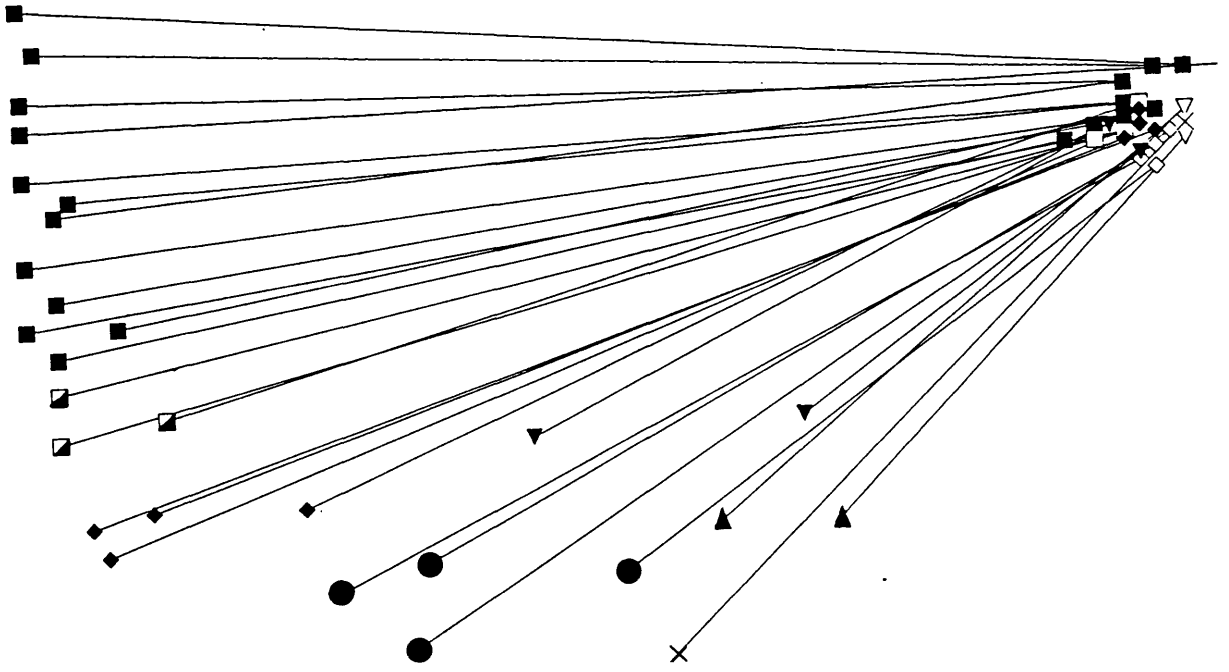
	ADDUCTOR POLLICIS		FIRST DORSAL INTEROSSEOUS
	Transverse head	Oblique head	
SMALL HAND	13	16	12
LARGE HAND	12	16	16

Measurements were made of the co-ordinates of the origin and insertion of each bundle with respect to an arbitrary reference point. Sarcomere length was measured at three places along each fibre bundle by diffraction of laser light and the three values averaged. The muscle fibre length and the total length of each bundle (i.e. muscle and tendon) were measured. These data were put into a computer model using Microsoft Excel. The following calculations were made for a range of thumb positions covering those that would be achieved in vivo:

1) sarcomere length - assuming that it would be uniform along each fibre and that the tendon is non-compliant and its tendon length is therefore fixed.

2) isometric force - assuming that the relationship between force and sarcomere length is the same for human muscle as it has been found to be in mouse muscle in vitro (Phillips & Woledge, 1992) and that force is proportional to CSA. The length of the

Fig 50. Two-dimensional reconstruction of the dissection of the "large hand" showing the orientation of the fibres with respect to one another



The attachment to the thumb is on the right-hand side of the diagram. The 12 fibre bundles with the symbol (■) on the left-hand side were dissected from the transverse head. The remaining fibre bundles were dissected from the oblique head. The length of each bundle in the diagram is proportional to its calculated isometric force.

line representing each bundle in Fig 50 is proportional to the calculated isometric force. 3) the torque produced in the thumb by the isometric force. This takes account of the fact that the bundles pull on the thumb at various angles (also shown in Fig 50). For this calculation we assumed that the carpo-metacarpal joint acts like a universal joint capable of rotation in any direction but not of sliding.

In the Figs 51-56 the ordinate represents the position of the thumb as it passes through a sequential movement, being moved from side to side while progressively lowered. Key points of this movement which covers the full range of possible length changes for adductor pollicis in vivo, are illustrated in the drawings underneath each ordinate. Figs 51-53 show the calculated sarcomere lengths for the various thumb positions.

Adductor pollicis is an example of a muscle which undergoes length changes that are large relative to the length of its fibres. If it were functionally entirely homogenous, tension could be near optimum only over a small part of the working range. A possible method of constructing a muscle in which force can be kept uniform through a wide range of movements is to have regions with optima at different muscle lengths. However, conventionally muscles are regarded as functionally homogenous structures consisting of an assemblage of sarcomeres all of the same length - a sufficient number in parallel to give the force needed and a sufficient number in series to give the required range and velocity of shortening.

The model shows that the transverse heads were composed of bundles that were functionally homogenous, that is, their sarcomere lengths vary by no more than $\pm$ 0.3 μm between one bundle and another over the whole range of the movements studied (Fig 51). The results were therefore grouped together by averaging the sarcomere lengths (AA in Figs 52-53). In contrast the oblique head was not functionally homogenous in either specimen. However, the bundles of the oblique heads could be divided into groups with similar sarcomere lengths which were averaged (BB - GG in Figs 52-53).

Fig 51

Sarcomere lengths of fibre bundles from the transverse head of AP – small hand

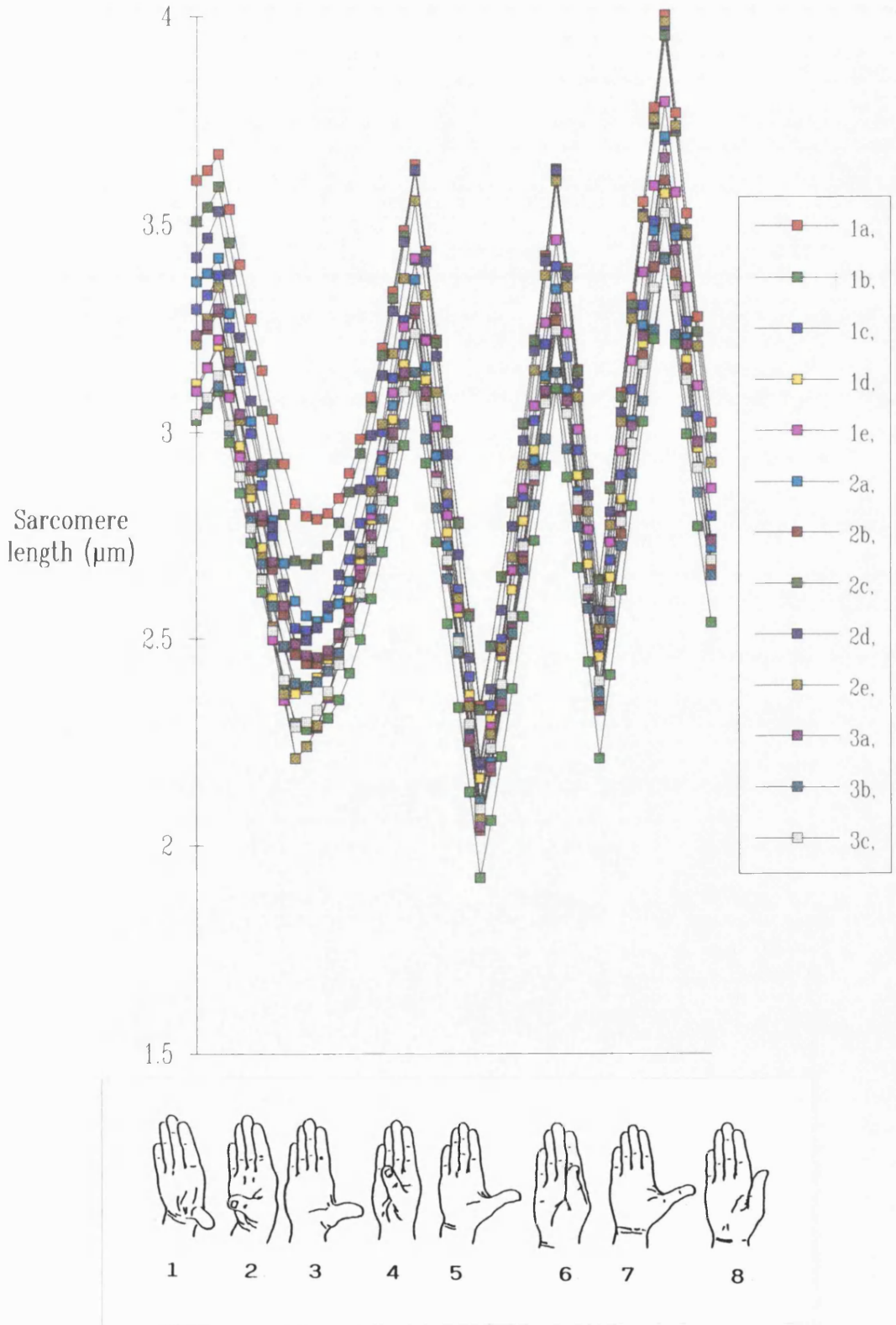


Fig 52

Sarcomere lengths of grouped fibre bundles of AP & FDI (last two lines) – small hand

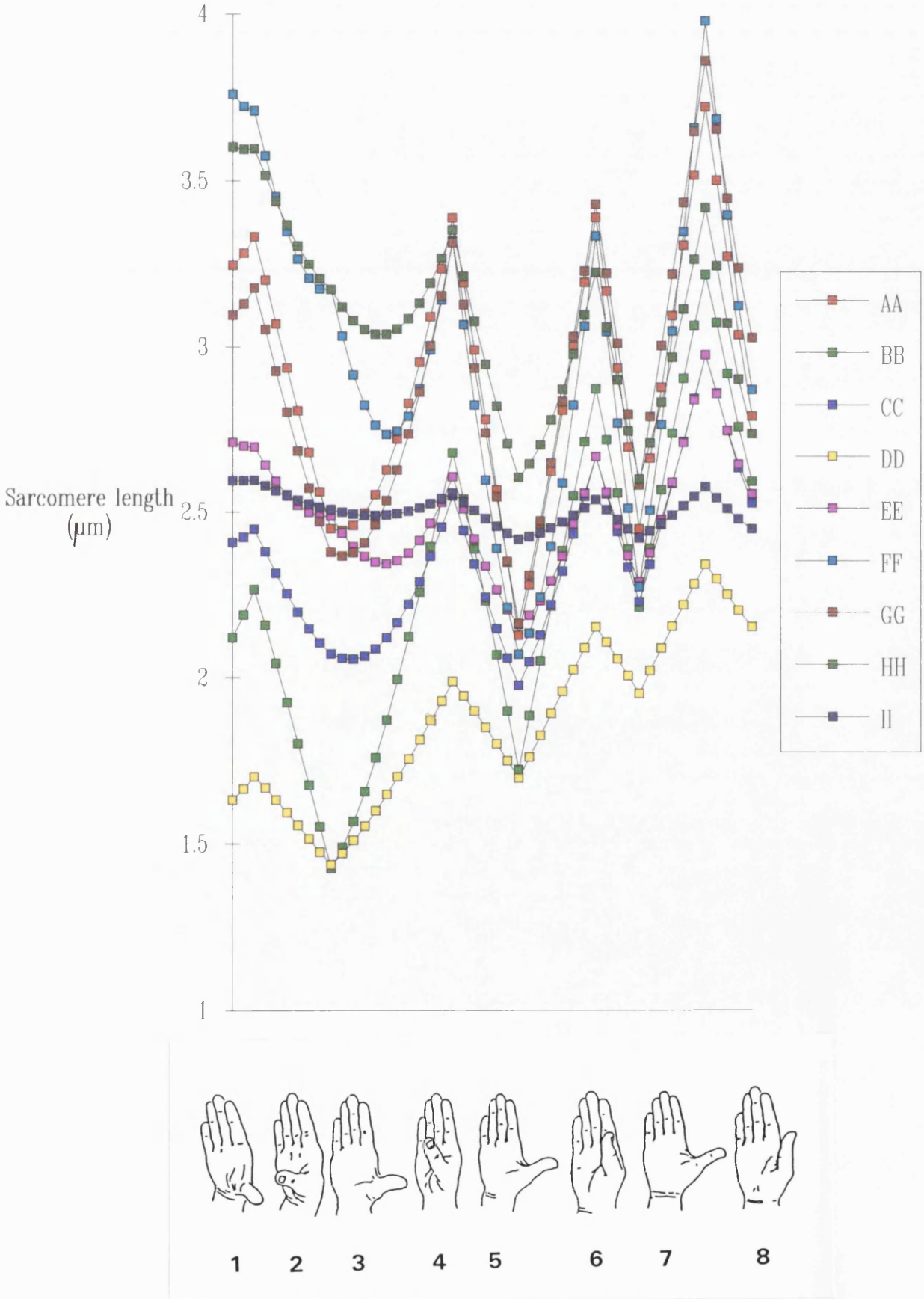
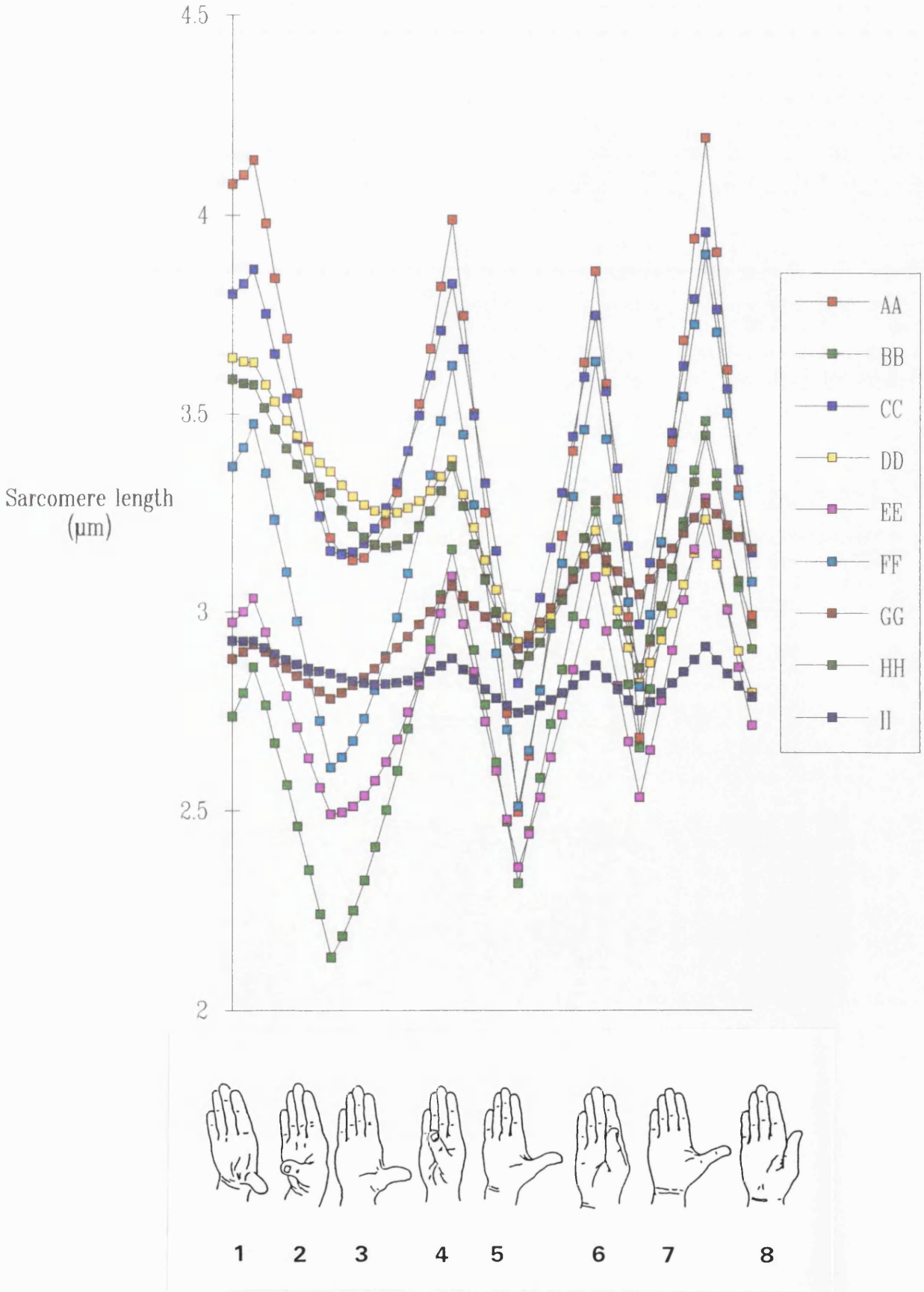


Fig 53

Sarcomere lengths of grouped fibre bundles of AP & FDI (last two lines) – large hand



One of these groups in each muscle had sarcomere lengths which were similar to those of the transverse head in all positions. The remaining five groups differed from one another quite considerably both in sarcomere length and in the way this varies with thumb position. In general the more oblique parts of the oblique head had shorter sarcomere lengths in most hand positions. These results suggest that there is functional specialisation between the transverse and oblique heads of adductor pollicis and within the oblique head itself.

In both specimens FDI could be divided into two functionally distinct sections (HH & II in Figs 52-55). The larger section, approximately three-fifths of both muscles, behaves like the more oblique parts of the oblique head of adductor pollicis. The smaller shows much less variation in calculated sarcomere length throughout the movement modelled. The larger of the two FDI muscles gave calculated sarcomere lengths which are rather longer than would be anticipated (Fig 53). Fig 54 shows the force in each group of fibre bundles as a function of hand position. It can be seen that there is always at least one section of adductor pollicis that is exerting force at or near to its maximum in each of the hand positions shown. There is a clear tendency for different sections of the muscle to compensate for one-another. To demonstrate this compensation quantitatively we must take account of the relative sizes of the different bundles and the angles at which they pull on the thumb.

We have therefore calculated the torque that each bundle exerts on the thumb during an isometric contraction. In Fig 55 they are grouped as in Figs 52-54. For Fig 56 we have summed the torques produced by each bundle within both the transverse and oblique heads of adductor pollicis and also show the total torque produced by the whole muscle. Vectorial addition has been used. The total torques produced by the transverse and oblique heads are of a similar order despite the fact that the oblique head is two-and-a-half times larger than the transverse head, though the transverse head is subject to much wider fluctuations in torque, reflecting a tendency for its sarcomere lengths to be greater than optimum.

Force of grouped fibre bundles of AP & FDI (last two lines) – small hand

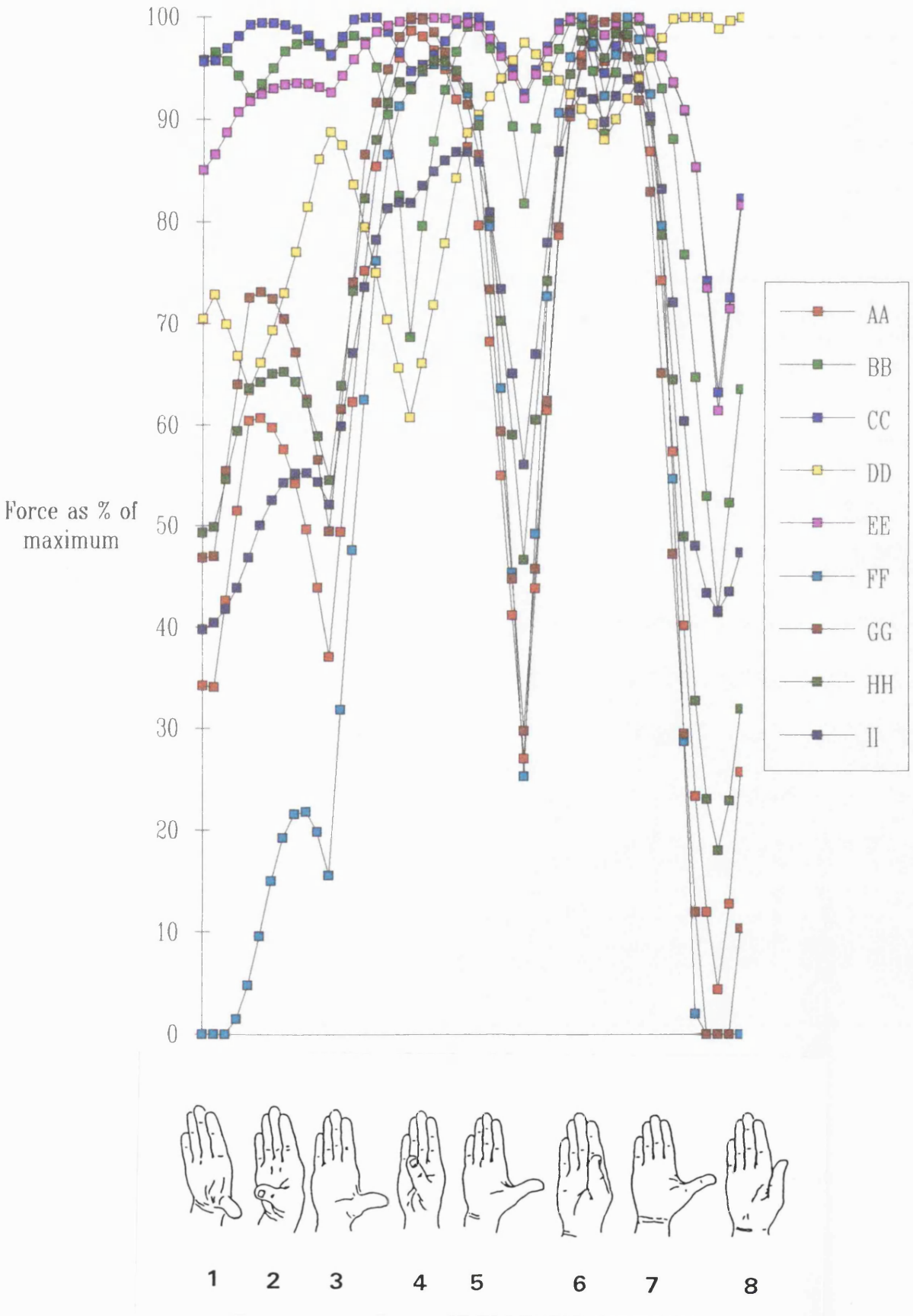
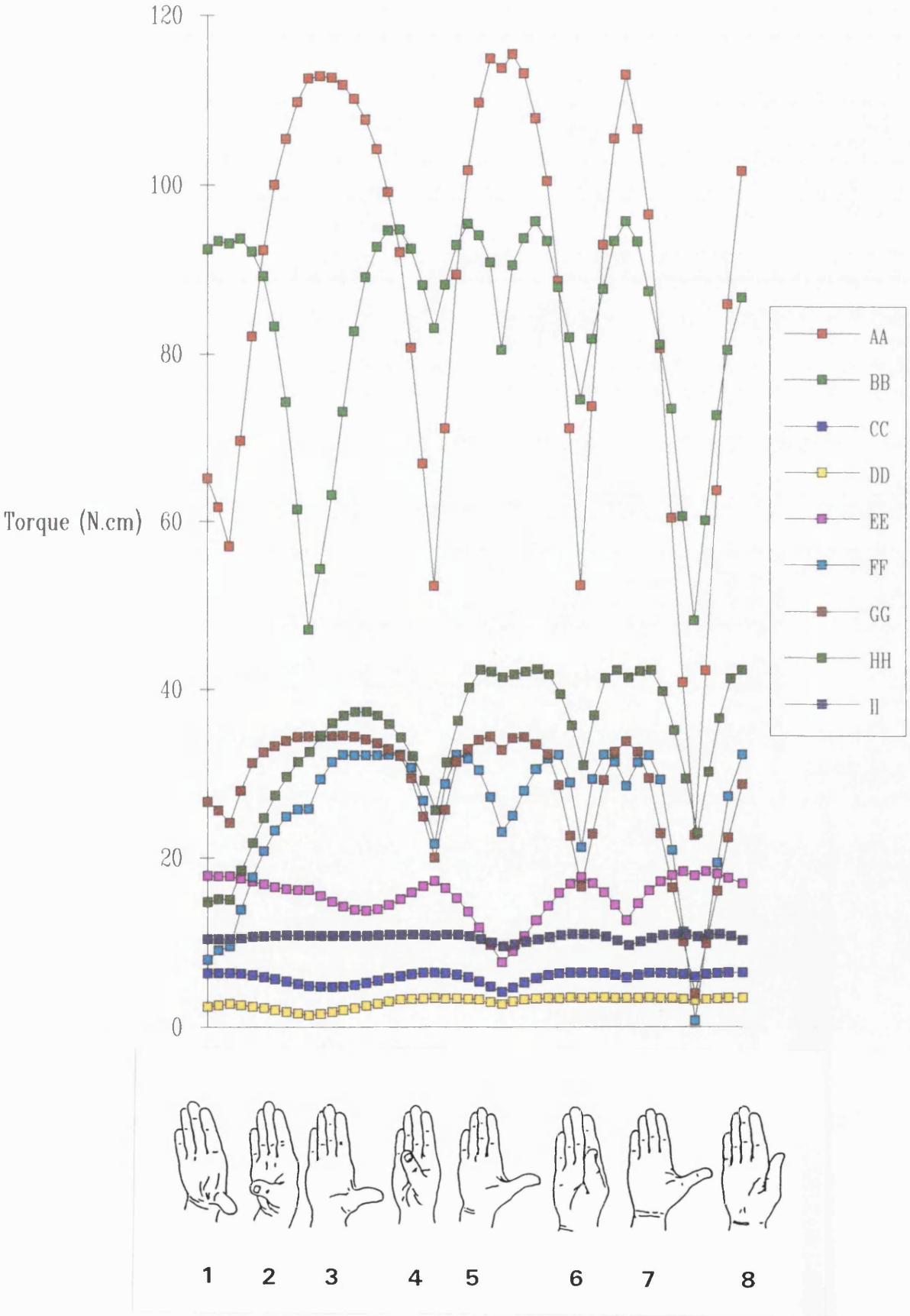
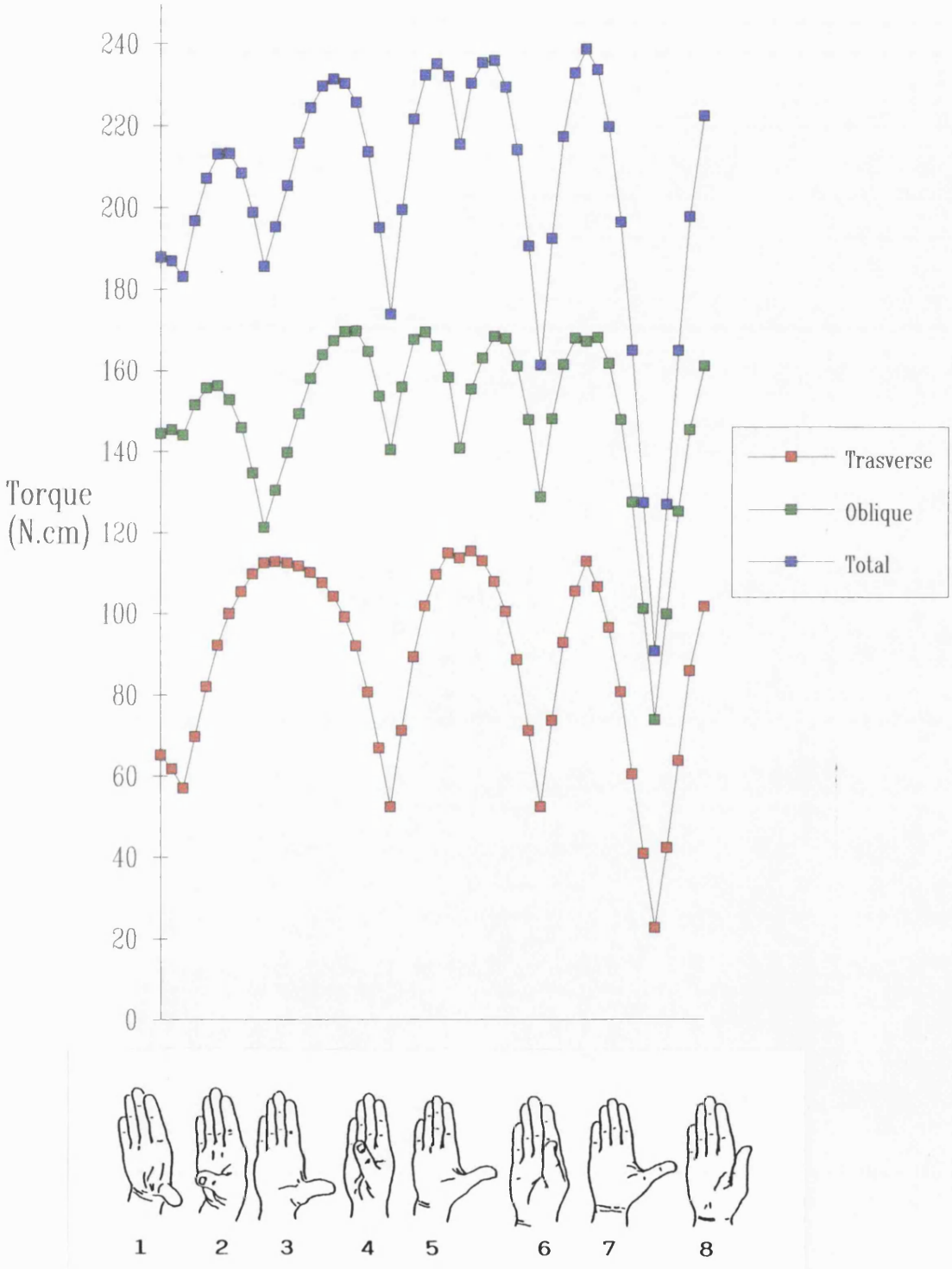


Fig 55

Torques of grouped fibre bundles of AP & FDI (last two lines) – small hand



Total torques of AP – small hand



Thus in hand positions one, three and five the transverse head is relatively ineffective because the sarcomeres are well beyond their optimum length. However, in these positions the oblique head exerts near to its optimum torque. Conversely, in positions two and four where the oblique head torque is low because the sarcomeres are shorter than their optimum length, the transverse head is producing its optimum torque. Only in position seven where nearly all bundles have sarcomeres beyond their optimum length, are both sections of the muscle exerting well below their optimum torques. Even in this position one bundle (EE) exerts its optimum torque as does the smaller section of FDI (II) though this bundle shows little variation in torque throughout the movement modelled. The result of these compensations is that the wider fluctuations particularly in the torque exerted by the transverse head are partially smoothed out. Thus the total torque exerted by the whole adductor pollicis muscle is relatively constant over most of the range of possible movements. Therefore the force measured is relatively independent of the exact position of the transducer provided that the action of other muscles is excluded and the introduction of levers between the points of attachment of the muscle and the opposition of the transducer is avoided.

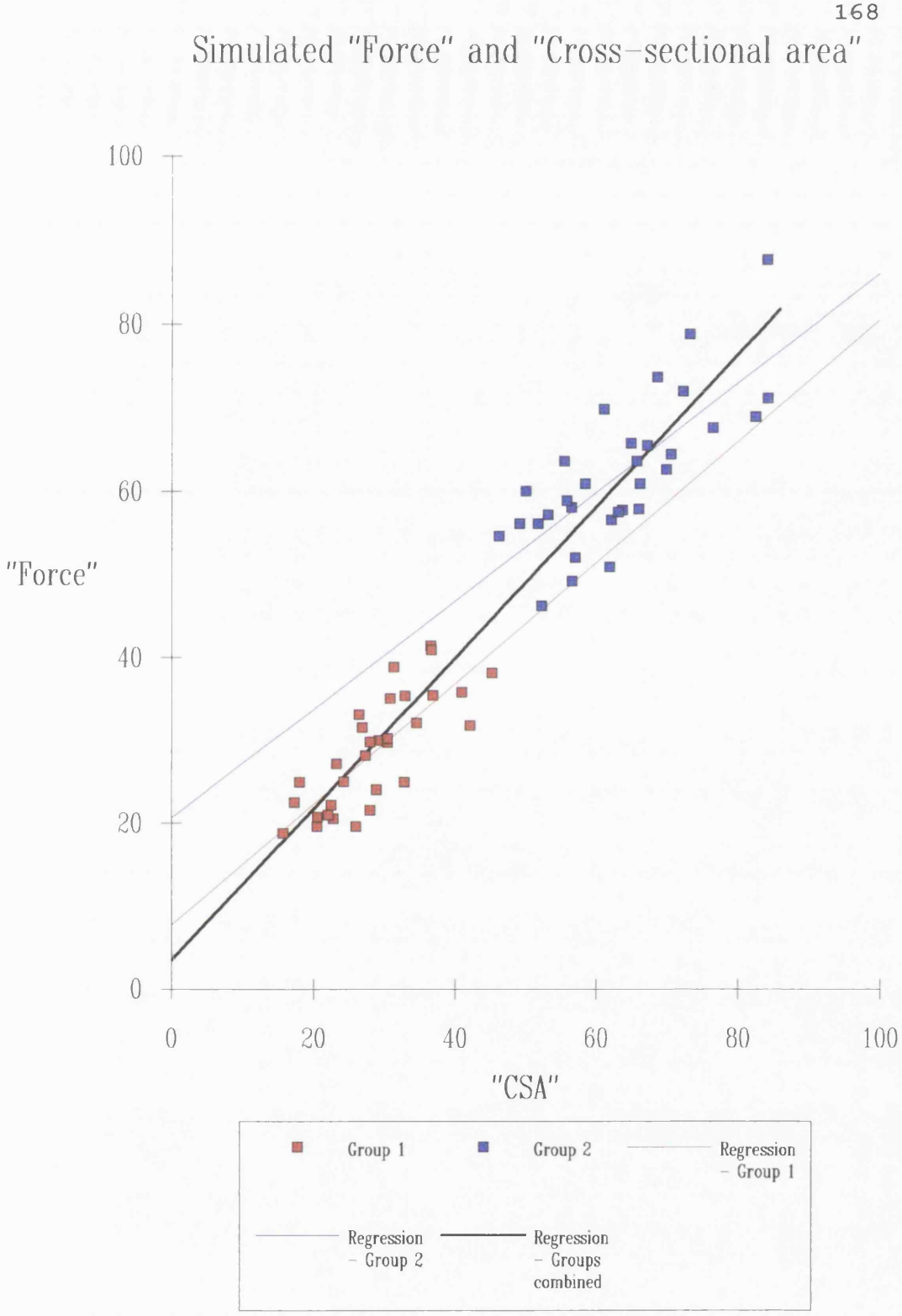
The main limitation of this model is that it assumes that the fibre bundles can take up positions in straight lines between their origins and insertions. In vivo this may be prevented by the relationship that the fibres have with one another within the overall structure of the muscle which maintains a constant volume as it shortens and lengthens. For this reason the model cannot be used to predict the degree of systematic error between the measured CSA and the sum of the cross-sectional areas taken at right angles to the individual fibres.

b) SIMULATED FORCE AND CROSS-SECTIONAL AREA MODEL

Our conclusion that young men and young women are able to produce the same MVF/CSA contrasts with that of Winter & Maughan (1991), who suggested that the quadriceps of young women were intrinsically weaker than those of young men. We suggest that their conclusion is the result of a statistical artefact, due to the assumption, implicit in the regression analysis, that only force measurements and not CSA are subject to error. Cross-sections taken at right angles to the long axis of multipennate muscles such as the quadriceps group contains, will not pass through all the fibres. In such muscles differences in size lead to differences in pennation angle and thus to differences in the proportion of fibres included in a cross-sectional area measurement at right angles to the long axis of the muscle (Maxwell et al., 1974). This constitutes a predictable error in CSA measurements of multipennate muscles (Haxton, 1944).

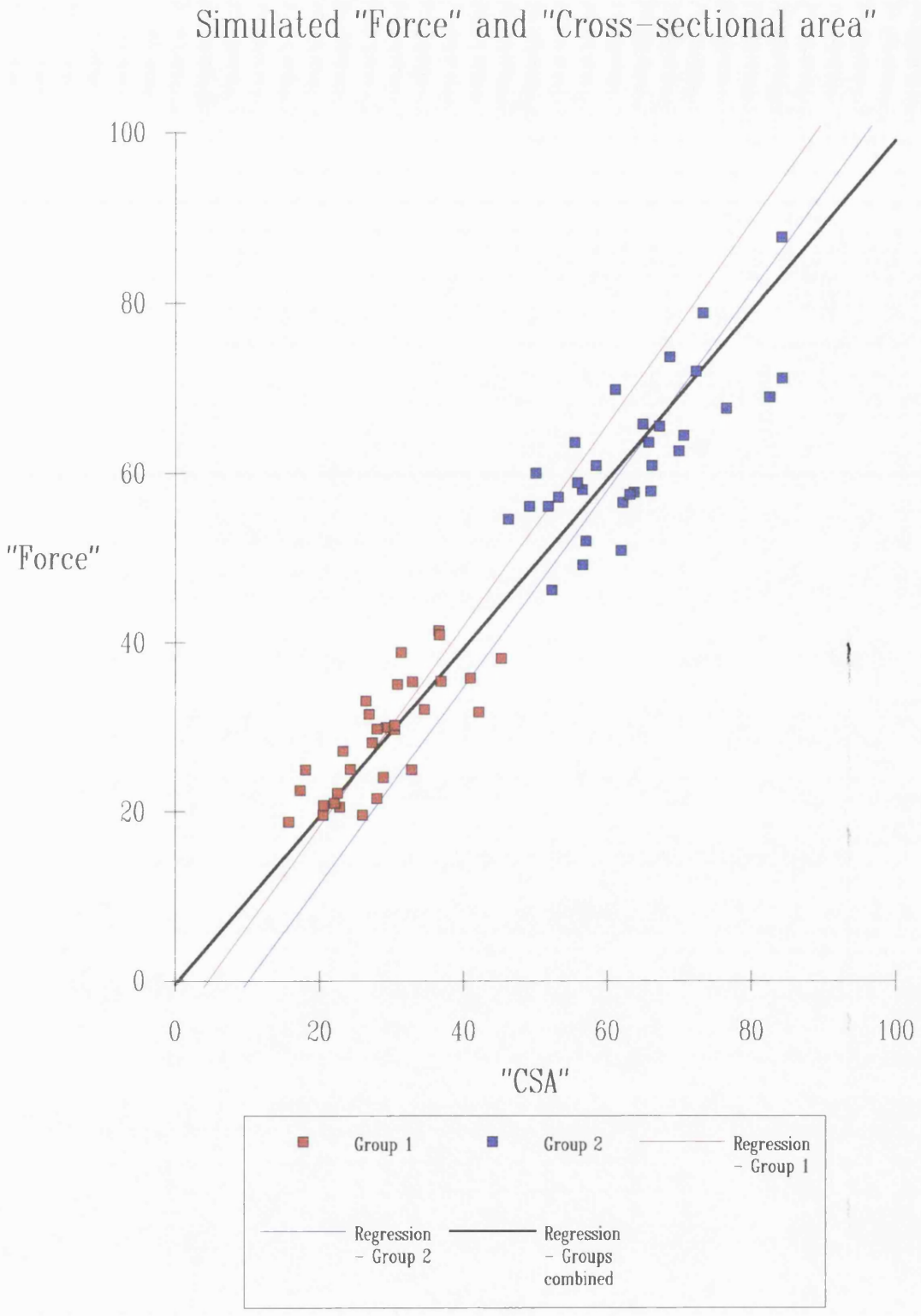
To illustrate the effects of errors in force and in CSA measurements, on the interpretation of data such as Winter and Maughan presented, a simulation of analogous data is shown in Fig 57. In this simulation two groups of 30 "CSA" values have been generated by randomly distributing values within the ranges 20-40 (Group 1) and 50-80 (Group 2). It is assumed that "MVF" is directly proportional to "CSA". "Measured CSA" values were obtained by adding randomly distributed errors to each of these values. The coefficient of variation was assumed to be 4%. "Measured MVF" values were obtained in the same way with the same coefficient of variation. The proportion of the total error assigned to "CSA" and "MVF" were equal. The regression for all the data in groups 1 and 2, calculated on the usual assumption (here false) that all the errors are in Y ("MVF"), had an intercept close to zero. Regression lines fitted to groups 1 and 2 separately can be seen in Fig 57 showing that the two lines each have a positive intercept. Group 2 appears to show a greater "MVF/CSA" with a higher regression line. This simulation reproduces the main features of the study by Winter and Maughan (1991).

Fig 57


Simulated "Force" and "Cross-sectional area"
"Force"
"CSA"
0
20
40
60
80
100
Group 1
Group 2
Regression - Group 1
Regression - Group 2
Regression - Groups combined

When the errors were reduced to give a higher correlation the apparently significant difference between groups 1 and 2 disappeared. We therefore think it likely that Winter and Maughan's conclusion that women are intrinsically weaker than men is due to their failure to take account of errors in measurements of CSA. Indeed, if the regression is calculated for "CSA" as Y against "MVF", (as suggested by Sir A.F. Huxley during the discussion after the presentation of our data from adductor pollicis (Bruce et al. 1992b)), that is all the error is assumed to be in "CSA" instead of in "MVF", group 1 appears to have the greater "MVF/CSA" (Fig 58). Since we cannot estimate the size of such errors in our experimental measurements it seems a reasonable approximation to assume MVF to be proportional to CSA. We have therefore used the ratio MVF/CSA to study the effect of the time-course of the effects of ageing discussed below.

Fig 58


Simulated "Force" and "Cross-sectional area"
"Force"
100
80
60
40
20
0
0
20
40
60
80
100
"CSA"
Group 1
Group 2
Regression - Group 1
Regression - Group 2
Regression - Groups combined

MUSCLE FUNCTION AND NUTRITIONAL STATUS

The measurements of MVF observed in this study are higher than in the other studies reported here and also higher than have previously been reported for adductor pollicis. This is partly because the lever ratio is small and because very strong subjects were deliberately selected for the control group. However, as explained in the "Methods" section above there is also some contribution from long flexor muscles of the fingers with the transducer used in this study.

In Fig 39 it can be seen that all the points for the subnourished patients fall below the regression line for the normally subjects confirming that the subnourished are weak relative to their height, which was chosen as an indicator of body build. Figs 39 & 41 show that this weakness is generally in proportion to muscle bulk; that is, when force is plotted against muscle area, there is no difference between the normally nourished and the subnourished, for most of the subnourished subjects studied. This is most clearly shown when adductor pollicis MVF and CSA are plotted but is also shown in the graph of maximal hand-grip and arm-muscle area. Here the confidence limits are wider and the correlation somewhat weaker ($r = 0.85$, cf. $r = 0.91$, for MVF/CSA) though both these correlations are highly significant ($p < 0.001$).

Observations from two of our patients with Crohn's disease fall outside the 95% confidence limits for the observations from the normally nourished group both when adductor pollicis MVF is compared with CSA and when maximal hand-grip is compared with arm-muscle-area (Figs. 38 & 41). One of these patients was on long-term steroids, the other had a history of alcohol abuse. Both steroid therapy (Kendall-Taylor & Turnbull, 1983) and alcohol (Martin & Peters, 1985) are known to cause myopathies which might have affected the results. The coefficient of variation of the force observations from the second of these two patients was 8.4% suggesting that her contractions may not have been maximal. Therefore these two points

do not provide evidence of any reduction in muscle force/CSA associated with subnutrition.

Even including these two observations the subnourished group does not significantly differ from the controls ($p = 0.2$ for MVF/CSA) This suggests that the most important effect of subnutrition on skeletal muscle function is weakness due to wasting resulting from catabolism (Ross et al., 1991). Once established, increased catabolism cannot simply be reversed by enteral or parenteral nutrition even though this supports protein synthesis (Ross et al., 1991). It appears that stresses such as trauma, sepsis and subnutrition alter the response to hormonal stimuli, the best understood being those to growth hormone and its mediator insulin-like growth factor-1 (IGF-1). Fasting normal subjects and critically ill patients become relatively insensitive to growth hormone with increased basal concentrations being associated with low concentrations of IGF-1. Ross and Buchanan (1990) suggest that this is an adaptive change during sickness and fasting whereby indirect anabolic actions of growth hormone (i.e. those mediated by IGF-1) are reduced in favour of the direct actions of growth hormone (increased lipolysis and anti-insulin). The benefits of such a change are in the provision of metabolic fuel but this is at the expense of reduced protein synthesis.

The concurrent administration of recombinant growth hormone promoted positive nitrogen balance for up to three weeks in nine stable subnourished patients receiving parenteral nutrition (Zeigler et al., 1988). Force of maximal hand-grip was maintained in four post-operative patients treated with recombinant growth hormone, compared with a ten per cent loss of force after fourteen days post-operatively in five controls, both groups on a similar regime of parenteral followed by "ad lib" oral nutrition (Jiang et al 1989). In this study muscle bulk was not measured but force of quadriceps contraction increased proportionately to muscle bulk after six months' recombinant growth hormone administration in growth hormone deficient adults (Cueno et al., 1991). This suggests that the maintenance of force in the post-operative patients was due to the prevention of muscle wasting.

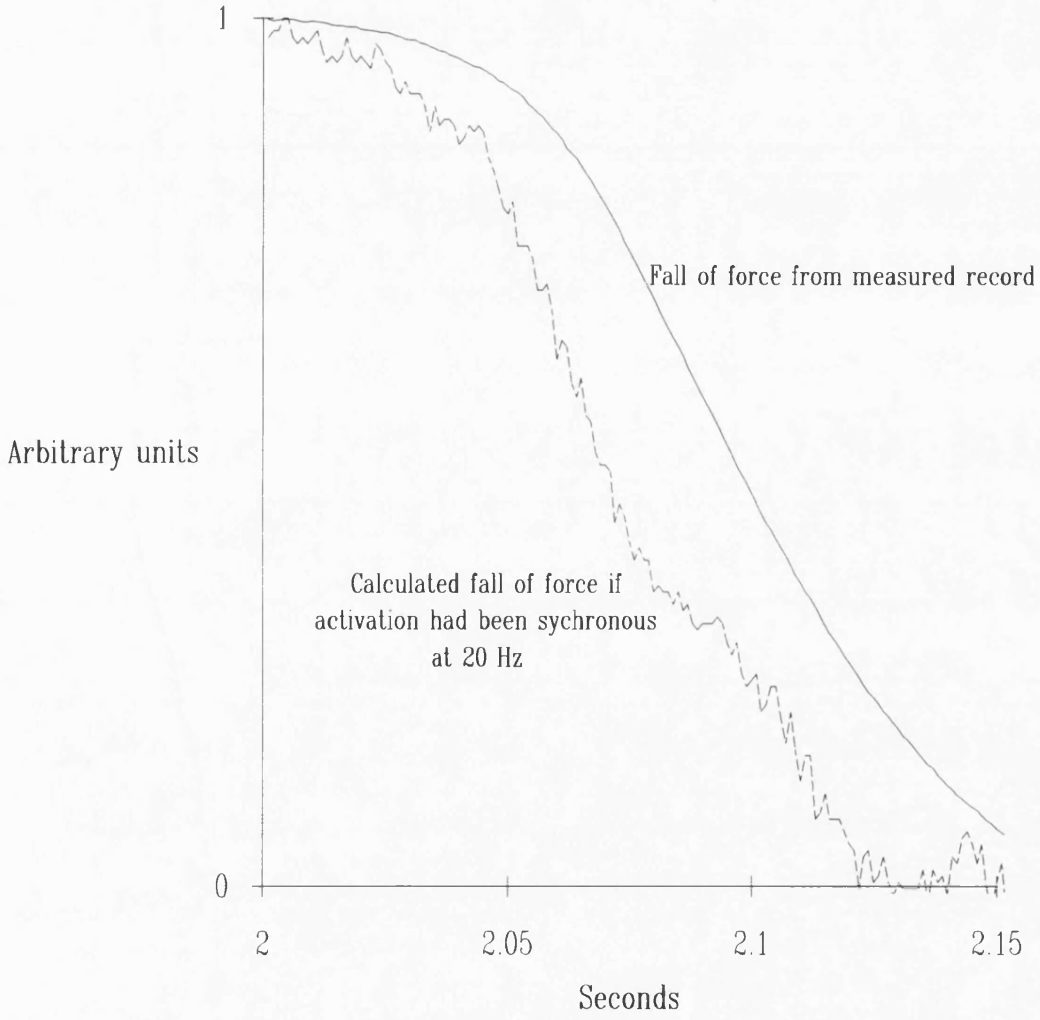
The difficulties in interpreting studies from Jeejeebhoy's group (Lopes et al., 1982, Russsell et al., 1983a & 1983b) which claimed specific abnormalities in muscle function relating to changes in nutritional status are outlined on pages 30 -32. Apart from wasting, the most consistently abnormal muscle variable in subnourished patients is the relaxation rate and previously reported changes in the force-frequency relationship (Lopes et al., 1982, Russsell et al., 1983a & 1983b, Brough et al., 1986, Chan et al., 1986) are probably largely explained by the prolonging of relaxation (Newham, 1986). Our finding that relaxation rate measured in voluntary contractions is also demonstrably slower in subnourished patients could make the test more widely available and more readily tolerated.

The maximal relaxation rate of our control subjects is approximately twenty-five per cent slower than those previously published for stimulated relaxation rates (Newham, 1986). A large part of this difference is probably due to asynchronous activation of motor units during voluntary contraction. A numerical calculation of the probable effect of this asynchrony was carried out by deconvolution of a force record from one of our control subjects assuming a stimulation frequency of 20 Hz (Fig 59). This increased the peak value of fall of force by approximately twenty-eight per cent suggesting that this explanation is likely to be correct.

Our results suggest that force generated during maximal voluntary contractions is unlikely to be a useful measurement in the diagnosis or follow-up of subnourished patients as the major change is on muscle bulk which is non-specific. This is in contrast to the indirect inference, from results of submaximal stimulated contractions, in the work cited above that subnutrition has a specific effect on the ability of muscle protein to develop force, perhaps through changes in calcium kinetics (Russell et al., 1984). However relaxation rate may well be a useful additional test in demonstrating marginal subnutrition and in assessing the efficacy of re-feeding regimes in subnourished patients.

Fig 59

Calculation of the effect of asynchronous activation on relaxation rate



MUSCLE FUNCTION AND AGEING

The very elderly subjects whose adductor pollicis MVF/CSA we tested, produced less force for a given CSA than the young subjects. This is in contrast with the results from the subnourished subjects. The reduction in MVF/CSA in the elderly subjects is of the order of twenty-five per cent (26 ± 3% (mean ± SEM)) compared with that predicted from their respective CSA using the regression line for the young subjects. The results of the data for force versus height showing a decline in force of the order of thirty-five per cent with age. This is in good accord with previous studies (Grimby and Saltin, 1983) and confirms that atrophy also contributes to the weakness of old age. (Loss of height with age will tend to underestimate this.) The results from the young subjects show less scatter than the results from the elderly subjects. Several of the elderly subjects achieved measurements of MVF/CSA comparable with the younger subjects. There was no correlation between age and the ratio of MVF/CSA within the very elderly group and no difference in this ratio between elderly males and females. We attribute the greater variability to the fact that these subjects included individuals, who despite their chronological age, did not appear biologically aged. The elderly were selected as fully independent out of doors by means of an activity questionnaire. There is evidence that fitness is an indicator of physiological reserve and therefore of biological as opposed to chronological age (Editorial, Lancet 1991). Greater variability in the results from the elderly subjects is a characteristic finding in cross-sectional studies of the effects of age on a variety of physiological parameters (Davies, 1983) and may account for some of the difficulty previously encountered in demonstrating differences in MVF/CSA measurements between young and elderly subjects.

As stated in the introductory section on muscle function and ageing (pp 67-71 & 95-96) a number of studies have suggested a specific decline in the ability of ageing mammalian muscle to produce force though this was still controversial at the start of our study. There are several

possible reasons why it has proved so difficult to show this consistently. Firstly the effect may be quite small relative to the loss of strength due to atrophy and may affect some muscles more than others (Brooks and Faulkner, 1987). Secondly the results from quadriceps (Young et al., 1984 & 1985) are difficult to interpret. Some of the reasons for this are discussed on pages 20-27 and 167-169. Other factors affecting the interpretation of data comparing quadriceps MVF/CSA in young and elderly subjects include:

(i) disuse atrophy is particularly likely to affect proximal leg muscles,

(ii) increase in muscle bulk of a mature multipennate muscle, due to hypertrophy, leads to a change in the angle of pennation of the fibres. This changes the effective lever ratio (Binkhorst & van't Hof, 1973) and the proportion of the total number of fibres included in a CSA measurement taken at right angles to the long axis of the muscle (Maxwell et al., 1974). It seems likely that loss of muscle bulk secondary to ageing would have an analogous effect.

TWITCH INTERPOLATION IN ELDERLY SUBJECTS

One reason for the greater variability in the elderly subjects could be varying degrees of activation with only those elderly subjects whose MVF/CSA was similar to the young subjects achieving maximal activation. We studied this using the twitch interpolation experiment (Merton, 1954). Figs 44 & 45 show that elderly with reduced MVF/CSA measurements were nevertheless fully activated during a maximal voluntary contraction. We studied the whole relation of twitch height against levels of voluntary force, as Merton (1954) did, rather than merely trying to observe the twitch size at MVF. The plateau of a maximum voluntary contraction is not a steady baseline and it is therefore difficult to be sure of the absence of small superimposed twitches near to MVF (Fig 36). Measurements at low percentages of MVF are more reliable because twitch heights are larger relative to the baseline. Vandervoort & McComas (1986) also studied twitch interpolation in elderly subjects. They reported that there was no evidence of failure to activate in the dorsi-flexors of the foot in their elderly

subjects and that the majority could also fully activate their plantar-flexors. However their results are more difficult to interpret than ours. They only studied superimposed twitches at MVF, and CSA was not measured in all subjects. Although a reduced mean MVF/CSA is reported for the plantar-flexors it is not clear whether the individuals with reduced MVF/CSA were among those who could achieve full activation.

Our results exclude an important possible cause of weakness by showing that even those elderly with reduced MVF/CSA measurements were fully activated during a maximal voluntary contraction.

MUSCLE FUNCTION AND OSTEOPOROSIS

There is a close similarity between the declines in bone mass and in muscle mass observed during human ageing (Cooper, 1989). Total body calcium and total body potassium were significantly correlated ($r = 0.51$, $p < 0.001$) in a cross-sectional study of over 300 Caucasian women aged 20 - 80 years, none of whom had ever received hormone-replacement-therapy (Aloia et al., 1991). Aloia and colleagues (1991) also reported longitudinal observations from twenty-five of their subjects during the first three years after their menopause. These showed a significantly greater rate of decline of total body potassium compared with that seen in pre-menopausal women and in women greater than six years post-menopause. There was no significant difference in the rate of decline of total body potassium between the latter two groups. This accelerated loss of muscle mass in the three years immediately after the menopause is very similar to the pattern of bone loss in women, most bone being lost in the first three to six years after the menopause (Riggs and Melton, 1992).

Significant correlations have also been reported between un-normalised muscle force and bone mineral content. Sinaki and colleagues (1986) measured isometric force of back extensors, by upward pressure of the back against a transducer positioned between the scapulae, with the subjects lying prone. This measurement was significantly correlated with bone mineral density of the second to fourth lumbar vertebral bodies measured by dual photon absorptiometry ($r = 0.34$, $p < 0.004$). Beverly and colleagues (1989) found that maximal grip force was significantly correlated with forearm bone mineral content measured by single photon absorptiometry ($r = 0.66$, $P < 0.001$) in ninety-nine women, the majority of whom were post-menopausal, and thirty of whom had had a forearm fracture. Rutherford and Jones (1992) studied 216 healthy Caucasian women aged 21 - 82 years and found significant correlations between quadriceps MVF and bone density of distal and cortical femur (measured from CT scans) and spine (measured by dual photon absorptiometry) - $p < 0.0001$ in all three cases.

Extremes of activity are well recognised to have consequences for the skeleton. Immobility and weightlessness result in bone loss, despite adequate calcium intake, and intensive athletic training results in increased bone mass. There are thus two forces acting on the skeleton, gravity and muscle contraction. The mechanism whereby local bone mass is controlled through the stresses placed upon the bone is poorly defined (Cooper, 1989) but one might expect subjects with osteoporotic fractures to represent another extreme situation and that they might be particularly weak. Jones and Rutherford (1990) reported quadriceps MVF/CSA to be significantly lower in thirteen women with osteoporotic fractures (all had vertebral crush fractures; five in addition had fractures of the proximal femur) than fifty-one pre-menopausal and twenty-six post-menopausal women who had not suffered osteoporotic fractures. Our results show an additional significant percentage loss of force of adductor pollicis MVF/CSA in hip fracture patients compared with elderly subjects who had not suffered an osteoporotic fracture (table 10) confirm Jones and Rutherford's (1990) observations and also emphasises that osteoporotic subjects are generally weak. These results also predict that there might be observable differences in the time-course of the decline in force/CSA in men and women.

THE TIME-COURSE OF THE DECLINE IN MVF/CSA WITH AGE

Fig 47 shows that the time course of the decline in a adductor pollicis MVF/CSA in men and women is indeed very different. In men MVF/CSA was maintained until about the age of 60 years after which it gradually declined. In women there was a dramatic loss of MVF/CSA around the time of the menopause to an apparent plateau. Therefore it seems that, in women, the decrease in MVF/CSA seen in the very elderly has actually occurred in the early post-menopausal years. In their study of 216 women aged 21-82 years Rutherford and Jones (1992) observed a twenty-seven per cent decline in quadriceps MVF/CSA between the third and eighth decades. There was a particularly large and significant ($p < 0.02$) reduction in quadriceps MVF/CSA between the fifth and sixth decades in this study although the authors did not specifically relate this to the menopause of their subjects.

It is well established that bone loss is delayed by therapeutic replacement of oestrogen (Riggs and Melton, 1992) and our results from women on hormone-replacement-therapy (HRT) (fig 48) show that the menopausal decline in adductor pollicis muscle function in these subjects was also prevented by HRT. Cauley and colleagues (1987) measured un-normalised grip-force in 255 post-menopausal women aged 40 - 68 years. Fifty-five of these women were taking HRT. Mean grip-force was lower ($p < 0.05$) in the 200 women who were not taking HRT. A significant negative correlation between grip-force and age in the women not taking HRT was also reported in this study but there was no decline in grip-force in the fifty-five women on HRT whose age-range was similar.

SEX HORMONES AND MUSCLE

The effect of oestrogen on skeletal muscle is commercially exploited by the agricultural industry to improve meat production but the mechanism of action is not completely understood (Florini, 1987). Oestrogen receptors have been demonstrated in rat muscle (Dahlberg, 1982), bovine muscle (Meyer & Rapp, 1985) and in levator ani muscle in women (Smith et al., 1990) suggesting a direct effect at least in some muscles. Oestrogen has been shown to influence energy metabolism in rodent skeletal muscle. Ten to twelve week old oophorectomized Theiller original albino mice were given ten weeks treatment with 17-β-oestradiol (5 μg/kg/day), progesterone (1 mg/kg/day) alone or in combination, or placebo (Puah and Bailey, 1985). Three parameters were studied in the soleus muscles of these animals: 1) uptake of 2-deoxy-D-glucose, 2) glucose oxidation to carbon dioxide using ^{14}C-labelled glucose and 3) glycogen synthesis. These parameters were studied with and without the influence of insulin. After oophorectomy and placebo there was no change in basal uptake of 2-deoxy-D-glucose but a significant reduction in insulin-stimulated uptake. Under basal conditions oophorectomy did not affect glucose oxidation to carbon dioxide or glycogen synthesis. The effects of hormone administration after oophorectomy compared with placebo are shown in the table 12 ($p < 0.05$ in all cases where a difference was shown).

Table 12

	Oestrogen	Progesterone	Oestrogen & Progesterone
Basal uptake of 2-deoxy-D-glucose	no change	no change	no change
Insulin-stimulated uptake of 2-deoxy-D-glucose	increased	no change	increased
Insulin-stimulated glucose oxidation	increased	no change	no change
Insulin-stimulated glycogen synthesis	increased	no change	no change

As can be seen, progesterone had no effect on its own but appeared to antagonise the effect of oestrogen on insulin-stimulated glucose oxidation to carbon dioxide and glycogen synthesis. The time-course for the decline in adductor pollicis force/CSA in males is similar to that of the decline in serum testosterone measurements in men (Vermeulen 1991). Uptake of 2-deoxy-D-glucose has also been shown to be enhanced by testosterone in the levator ani and EDL muscles of three to four week old male CO strain rats, though no testosterone effect was seen in soleus or biceps brachii of these animals (Max and Toop, 1983). There is evidence for a synergistic effect of androgens and oestrogens in inducing skeletal muscle glucose-6-phosphate dehydrogenase, possibly due to induction of the androgen receptor by oestradiol (Rance and Max 1984).

Fatty-acid binding protein, which has been shown to be quantitatively related to mitochondrial fatty-acid oxidation, was increased in cardiac and soleus muscle of female Brown-Norway rats by two-weeks administration of testosterone ($p < 0.005$) (van Breda et al., 1992). In the soleus muscle the effect was abolished by inhibiting aromatisation of testosterone to oestradiol suggesting that in this muscle the increase in fatty acid binding protein was due to oestrogen

rather than testosterone directly. In cardiac muscle, fatty acid binding protein was still increased after inhibition of aromatisation of testosterone to oestradiol suggesting a direct effect of testosterone. No effects attributable to either oestrogen or testosterone were seen in the EDL muscles of these animals.

To summarise, the time-courses of the declines in adductor pollicis force/CSA in men and women are similar to those of testosterone and oestrogen respectively. Maintenance of oestrogen by means of HRT administration appears to prevent the decline in force/CSA in women. Effects of these hormones on both carbohydrate and fatty-acid metabolism has been demonstrated in some rodent muscles.

THE RELATIONSHIP BETWEEN MUSCLE ENERGY METABOLISM AND FORCE/CSA

In mitochondrial suspensions from cardiac muscle there is a linear relationship between ATP synthesis (units - $nmol.s^{-1}.cm^{-3}$) and "driving force" which is taken to be the difference between the mitochondrial redox potential (units - V) for synthesising one molecule of ATP and the free energy of cytosolic ATP hydrolysis or synthesis (ΔG_{ATP}) (Kj/mol) (Daut, 1987). The mitochondrial redox potential depends on supply of oxygen and on the $NADH/NAD^+$ ratio. The mitochondrial $NADH/NAD^+$ ratio in turn depends on supply of acetyl-CoA, principally from fatty-acid and carbohydrate metabolism (Alberts et al., 1989). Since

$$\Delta G_{ATP} = \Delta G^0_{ATP} + RT \ln([ADP][Pi]/[ATP])$$

a decline in ATP synthesis will lead to a rise in ADP and Pi concentrations. Daut (1987) shows that his model predicts that this happens when a reduced coronary perfusion rate with consequent reduction in myocardial supply of oxygen is simulated. The model also predicts that changes in substrate will effect energy metabolism. Daut and Elzinga (1989) showed that resting and contraction-related heat production and isometric force of trabeculae isolated from guinea-pig heart muscle were all markedly increased by substituting pyruvate for glucose in the solution perfusing their preparations. Phillips and colleagues (1993b) showed an eighteen per cent increase in isometric tetanic force in mouse soleus muscle when pyruvate was substituted for glucose. Using ^{31}P-NMR, Phillips and colleagues (1993b) also showed that in soleus muscle Pi declined to an undetectable level when pyruvate was substituted for glucose. With EDL, Pi was undetectable when both glucose and pyruvate Ringers solutions were used, and changing the substrate had no effect on isometric tetanic force of this muscle.

Thus the changes in energy metabolism reported to occur in rodent muscle could result in increases in Pi which might be expected to effect MVF/CSA measurements as described in the next section.

THE STRETCH EXPERIMENT

Stretching an active muscle results in the production of extra force above the isometric level. Katz (1939) first systematically described the mechanical behaviour of active muscle during stretch having performed steady isotonic lengthening experiments on frog and tortoise muscle. He found that:

a) for loads of up to about 1.8 times the isometric force, when velocity is plotted against the load, the force is greater than would be predicted from the line extrapolated from the force-velocity relation during shortening,

b) above about 1.8 times the isometric force the muscle "gives", following which it behaves as if completely relaxed.

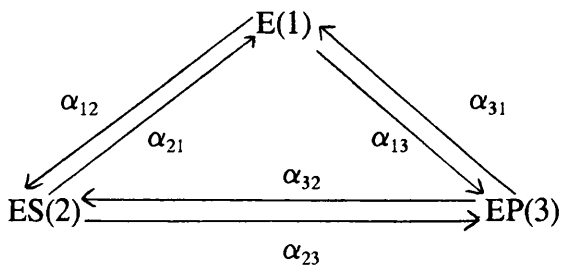
Using isovelocity lengthening of frog single muscle fibres, Edman and colleagues (1978) found that, with high velocities of stretch, force rises to a peak followed by a decline to a steady level. Both the peak and the steady level are greater than the isometric force. Katz (1939) observed an initial reversible lengthening due to elastic parts of the muscle and lever system. The proportion of the measured force that is due to parallel elasticity can be found by measuring force during lengthening with and without stimulation. After subtracting the force measured during lengthening without stimulation from that measured during lengthening with stimulation, the stretch force

due to the contractile elements of the muscle remains. This increase in force above the isometric level during stretch, is also seen after "skinning" of the rabbit psoas muscle fibres (Elzinga et al. 1989). This process removes connective tissue thereby confirming that the increased force is not due to parallel elasticity in non-contractile components of the muscle.

Thus it appears that the phenomenon of enhanced force during stretch is due to an alteration in the interaction between the contractile elements in muscle and we therefore need to review current theories of contraction to try to understand it further. Sir Andrew Huxley was responsible for what, with subsequent modifications, is still the most complete analysis of muscle contraction (Huxley, 1957, Huxley & Simmons, 1971 & 1973). His theory is based on assumptions about the kinetic properties of individual cross-bridges. Its basic premises as summarised by Woledge, Curtin and Homsher (1985) and T.L. Hill (1977) are:

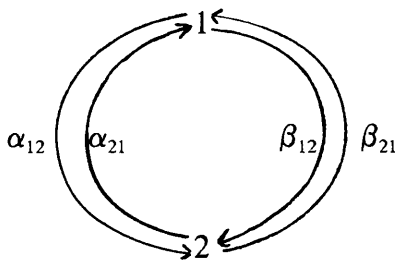
a) a cross-bridge, which is taken to be equivalent to a single myosin head, can exist in one of a number of different states.

In general, macromolecular units which may exist in a number of discrete states can be represented diagrammatically thus:



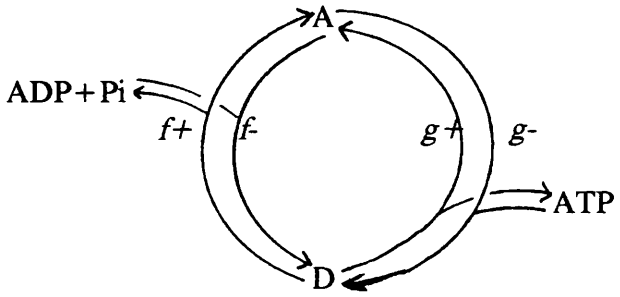
In this diagram enzyme (E) = state 1, enzyme-substrate complex (ES) = state 2 and enzyme-product complex (EP) = state 3. The first-order rate constants for the

transitions are denoted by α and their direction by the subscripted numerals. This nomenclature is that used by Hill (1977). If one of the intermediates in such a three state system is transient the above diagram may be condensed:



b) transitions between these states include the binding and splitting of ATP.

In Huxley's 1957 model there are only two states - attached - (A) and detached (D). The concentrations of ATP, ADP and Pi are assumed to be constant so that the rate constants can be made pseudo-first-order. The system can be represented thus:



In this case the left of the diagram represents attachment and the right detachment. Huxley uses the nomenclature *f* and *g* for the rate constants for the transitions between states: *f* for attachment and *g* for detachment, + and - denoting the forward and backward reactions respectively.

c) force (F) is exerted by a cross-bridge on the thin filament.

This only occurs in the attached state. The amount of force exerted by any one cross-bridge depends on the displacement *(x)* between the thick and thin filaments. x is variable and can be positive or negative. As the muscle shortens x decreases and when $x = 0$, $F = 0$. Sites of attachment on the actin filament are assumed to be a sufficient distance apart *(l)* so that at most only one site at a time is available to any one cross-bridge for attachment.

d) the rate constants for the transition between attached and detached states are functions of *x*.

This feature distinguishes the kinetics of actin-myosin-ATP interactions from that of other enzyme-substrate-ligand systems. These functions of x are given values such that cross-bridges attach more rapidly when x is positive than when x is negative, the converse being true for detachment. It is this asymmetry that results in shortening and the production of force.

The simplest explanation for the increased force during stretch would be that it results from an increase in the overall number of attached cross-bridges. However assuming that the elasticity of the cross-bridges remains constant, this would result in an increase in muscle stiffness concomitant with the rise in force. In isolated frog muscle fibres either no increase in muscle stiffness has been observed during or after stretch (Julian & Morgan, 1979) or only a small increase at low velocities of stretch (Lombardi and Piazzesi, 1990).

A further possibility might be that the increase in force results from a non-uniformity

of sarcomere length along the fibre during an isometric contraction. This apparently accounted for the increase in force above isometric which was observed by Julian and Morgan (1979) on stretching frog single muscle fibres. In these experiments stretch was started above the optimum sarcomere length measured in the middle of the fibres. However sarcomeres at the ends of the fibres were found to be shorter than those in the middle and thus resisted stretch. This led to extra force being recorded after stretch, above that appropriate to the longer sarcomere length in the middle of the fibre. This was excluded as a general explanation by experiments carried out by Lombardi and Piazzesi (1990), using frog single tetanized muscle fibres at around optimum sarcomere length. They studied the force developed during steady lengthening at different velocities, in relation to the actual lengthening of short segments along the fibres. Tendon compliance and non-uniformity of sarcomere length were carefully controlled and the mechanical characteristics of the resulting responses investigated "with much improved resolution". They found that an increase in force was still measured with stretches within the plateau of the tension-length curve and confirmed previous descriptions of a bi-phasic response - an initial peak force greater than twice the isometric force being followed by a steady state force of about 1.9 times the isometric force.

A third possibility to account for the increased force is that, although there is no increase in the number of attached cross-bridges, the individual cross-bridges produce more force. The 1957 model can qualitatively accommodate this explanation but neither it nor the subsequent modifications by Huxley and Simmons (1971, 1973) developed it quantitatively. There are two difficulties:

i) accounting for the relative constancy of stiffness (Julian & Morgan, 1979, Lombardi

and Piazzesi, 1990). This raises two conceptual problems: it seems to require either great elongation of the cross-bridges that are attached as the stretch is applied, and/or an unexpectedly large rate constant for the attachment of unattached cross-bridges during stretch (Huxley, 1980).

ii) accounting for the association of a very high force with a very low rate of ATP splitting (as observed by Curtin and Davies, 1975). It has to be postulated that cross-bridges detach during stretch by a process that does not use ATP, perhaps therefore a simple reversal of the process that attaches them (the process for which $f-$ is the rate constant as opposed to $g+$ in the diagram of the 1957 model above) (Woledge et al., 1985). This could follow from Huxley's concept that chemical and mechanical events alternate in the cross-bridge cycle: that a particular chemical event "permits" the next mechanical event, the completion of which necessitates the next chemical event and so on. Thus detachment-binding of ATP and its hydrolysis are only needed after the cross-bridge has been "allowed" to complete its work-stroke. As this would not occur during stretch no detachment-binding or splitting of ATP would be required (Huxley, 1980).

These unanswered questions regarding the behaviour of cross-bridges during stretch led Huxley in his Sherrington lectures to postulate "special features" to allow elongation of active muscle to occur without muscle damage. He pointed out the potential evolutionary advantages of this since it is something that happens in very many animal movements. He concluded that these special features might have little relation to the processes that take place during shortening (Huxley, 1980).

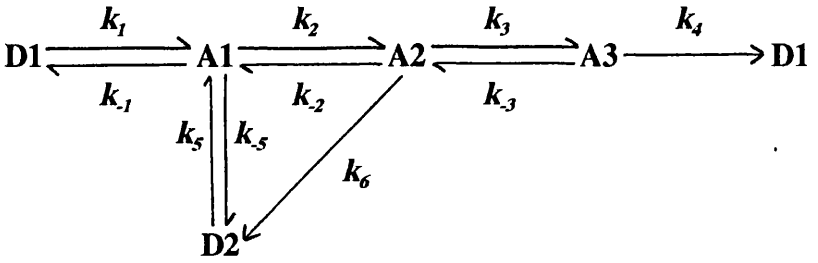
Lombardi and Piazzesi (1990) interpreted their results by a further development of

Huxley's model envisaging five cross-bridge states, three attached and two detached. The transitions between these states and their rate constants is shown in Fig 60a. A second weakly attached state preceding the force generating state had previously been postulated (Huxley, 1973) to account for revised heat measurements of A.V. Hill (1964) which indicated a fallacy in the 1957 calculation for the rate of turnover of cross-bridges during an isometric contraction (Huxley, 1980). In Lombardi and Piazzesi's model this weak state, which produces very little force during an isometric contraction, produces force during stretch due to the D2 state becoming populated and very rapid re-attachment occurring between D2 and A1 (some 200 times faster than the turnover of cross-bridges during an isometric contraction or during shortening). This attached state is thus very transient and, following Huxley, it is envisaged that it becomes populated without the need for binding and hydrolysis of ATP.

A hypothetical set of basic free energy levels in a model with three attached and two non-attached states can be represented diagrammatically as in Fig 60b. This diagram is simplified from T.L. Hill (1977) incorporating the nomenclature of Lombardi and Piazzesi (1990). The parabolic shape of the free energy profiles as a function of x is implicit in Huxley's (1957) assumptions regarding the elastic properties of attached cross-bridges.

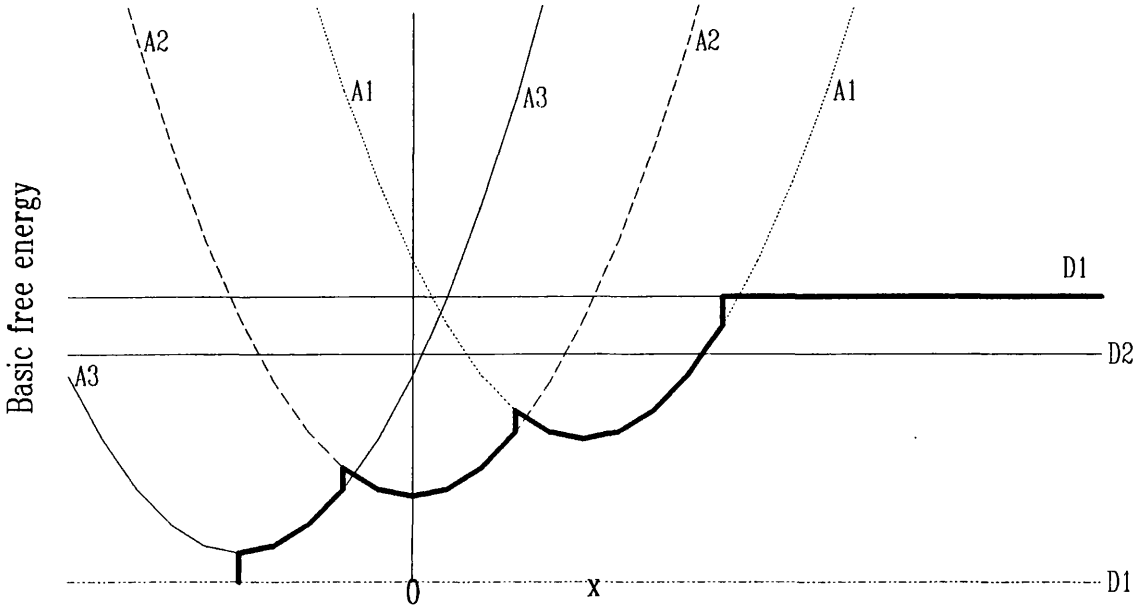
During steady shortening it is imagined that a single site appears to the right of the diagram. During the "pass" of the actin site by the cross-bridge which for example, may initially be in state D1, the cross-bridge may interact via the transitions through some sequence of states. The transitions are represented by vertical steps, up or down (usually down) and the black line shows a possible stochastic sequence of events.

Fig 60a The transitions, and their rate constants, between the three attached and two detached states of Lombardi and Piazzesi's model.



The force produced by A1 < A2 < A3). This diagram is reproduced from Lombardi and Piazzesi's paper (1990). It should be noted that their nomenclature for the rate constants neither follows the convention of T.L. Hill, who uses k_n and k_{-n} for the sum of the rate constants of a complete cycle, nor that of Huxley, who has different symbols for attachment and detachment.)

Fig 60b. A hypothetical set of basic free energy levels in a model with three attached and two non-attached states (see text).

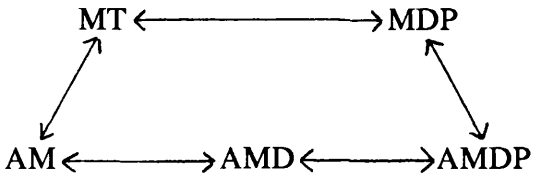


In Fig 60b as in Lombardi and Piazzesi's model steady shortening causes a redistribution of cross-bridges towards A3 and detachment occurs predominantly from A3 → D1. During an isometric contraction, at any particular *x* value, a cross-bridge will perform a "biased random walk" on the basic free energy levels at that value of *x*. The general trend of the walk will be downhill but small uphill transitions can sometimes occur. In isometric conditions in Lombardi and Piazzesi's model the equilibrium of the reaction A1 → D2 is fully in favour of the attached state. Thus D1 is the only detached state and attached cross-bridges are mainly in states A1 and A2.

During steady lengthening in Lombardi and Piazzesi's model, extension of attached cross-bridges increases, i.e. *x* becomes more positive causing a redistribution towards A1. Because the rate constants for the transitions between states are functions of *x* those for the reactions A1 → D2 and A2 → D2 become progressively larger. D2 thereby becomes populated allowing the very rapid reattachment between D2 → A1.

A number of experimental conditions are associated with an even higher percentage increase in force during stretch than is seen under control conditions. These conditions are a) raised intracellular inorganic phosphate (Pi) (Elzinga et al., 1989), b) raised intracellular hydrogen ion (reduced pH) (Curtin, 1990), c) fatigue (Flitney & Jones, 1990), and d) hypertonicity (Månsson, 1989). The other characteristic of all these situations is that isometric force/CSA is lower than under control conditions so that the higher than normal percentage stretch force restores the absolute measurements of force during stretch to values near to the absolute stretch force measured under control conditions.

The mechanism whereby an increased intracellular phosphate might result in a reduced isometric force/CSA has been modelled by Pate and Cooke (1989). Their model of cross-bridge action also envisages three attached and two detached states:



M = myosin, A = actin, T = ATP, D = ADP, P = Pi

The specific purpose of their model is to explain the effects of ligands that are known to bind to the nucleotide site of myosin.

There are a number of obvious similarities between Pate and Cooke's model and Lombardi and Piazzesi's. Both have a transient weakly bound initial attached state that does not produce much force during isometric contraction or during steady shortening. Pate and Cooke identify this with the actomyosin(AM)-ADP-Pi complex. In Lombardi and Piazzesi's model this transient weakly bound initial attached state is A1. During an isometric contraction the main force producing state in Pate and Cooke's model, AM-ADP becomes populated (analogous to A2 in Lombardi and Piazzesi) and the attached cross-bridges are mainly in this and the weakly attached AM-ADP-Pi state (A2 and A1 in Lombardi and Piazzesi). During steady shortening there is a redistribution to the AM state which also produces force (analogous to A3 in Lombardi and Piazzesi). Pate and Cooke show that their model predicts the observed decline in isometric force/CSA seen with increasing Pi. This is due to a net shift of cross-bridges from the force producing AM-ADP state to the weakly bound AM-ADP-Pi state.

They do not consider the effects of steady lengthening. However it will be remembered that in Lombardi and Piazzesi's model the A1 state is induced to produce force during stretch. Thus taking Pate and Cooke's weakly bound state of initial attachment, AM-ADP-Pi to be analogous to Lombardi and Piazzesi's A1, we have a plausible explanation for Pi causing a decline in isometric force/CSA but having no effect on absolute force during stretch i.e. when the muscle is stretched the extra force is due to the A1 state producing force and therefore the more the A1 state is populated the greater will be the stretch force relative to the isometric force.

No such clear model exists for the effects of hydrogen ion. One important effect may be that reduced pH favours the production of the monobasic form of inorganic phosphate ($H_2PO_4^-$). The specific presence of this ion has been reported to be important in depressing isometric force (Nosek et al., 1987). As the pK of the reaction

$$HPO_4^{2-} + H^+ = H_2PO_4^-$$

is close to 7, changes of pH around the physiological range would be expected to cause large variations in the proportions of the HPO_4^{2-} and $H_2PO_4^-$ ions.

THE STRETCH EXPERIMENT IN AGEING MUSCLE

Though preliminary our result from applying rapid stretch during a maximal voluntary contraction in post-menopausal women with low MVF/CSA results confirm that ageing is another condition of skeletal muscle in which a reduction in isometric force/CSA is associated with a higher than normal percentage increase in force during stretch.

Isometric MVF/CSA was reduced in the post-menopausal women by more than thirty per cent. Force during stretch was of the order of 1.6 times the isometric force in the young male and female subjects tested, but more than twice the isometric force in the post-menopausal women. This strongly suggests that the decline in force/CSA in these subjects is occurring at the level of the cross-bridge. We have also reported similar results in aged mouse soleus muscle (Phillips et al., 1991). These observations raise the question as to whether raised Pi and/or reduced pH can be shown to account for the decline in force/CSA with age. Two published studies have compared Pi and pH in muscle from young and aged subjects using ^{31}P-NMR spectroscopy. As mentioned on pages 81-82 Taylor and colleagues (1984) found no differences with age in either Pi or pH in resting human flexor digitorum superficialis muscle and the changes that were associated with aerobic dynamic exercise were also similar. Phillips and colleagues (1993c), using isolated mouse soleus muscle also found no differences in intracellular Pi and pH between six month old (n = 11) and twenty-eight month old (n = 9) mice despite an average twenty-one per cent reduction in isometric force/CSA in the soleus muscles from the older mice. As noted above (p 184) Phillips and colleagues (1993b) had previously demonstrated a five-fold difference in Pi associated with an eighteen per cent increase in force in mouse soleus muscle, after substituting pyruvate for glucose in the solution perfusing their preparation. Since the same technique was used in the study of ageing muscle (1993c) any differences in Pi between young and aged mouse soleus should have been easily measurable.

Thus it appears that simple increases in intracellular phosphate and hydrogen ion in resting muscle cannot account for our observations. Although it remains possible that such differences might be associated with ageing in active muscle, and that Taylor and

colleagues (1984) did not observe them either because their techniques were not sensitive enough or because their aged subjects were not weak (neither force nor muscle size were measured in this study), other hypothetical models need to be sought for the decline in force/CSA with age. As noted above two other experimental situations are known to produce a reduced force/CSA and an increased stretch force, fatigue and hypertonicity. Fatigue is a complex and incompletely understood phenomenon. Although reduced central drive may be important clinically (Stokes et al., 1988), Merton (1954) in his seminal paper referred to previously showed that in normal subjects, during a prolonged voluntary contraction of adductor pollicis "at any point in the slope of decreasing tension an interpolated tetanus causes no return of tension". Thus in his subjects the decline in force had occurred due to changes within the muscle itself as stimulation of the motor nerve did nothing to restore force.

The cellular basis of fatigue in skeletal muscle has recently been reviewed (Westerblad et al., 1991). The factors that may cause a decline in force during stimulation fall into three categories.

1) reduced calcium release from the sarcoplasmic reticulum

2) reduced sensitivity of the myofilaments to calcium

3) reduced force per cross-bridge (referred to by Westerblad and colleagues as "reduced maximum calcium-activated force").

Unfortunately there is no agreed standard protocol for studying fatigue. Two categories of experimental regime are used - prolonged high frequency stimulation and repeated tetani. The time-course of the development of, and recovery from, fatigue induced by these methods is very different and the situation is further complicated by the fact that

high frequency stimulation is not analogous to a prolonged maximal voluntary contraction. Force declines more slowly during a prolonged maximal voluntary contraction because there is a gradual reduction in α-motor-neurone firing-frequency coincident with a progressive slowing of relaxation. Thus adequate summation occurs later during a prolonged maximal voluntary contraction due to a reduced stimulation frequency.

Fatigue from high-frequency stimulation develops rapidly (with a half time of 5 - 30 s) and recovery is also rapid. Failure of calcium release due to failure of propagation of action potentials into the T-tubule system seems to be the most important factor in high-frequency fatigue (Westerblad et al., 1991). The exact time-course of the development of fatigue during repeated tetanic stimulation is dependent on the stimulation protocol but is generally much slower and varies with motor unit and fibre type (Burke et al., 1973). The time-course of the recovery from this kind of fatigue is also much slower. Westerblad and Allen (1991) related force measurements in single fibres from mouse flexor brevis muscle of the foot, to intracellular calcium measurements, using the calcium indicator fura-2. Fatigue was induced by repeated 100 Hz tetani and occurred in three phases.

Phase 1: there was a rapid decline in force to about ninety per cent of the maximum force during which intracellular calcium significantly increased. Application of caffeine caused a further increase in intracellular calcium but no increase in force.

Phase 2: a prolonged period of almost stable force production and intracellular calcium concentration. During this phase the application of caffeine caused a marked increase in intracellular calcium but again no increase in force.

Phase 3: a rapid decline in force to about thirty per cent of the maximum tetanic force. During this phase caffeine-induced increase in intracellular calcium was associated

with an increase in force from thirty per cent to eighty per cent of the control value.

Thus the decline in force in phase three appears to be due to a reduction in calcium release from the sarcoplasmic reticulum as force is enhanced by application of caffeine. That this is not the case in phases one or two suggests that the decline in force in these phases is due to a reduced force per cross-bridge and/or a reduction in the sensitivity of the myofilaments to calcium.

A five-fold increase in Pi was measured using ^{31}P-NMR during fatigue in human muscle (Dawson et al., 1978) and the rise is believed to occur early during prolonged activity (Westerblad et al., 1991). Thus a reduced force per cross-bridge could occur by the mechanism described above (Pate and Cooke, 1989 - see p 194), i.e. by Pi causing a net shift of cross-bridges from the force producing AM-ADP state to the weakly bound AM-ADP-Pi state. Additionally a decline in pH from 7.0 to 6.5 typically occurs in fatigue produced by repeated tetani Westerblad et al., 1991). This could contribute to the reduction in force per cross-bridge by favouring the production of the dipropionated $H_2PO_4^-$ ion (Nosek et al 1987). Hydrogen ion may also reduce tetanic force by competing for the same troponin-C binding site as calcium, thereby reducing the sensitivity of the myofilaments to calcium. This is known to occur in cardiac muscle (Blanchard & Solaro 1984). Given these metabolic changes it would be surprising if stretch were not demonstrably greater than normal in muscle fatigued by repeated tetani. It is of interest however that it is in high-frequency fatigue that stretch force has been shown to be increased (Flitney and Jones, 1990). As noted above in high frequency fatigue changes in Pi and pH are thought to be relatively unimportant, the major change being T-tubule conduction failure leading to reduced

calcium release (Westerblad et al., 1991).

Declines in energy metabolism in ageing muscle brought about by the hormonal mechanisms described above, would be expected to affect intracellular calcium as the re-uptake of calcium by the sarcoplasmic reticulum is ATP-dependent. The effects of Pi on force are inter-related with those of calcium. In skinned rat ventricle muscle Kentish (1986) found that the presence of phosphate not only caused a reduction in maximum force but also a decrease in the calcium-sensitivity of the myofibrils when the calcium concentration was submaximal. When force, as a percentage of maximal force, was plotted against calcium concentration, a sigmoid curve was produced. The presence of Pi changed the shape of this curve such that a greater calcium concentration was required to produce a given percentage of the maximum force. The effects on maximum force and on myofibrillar calcium-sensitivity at submaximal calcium concentrations occurred over the same range of Pi concentrations suggesting that the same mechanism might account for both observations. Kentish explains the effect of Pi in reducing maximum calcium-activated force in the familiar way i.e. by Pi causing a net shift of cross-bridges from the force producing AM-ADP state to the weakly bound AM-ADP-Pi state. He also suggests that in the AM-ADP-Pi state the calcium affinity of troponin or actin may be lower than when the cross-bridge is in the AM-ADP state thus accounting for the decrease in calcium sensitivity with increased Pi. Similar results, an increase in maximum force and calcium sensitivity at submaximal stimulation frequencies, were reported in intact mouse soleus muscle when Pi was lowered by the addition of pyruvate (Phillips et al., 1993a). However an observation in this study suggests that the situation is more complex since at maximum stimulation frequencies rate of rise of force was faster and relaxation slower with

pyruvate. This observation is puzzling. Within the physiological range, calcium release is independent of the ATP concentration (Westerblad et al., 1991) so the effect on rate of rise of force is hard to explain in terms of increased intracellular calcium, though the reduction in Pi due to pyruvate could reduce cytoplasmic binding of calcium. However this is unlikely to explain the slowing of relaxation. Indeed one would expect an increase in ATP to either have no effect or to speed relaxation, since uptake of calcium is ATP-dependent, unless intracellular calcium is raised sufficiently to saturate the pump molecules which seems unlikely.

The other factor known to depress maximum isometric force and to be associated with an enhanced stretch force is hypertonicity. It is the least well understood but its known effects as summarised by Woledge and colleagues (1985) are:

1) increased concentrations of fibre contents and ionic strengths,

2) decreased cell volume with a consequent change in the spacing between the filaments

3) inhibition of calcium release from the sarcoplasmic reticulum.

Of these the first (an increase in the concentration of fibre contents and ions) could cause depressed maximum isometric force with an enhanced stretch force by the mechanism described above i.e. an increase in Pi and decreased pH. The second (a change in the spacing between filaments) was investigated in single fibres from frog semitendinosus muscle by Edman and Hwang (1977). They increased the osmolality of the Ringer solution in which their fibres were immersed, to 1.22 times that of isotonic Ringer, by adding sucrose to which the fibre is impermeable. This resulted in a twelve per cent reduction in isometric force, a twenty-two per cent reduction in maximum speed of shortening and a thirteen per cent reduction in fibre CSA. Using the fact that

the fibre maintains a virtually constant volume as its length changes, they varied the sarcomere length, within the range 2.0 - 2.5μm, in isotonic Ringer to achieve the same reduction in fibre CSA and thus the same change in the spacing between the filaments. In the isotonic solution changing the filament spacing in this way had no effect on isometric force or on maximum speed of shortening. Thus the relevant factors in producing a decline in isometric force may be similar in hypertonicity and in fatigue - a rise in intracellular phosphate and hydrogen ion with a reduction in calcium release.

Whether inhibition of calcium release from the sarcoplasmic reticulum increases force during stretch as well as depressing isometric force does not seem to have been systematically investigated. An indication that it might do so comes from the observation noted above that stretch force is increased in high-frequency fatigue (Flitney and Jones, 1990) remembering that in high-frequency fatigue metabolic changes causing raised Pi and lowered pH are thought to be relatively unimportant, the major change being T-tubule conduction failure and a subsequent decline in calcium release (Westerblad et al. 1991). Inhibition of calcium release might be expected to depress isometric force by reducing the number of attached cross-bridges. If this were overcome in some way by stretch, the increased force would be expected to be associated with an increased stiffness for the reasons outlined above. This was not the case in frog tibialis anterior (Månsson, 1989) when tonicity was changed in a similar way to that used by Edman and Hwang (1977). The relative importance of intracellular phosphate, hydrogen ion and calcium to the changes in the force-velocity relation observed with hypertonicity is unknown and stiffness was not reported in the fatigue experiments (Flitney and Jones, 1990).

A possible way of separating these factors would be to perform the stretch experiment on muscle fibres which had been weakened by treatment with dantrolene, a drug known to suppress calcium release but to have no known effects on energy metabolism.

CONCLUSION

Without this end that constantly eludes us we would not journey forth, nor would there be any paths. But the end is the refutation and condemnation of the path: at the end the path dissolves, the meeting fades away to nothingness...
Setting forth once more, embarking upon the search once again: the narrow path that snakes among livid rocks and desolate, camel-coloured hills;... images, memories, fragmentary shapes and forms - all those sensations, visions, half thoughts that appear and disappear in the wink of an eye...

Octavio Paz - The Monkey Grammarian

The weakness that accompanies ageing has a number of factors underlying it. Firstly there is wasting which appears to be mainly due to loss of motor units (Tomlinson & Irving, 1977, Vandervoort & McComas, 1986). The wasting associated with subnutrition is related to an altered response to hormonal stimuli especially growth hormone and its mediator insulin-like-growth-factor-1 (Ross et al., 1991). Administration of recombinant growth hormone to normally nourished but growth hormone deficient adults, resulted in increases in muscle force and bulk (Cueno et al., 1991) In the only major study so far, of the administration of recombinant growth hormone to normal aged subjects muscle force was not reported but there was a 9% ($p < 0.0005$) increase in lean body mass in twenty-one men aged 61 - 81 years, over the six month treatment period (Rudman et al., 1990).

Secondly there is a decline in force/CSA of the muscle that remains. In adductor

pollicis we have shown this to be of the order of twenty per cent between young and post-menopausal women and more than thirty per cent between young adults and very elderly subjects. Narici and colleagues (1991) have reported a decline in un-normalised MVF of adductor pollicis in male subjects of the order of forty per cent between the second and eighth decades. Thus, assuming their subjects to be of similar body build, the decline in force/CSA probably accounts for rather more than half of the observed decline in overall force in adductor pollicis muscle. The relative contributions to the overall weakness of atrophy and decline in force/CSA may vary between different muscles, atrophy probably being more important in lower limb (i.e. weight-bearing) muscles (Bassey, 1985).

The results of the stretch experiment reported here, although preliminary, show that in human adductor pollicis, the decline in force/CSA is accounted for by a change in cross-bridge function. We have reported a similar finding with mouse soleus muscle (Phillips et al., 1991) and an analogous result has been reported in humans, with the extensors and flexors of the knee (Vandervoort et al., 1990). Other possible causes of a decline in force/CSA may be more important in other muscles. For example, significant replacement of muscle by non-contractile tissue seems to be associated with ageing in the rectus abdominis muscle (Inokuchi et al., 1975) but is unlikely to be an important factor in most muscles (Faulkner et al., 1990). A relative decline in the proportion of type II fibres had been thought to be an important factor in the weakness of ageing (Bassey, 1985) following studies of the human quadriceps muscle group (Larsson, 1978). However this is not a consistent finding even in this muscle group (Grimby et al., 1984, Lexell et al., 1988); neither is it found consistently in animal muscles (Florini & Ewton 1989). As shown on p 80, larger changes in the proportion

of type I to type II fibres than those that have been reported, would be required to account for observed decline in force/CSA with age, even in muscles that have a large proportion of type II fibres in young adults. Post mortem data from six male subjects aged 17 - 30 showed that adductor pollicis is composed of eighty per cent (69.5 - 92.5%) type I fibres (Johnson et al., 1973) so the effect of a change in relative fibre types is going to be small in this muscle. There appears to be no evidence of failure of activation, the fourth possible cause for decline in force/CSA, in any published study of ageing muscle including ours reported here.

The relationship between oestrogen and skeletal muscle force/CSA was unknown prior to our study. The causative link remains elusive but is almost certainly mediated by an effect of oestrogen on muscle energy metabolism. In rodents there is evidence of direct effects of oestrogen on skeletal muscle carbohydrate (Puah & Bailey, 1985) and fat metabolism (van Breda et al., 1992). Though not consistently convincing, there is evidence for a decline in energy metabolism with age in human (Costell et al., 1989, Trounce et al., 1989) and animal skeletal muscle (Ermini, 1976, Holloszy et al., 1991).

A post-menopausal decline in knee-extensor MVF/CSA has been reported (Rutherford & Jones, 1992) and it seems that stretch force is increased in elderly subjects in this muscle group (Vandervoort et al., 1990). These results suggest that similar changes to those we have found in human adductor pollicis and mouse soleus may occur more generally though this, of course needs to be confirmed by direct comparisons in the same subjects. There appears to be a variation in the ratio of stretch force to MVF of adductor pollicis during the menstrual cycle, in young women, consistent with an

effect of oestrogen (Phillips et al., 1993d). Further experiments are planned to test highly trained female athletes, another group of women who suffer oestrogen lack, and to test for reversibility if oestrogen replacement therapy is started after the post-menopausal decline in force/CSA has occurred.

The functional consequences of the weakness that accompanies ageing has been a commonplace observation since Old Testament times. Both decline in grip force (Askham et al., 1990) and in muscle mass (Melton & Riggs, 1985) are known to be risk factors for falls in the elderly. Although it has not been systematically investigated it would seem likely that a decline in force/CSA would also increase the predisposition to falls and intuitively that this risk would be greater when there is a marked and rapid change occurring. We have demonstrated such a change in the early post-menopausal years. The previously unexplained high incidence of Colles' fractures in the first decade after the menopause (Winner et al., 1989) could thus be accounted for by our observations and the preservation of skeletal muscle function by the administration of hormone replacement therapy that we have demonstrated, suggests that the decline in fracture rate associated with this treatment (Riggs & Melton, 1992) is probably in part accounted for by maintenance of muscle function as well as bone mass.

REFERENCES

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson., J.D. (1989). "The molecular biology of the cell." Garland, New York.

Allen, T.H., Andersen, E.C., Langham, W.H. (1960). Total body potassium and gross body composition in relation to age. Journal of Gerontology 15, 348-357.

Alnaqeeb, M.A., al Zaid, N.S., Goldspink, G. (1984). Connective tissue changes and physical properties of developing and ageing muscle. Journal of Anatomy 139, 677-689.

Aloia, J.K., McGowan, D.M., Vaswani, A.N., Ross, P., Cohn, S.H. (1991). Relationship of menopause to skeletal and muscle mass. American Journal of Clinical Nutrition 53, 1378-1383.

Aniansson, A., Grimby, G., Hedberg, M., Krotkiewski, M. (1981). Muscle morphology, enzyme activity and muscle strength in elderly men and women. Clinical Physiology 1, 73-86.

Aniansson, A., Hedberg, M., Henning, G-B., Grimby, G. (1986). Muscle morphology, enzymatic activity and muscle strength in elderly men : A follow-up study. Muscle and Nerve 9, 585-591.

Ashley, C.C., Mulligan, I.P., Lea, T.J. (1991). Ca^{2+} and activation mechanisms in skeletal muscle. Quarterly Reviews of Biophysics 24, 1-73.

Askham, J., Glucksman, E., Owens, P., Swift, C., Tinker, A., Yu, G. (1990). "A review of research on falls among elderly people." Department of Trade and Industry, London.

Asmussen, E., Fruensgaard, K., Norgaard, S. (1975). A follow-up longitudinal study of selected physiologic functions in former physical education students - after 40 years. Journal of the American Geriatrics Society 23, 442-450.

Asmussen, E., Heeboll-Nielsen,K., (1961). Isometric muscle strength of adult men and women. "Communications from the Testing and Observation Institute of the Danish National Association for Infantile Paralysis, Nr. 11" (E. Asmussen, A. Fredsted, E. Ryge, Eds.) pp. 1-43. Hellerup, Denmark.

Barlett, H.L., Puhl, S.M., Hodgson, J.L., Buskirk, E.R., (1991). Fat-free mass in relation to stature: ratio of fat-free mass to height in children, adults and elderly subjects. American Journal of Clinical Nutrition 53,1112-1116.

Bassey, E.J. (1985). Benefits of exercise in the elderly. In "Recent Advances in Geriatric Medicine 3" (B. Isaacs, Ed), pp. 91-112, Churchill Livingstone, London.

Bassey, E.J., Bendall, M.J., Pearson, M. (1988). Muscle strength in the triceps surae and objectively measured customary walking activity in men and women over 65 years of age. Clinical Science 74, 85-89.

Belanger, A.Y., McComas, A.J. (1981). Extent of motor unit activation during effort. Journal of Applied Physiology 51, 1131-1135.

Beverley, M.C., Rider, T.A., Evans, M.J. Smith, R. (1989). Local bone mineral response to brief exercise that stresses the skeleton. British Medical Journal 299, 233-235.

Beyer, R.E., Starnes, J.W., Edington, D.W., Lipton, R.J., Compton, R.T., Kwasman, M.A. (1984). Exercise induced reversal of age-related declines of oxidative reactions, mitochondrial yield and flavins in skeletal muscle of the rat. Mechanisms of Ageing and Development 24, 309-323.

Binkhorst, R.A., van't Hof, M.A. (1973). Force-velocity relationship and contraction time of the rat fast plantaris muscle due to compensated hypertrophy. Pflugers Archiv 342, 145-158.

Blanchard, E.M., Solaro, R.J. (1984). Inhibition of activation and troponin calcium binding of dog cardiac myofibrils by acidic pH. Circulation Research 55, 382-391.

Botelho, S.Y., Condor, L., Guiti, N. (1954). Passive and active tension-length diagrams of intact skeletal muscle of normal women of different ages. Journal of Applied Physiology 7, 93-98.

Bottinelli, R., Schiaffino, S., Reggiani, C. (1991). Force-velocity relations and myosin heavy chain isoform compositions of skinned fibres from rat skeletal muscle. Journal of Physiology (London) 437, 655-672.

van Breda, E., Keizer, H.A., Vork, M.M., Surtel, D.A.M., de Jong, Y.F., van der Vusse, G.J., Glatz, J.F.C., (1992). Modulation of fatty-acid-binding protein content of rat heart and skeletal muscle by endurance training and testosterone treatment. Pflugers Archiv 421, 274-279.

Brooks, S.V., Faulkner, J.A. (1988). Contractile properties of skeletal muscles from young, adult and aged mice. Journal of Physiology (London) 404, 71-82.

Brough, W., Horne, G., Blount, A., Irving, M.H., Jeejeebhoy, K.N. (1986). Effects of nutrients intake, surgery, sepsis, and long-term administration of steroids on muscle function. British Medical Journal 293, 983-988.

Brown, M. (1987). Change in fibre size, not number, in ageing skeletal muscle. Age and Ageing 16, 244-248.

Brown, W.F. (1972). A method for estimating the numbers of motor units in thenar muscles and the changes in motor unit count with aging. Journal of Neurology, Neurosurgery and Psychiatry 35, 845-852.

Bruce, S.A., Phillips, S.K., Woledge, R.C., (1986a). Apparatus for measuring force and adduction of the thumb, and for measuring profiles of the hand in human subjects. Journal of Physiology (London) 372, 9P.

Bruce, S.A., Phillips, S.K., Woledge, R.C. (1986b). Isometric force in maximal voluntary contractions related to an estimate of the cross-sectional area of adductor pollicis in the human subject. Journal of Physiology (London) 372, 31P.

Bruce, S.A., Newton, D., Woledge, R.C. (1989a) Effect of subnutrition on normalised muscle force and relaxation rate in human subjects using voluntary contractions. Clinical Science 76, 637-641.

Bruce, S.A., Newton, D., Woledge, R.C. (1989b). Effect of age on voluntary force and cross-sectional area of human adductor pollicis muscle. Quarterly Journal of Experimental Physiology 74, 359-362.

Bruce, S.A., Johnson, S., Phillips, S.K., Woledge, R.C. (1992a). Prediction of the length force relation of adductor pollicis from its internal structure. In "Third Vienna Muscle Symposium." (G. Freilinger, M. Deutinger, Eds.). Blackwell-MZV, Vienna.

Bruce, S.A., Phillips, S.K., Woledge, R.C. (1992b). Strength and cross-sectional area of adductor pollicis muscle in men and women. Journal of Physiology (London) 446, 226P.

Burke, R.E., Levine, D.N., Tsairis, P., Zajac, F.E. (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. Journal of Physiology (London) 234, 723-748.

Burr, M.L., Phillips, K.M. (1984). Anthropometric norms in the elderly. British Journal of Nutrition 51, 165-169.

Caccia, M.R., Harris, J.B., Johnson, M.A. (1979). Morphology and physiology of skeletal muscle in aging rodents. Muscle and Nerve 2, 202-212.

Campbell, C.B., Marsh, D.R., Spriet, L.L. (1991). Anaerobic energy provision in aged skeletal muscle during tetanic stimulation. Journal of Applied Physiology 70, 1787-1795.

Campbell, M.J., McComas, A.J., Petito, F. (1973). Physiological changes in ageing muscles. Journal of neurology, Neurosurgery, and Psychiatry 36, 174-182.

Carlson, F.D., Wilkie, D.R. (1974). "Muscle Physiology." Prentice-Hall, Englewood Cliffs, New Jersey.

Cartee, G.D., Farrar, R.P. (1987). Muscle respiratory capacity and VO_{2max} in identically trained young and old rats. Journal of Applied Physiology. 63, 257-263.

Cauley, J.A., Petrini, A.M., LaPorte, R.E., Sandler, R.B., Bayles, C.M., Robertson, R.J., Slemenda, C.W. (1987). The decline of grip strength in the menopause: relationship to physical activity, estrogen use and anthropometric factors. Journal of Chronic Diseases 40, 115-120.

Chan, S.T.F., McLaughlin, S.J., Ponting, G.A., Biglin, J., Dudley, H.A.F. (1986) Muscle power after glucose-potassium loading in under-nourished patients. British Medical Journal 293, 1055-1056.

Chapman, S.J., Grindrod, S.R., Jones, D.A. (1984). Cross-sectional area and force production of the quadriceps muscle. Journal of Physiology (London) 353, 53P.

Clarkson, P.M., Dedrick, M.E. (1988). Exercise muscle induced damage, repair and adaptation in old and young subjects. Journal of Gerontology: Medical sciences 43, M91-96

Clarkson, P.M., Kroll, W., Melchionda, A.M., (1981). Age, isometric strength, rate of tension development and fiber type composition. Journal of Gerontology 36, 648-653.

Cooper, C., (1989). Bone mass, muscle function and fracture of the proximal femur. British Journal of Hospital Medicine 42, 277-280.

Costell, M., O'Connor, J.E., Grisolia, S. (1989). Age dependent decrease in carnitine content in muscle of mice and humans. Biochemical and Biophysical Research Communications 161, 1135-1143.

Cueno, R.C., Salomon, F., Wiles, C.M., Hesp, R., Sonksen, P.H. (1981). Growth hormone treatment in growth-hormone-deficient adults I. Effects on muscle mass and strength. Journal of Applied Physiology 70, 688-694.

Curtin, N.A. (1990). Force during stretch and shortening of frog sartorius: Effects of intracellular acidification due to increased carbon dioxide. Journal of Muscle Research and Cell Motility 11, 251-257.

Curtin, N.A., Davies, R.E. (1975). Very high tension with very little ATP breakdown by active skeletal muscle. Journal of Mechanochemistry and Cell Motility 3, 147-154.

Curtin, N.A., Edman, K.A.P. (1989). Effects of fatigue and reduced intracellular pH on segment dynamics in "isometric" relaxation of frog muscle fibres. Journal of Physiology (London) 413, 159-174.

Dahlberg, E. (1982). Characterisation of the cytosolic estrogen receptor in rat skeletal muscle. Biochemica et Biophysica Acta 717, 65-75.

Daniel, P.M., Pratt, O.E., Spargo, E. (1977). The metabolic homeostatic role of muscle and its function as a store of protein. Lancet ii, 446-448.

Daut, J. (1987). The living cell as an energy-transduction machine. A minimal model of myocardial metabolism. Biochemica et Biophysica Acta 895, 41-62.

Daut, J., Elzinga, G. (1989). Substrate dependence of energy metabolism in isolated guinea-pig cardiac muscle: a microcalorimetric study. Journal of Physiology (London) 413, 379-397.

Davies, C.T.M., White, M.J. (1982). Muscle weakness following dynamic exercise in humans. Journal of Applied Physiology 53,236-241.

Davies, C.T.M., White, M.J. (1983). Contractile properties of elderly human triceps surae. Gerontology 29, 19-25.

Davies, C.T.M., Thomas, D.O., White, M.J. (1986). Mechanical properties of young and elderly human muscles . Acta Medica Scandinavica Suppl. 711, 219-226.

Davies, C.T.M., White, M.J., Young, K. (1983). Muscle function in children. European Journal of Applied Physiology 52, 111-114.

Davies, I., (1983) " Ageing." Arnold, London.

Dawson, M.J., Gadian, D.G., Wilkie, D.R. (1978). Muscular fatigue investigated by phosphorus nuclear magnetic resonance. Nature (London) 274, 861-866.

Dawson, M.J., Gadian, D.G., Wilkie, D.R., (1980). Mechanical relaxation rate and metabolism studied in fatiguing muscle by phosphorus nuclear magnetic resonance. Journal of Physiology (London) 299, 465-484.

Denham, M.J., Crawley, J.C.W., Hodkinson, H.M., Smith, D.C. (1980). Cerebral blood flow and motor nerve conduction velocity in the elderly. "In the Ageing Brain: Neurobiological and mental disturbances." (G. Barbagallo-Sangiorgi, A.N.Exton Smith, Eds.). Plenum, New York.

Denham, M.J., Hodkinson, H.M., Qureshi, K.M. (1973). Loss of grip in the elderly. Gerontologia Clinica 15, 268-271.

Duchenne, G-B.A. (1862). "Mechanisme de la Physionomie Humaine." Jules Renouard, Paris. (English translation, R.A.Cuthbertson (1990). Cambridge University Press, New York.)

Eddinger, T.J., Cassens, R.G., Moss, R.L. (1986). Mechanical and histochemical characterisation of skeletal muscles from senescent rats. American Journal of Physiology 251 (Cell Physiol. 20), C421-C430.

Eddinger, T.J., Moss, R.L. (1987). Mechanical properties of skinned single fibres of identified type from rat diaphragm. American Journal of Physiology 253, C210-218.

Edman, K.A.P., Hwang, J.A.C. (1977). The force velocity relation in vertebrate muscle fibres at varied tonicity of the extracellular medium. Journal of Physiology (London) 269, 255-272.

Edman, K.A.P., Elzinga, G., Noble, M.I.M. (1978). Enhancement of mechanical performance by stretch during titanic contractions of vertebrate skeletal fibres. Journal of Physiology (London) 281, 139-155.

Editorial (1991). Intensive care for the elderly. Lancet 33, 209 -210.

Edström, L., Larsson, L. (1987). Effects of age on contractile and enzyme-histochemical properties of fast and slow-twitch single motor units in the rat. Journal of Physiology (London) 392, 129-149.

Edwards, R.H.T. (1978). Physiological analysis of skeletal muscle weakness and fatigue. Clinical Science and Molecular Medicine 54, 463-470.

Edwards, R.H.T., Hill, D.K., Jones, D.A. (1975). Metabolic changes associated with the slowing of relaxation in fatigued mice muscle. Journal of Physiology (London) 251, 287-301.

Edwards, R.H.T., Young, A., Hoskin, G.P., Jones, D.A. (1977). Human skeletal muscle function: description of tests and normal values. Clinical Science and Molecular Medicine 52, 283-290.

Elzinga, G., Stienen, G.J.M., Versteeg, P.G.A. (1989). Effect of inorganic phosphate on length responses to changes in load in skinned rabbit psoas muscle. Journal of Physiology (London) 415, 132P.

Ermini, M. (1976). Ageing changes in mammalian skeletal muscle. Gerontology 22, 301-316.

Essén-Gustavsson, B., Borges, O. (1986). Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiologica Scandinavica 126, 107-114.

Faulkner, J.A., Brooks, S.V., Zerba, E. (1991). Skeletal muscle weakness and fatigue in old age: underlying mechanisms. In "Annual Review of Gerontology and Geriatrics, vol.10, 1990." (V.J.Cristofalo, Ed.) pp.147-146 Springer, New York.

Fitts, R.H., Troup, J.P., Witzmann, F.A., Holloszy, J.O. (1984). The effect of ageing and exercise on skeletal muscle function. Mechanisms of Ageing and Development 27, 161-172.

Flitney, F.W., Jones, D.A. (1990). The effects of stretch on force production in fresh and fatigued skeletal muscle. Journal of Muscle Research and Cell Motility 11, 75-76.

Florini, J.R. (1987). Hormonal control of muscle growth. Muscle and Nerve 10, 577-598.

Florini, J.R., Ewton, D.Z. (1989). Skeletal muscle fibre types and myosin ATPase do not change with age or growth hormone administration. Journal of Gerontology: Biological Sciences 44, B110-117.

Flynn, M.A., Nolph, G.B., Baker, A.S., Martin, W.M., Krause, G. (1989). Total body potassium in humans: a longitudinal study. American Journal of Clinical Nutrition 50, 713-717.

Forse, R.A., Shizgal, H.M. (1980). The assessment of malnutrition. Surgery 88, 17-24.

Forsberg, A.M., Nilsson, E., Wernemam, J., Bergstrom, J., Hultman, E. (1991). Muscle composition in relation to age and sex. Clinical Science 81, 249-246.

Greaser, M.L., Moss, R.L., Reiser, P.J. (1988). Variations in contractile properties of rabbit single muscle fibres in relation to troponin T isoforms and myosin light chains. Journal of Physiology (London) 406, 85-98.

Greig, C.A., Young, A. (1991). Changes in human knee extensor strength in old age: a longitudinal study. Journal of Physiology (London) 438, 199P.

Grimby, G., Aniansson, A., Zetterberg, C., Saltin, B. (1984). Is there a change in relative muscle fibre composition with age? Clinical Physiology 4, 189-194.

Grimby, G., Danneskiold-Samsoe, B., Hvid, K., Saltin, B. (1982). Morphology and enzyme capacity in arm and leg muscles in 78 - 81 year old men and women. Acta Physiologica Scandinavica 115,125-134.

Grimby, G. Saltin, B. (1983). The ageing muscle. Clinical Physiology 3, 209-218.

Grindrod, S., Round, J.M., Rutherford, O.M. (1987). Type 2 fibre composition and force per cross-sectional area of the human quadriceps. Journal of Physiology (London) 390, 154P.

Gutmann, E., Hanzlíková, V. (1966). Motor unit in old age. Nature (London) 209, 921-922.

Gutmann, E., Hanzlíková, V. (1976). Fast and slow motor units in ageing. Gerontology 22, 280-300.

Harris, R., Hultman, E., Nordesjo, L-O. (1974). Glycogen glycolytic intermediates and high-energy phosphates in biopsy samples of m. quadriceps femoris of man at rest. Methods and variance of values. Scandinavian Journal of Clinical and Laboratory Investigation 33, 109-113.

Hardy, R.N. (1982). " Homeostasis." Arnold, London.

Haxton, H.A. (1944). Absolute muscle force in ankle flexors of man. Journal of Physiology, (London) 103, 267-273.

Hill, A.V. (1964). The effect of load on the heat of shortening muscle. Proceedings of The Royal Society of London, Series B 159, 297-318.

Hill, T.L. (1977). "Free energy transduction in biology." Academic Press, New York.

Hopper, A.C.B. (1981). Length, diameter and number of ageing skeletal muscle fibres. Gerontology 27, 121-126.

Holloszy, J.O., Chen, M., Cartee, G.D., Young, J.C. (1991). Skeletal muscle atrophy in old rats: differential changes in three fibre types. Mechanisms of Ageing and Development 60, 199-213.

Hunt, D.R., Rowlands, B.J., Johnston, D. (1985). Hand grip strength - a simple prognostic indicator in surgical patients. Journal of Parenteral and Enteral Nutrition 9, 701-704.

Huxley, A.F. (1957). Muscle structure and theories of contraction. Progress in Biophysics and Biophysical Chemistry 7, 255-318.

Huxley, A.F. (1973). A note suggesting that the cross-bridge attachment during muscle contraction may take place in two stages. Proceeding of The Royal Society of London, Series B 183, 83-86.

Huxley, A.F. (1980). "Reflections on muscle." Liverpool University Press, Liverpool.

Huxley, A.F., Simmons, R.M. (1971). Proposed mechanism of force generation in striated muscle. Nature (London) 233, 533-538.

Huxley, A.F., Simmons, R.M. (1973). Mechanical transients in the original of muscular force. Cold Spring Harbour Symposium on quantitative Biology 37, 669-680.

Hyatt, R.H., Whitelaw, M.N., Bhat, A., Scott, S., Maxwell, J.D. (1990). Association of muscle strength with functional status of elderly people. Age and Ageing 19, 330-336.

Ihemelandu, E.C. (1980). Decrease in fibre numbers of dog pectineus muscle with age. Journal of Anatomy 130, 69-73.

Inokuchi, S., Ishikawa, H., Iwamoto, S., Kimura, T. (1975). Age related changes in the histological composition of the rectus abdominis muscle of the adult human. Human Biology 47, 231-249.

Jennekens F.G.I., Tomlinson, B.E., Walton, J.N. (1971). Histochemical aspects of five limb muscles in old age: an autopsy study. Journal of the Neurological Sciences 14, 259-276.

Jiang, Z-M., He, G-Z., Zhang, S-Y., Wang, X-R., Yang, N-F., Zhu, Y., Wilmore, D.W. (1989). Low dose growth hormone and hypocaloric nutrition attenuate the protein-catabolic response after major operation. Annals of Surgery 210, 513-524.

Johnson, M.A., Polgar, J., Weightman, D., Appleton, D. (1973). Data on the distribution of fibre types in thirty-six human muscles: an autopsy study. Journal of the Neurological Sciences 18, 111-129.

Jones, D.A., Round, J.M. (1990). "Skeletal muscle in health and disease." Manchester University Press, Manchester.

Jones, D.A., Rutherford, O.M. (1990). Effect of ageing and osteoporosis on the force-generating capacity of the quadriceps muscle in women. Journal of Physiology (London) 423, 84P.

Jones, P.R.M., Pearson, J. (1969). Anthropometric determination of leg fat and muscle plus bone volumes in young male and female adults. Journal of Physiology (London) 204, 63P-66P.

Julian, F.J., Morgan, D.L. (1979). The effect on tension of non-uniform distribution of length changes applied to frog muscle fibres. Journal of Physiology (London) 293, 379-392.

Kallman, D.A., Plato C.C., Tobin, J.D. (1990). The role of muscle loss in the age-related decline of grip strength: Cross-sectional and longitudinal perspectives. Journal of Gerontology: Medical Sciences 45, M82-88.

Kanda, K., Hashizume, K. (1989). Changes in properties of the medial gastrocnemius motor units in aging rats. Journal of Neurophysiology 61, 737-746.

Katz, B. (1939). The relation between force and speed in muscular contraction. Journal of Physiology (London) 96, 45-64.

Kendall-Taylor, P., Turnball, D.M. (1983). Endocrine myopathies. British Medical Journal 287, 705-708.

Kentish, J.C., (1986). The effects of inorganic phosphate and creatine phosphate on force production in skinned muscle fibres from rat ventricle. Journal of Physiology (London). 370, 585-604.

Klidjian, A.M., Foster, K.J., Kammerling, R.M., Cooper, A., Karran, S.J. (1980). Relation of the anthropometric and dynamometric variables to serious postoperative complications. British Medical Journal 281, 899-901.

Klitgaard, H., Marc, R., Brunet, A., Vandewalle, H., Monod, H. (1989). Contractile properties of old rat muscles: effect of increased use. Journal of Applied Physiology 67, 1401-1408.

Klitgaard, H., Mantoni, M., Schiaffino, S., Ausoni, S., Gorza, L., Laurient-Winter, C., Schnohr, P., Saltin, B. (1990). Function, morphology and protein expression of ageing skeletal muscle: a-cross sectional study of elderly men with different training backgrounds. Acta Physiologica Scandinavica 140, 41-54.

Lannergren, J., Anders, A. (1992). Relaxation rate of intact striated muscle fibres after flash photolysis of a caged calcium chelator (diazo-2). Journal of Muscle Research and Cell Motility 13, 630-634.

Larsson, L. (1978). Morphological and functional characteristics of the ageing skeletal muscle in man. A cross-sectional study. Acta Physiologica Scandinavica Suppl. 457, 1-36.

Larsson, L. (1982). Aging in mammalian skeletal muscle. In "The Aging Motor System" (J.A. Mortimor, F.J. Pirozzolo, G.J. Maletta, Eds.) pp. 60-97. Praeger, New York.

Larsson, L., Edström, L. (1986). Effects of age on enzyme-histochemical fibre spectra and contractile properties of fast and slow-twitch skeletal muscles in the rat. Journal of the Neurological Sciences 76, 69-89.

Larsson, L., Grimby, G., Karlsson, J. (1979). Muscle strength and speed of movement in relation to age and muscle morphology. Journal of Applied Physiology, Respiratory Environmental and Exercise Physiology, 46, 451-456.

Larsson, L., Sjodon, B., Karlsson, J. (1978). Histochemical and biochemical changes in human skeletal muscle with age in sedentary males aged 22-65 years. Acta Physiologica Scandinavica 103, 31-39.

Larsson, L., Ansved, T., Edstrom, L., Gorza, L., Schiaffino, S. (1991). Effects of age on physiological, immunohistochemical and biochemical properties of fast -twitch single motor units in the rat. Journal of Physiology (London) 446, 257-275.

Layzer, R.B. (1991). How muscles use fuel. New England Journal of Medicine 324, 411-412.

Lennmarken, C., Sondstedt, S., von Schenk, H., Larsson, J. (1986a). Effect of starvation on skeletal muscle function in man. Clinical Nutrition 5, 99-103.

Lennmarken, C., Sondstedt, S., von Schenk, H., Larsson, J. (1986b). Skeletal muscle function and metabolism in obese women. Journal of Parenteral and Enteral Nutrition 10, 583-587.

Lexell, J., Taylor, C.C., Sjostrom, M. (1988). What is the cause of ageing atrophy? Total number, size and proportion of different fibre types studied in whole vastus lateralis muscle from 15-83 year old men. Journal of the Neurological Sciences 84, 275-294.

Lombardi, V., Piazzesi, G. (1990). The contractile response during steady lengthening of stimulated frog muscle fibres. Journal of Physiology (London). 431, 141-171.

Lopes, J., Russell, D., McR., Whitwell, J., Jeejeebhoy, K.N. (1982). Skeletal muscle function in malnutrition. American Journal of Clinical Nutrition 36, 602-610.

McCarter, R., McGee, J. (1987). Influence of nutrition and ageing on the composition and function of rat skeletal. Journal of Gerontology 42, 432-441.

McComas, A.J., Kereshi, S., Quinlan, J. (1983). A method for detecting muscle weakness. Journal of Neurology, Neurosurgery and Psychiatry 46, 280-282.

McCullagh, P., Maughan, R.J., Watson, J.S., Weir, J. (1984). Biomechanical analysis of the knee in relation to measured quadriceps strength and cross sectional area in man. Journal of Physiology (London) 346, 60P.

McDonagh, M.J.N., White, M.J., Davies, C.T.M. (1984). Different effects of ageing on the mechanical properties of human arm and leg muscles. Gerontology 30, 49-54.

MacLennan, W.J., Hall, M.R.P., Timothy, J.I., Robinson, M. (1980). Is weakness in old age due to muscle wasting? Age and ageing 9, 188-192.

Månsson, A. (1989). Changes in force and stiffness during stretch of skeletal muscle fibres, effects of hypertonicity. Biophysics Journal, 56, 429-433.

Marini, J.J. (1991). Weaning from mechanical ventilation. New England Journal of Medicine 324, 1496-1498.

Martin, F.C., Peters, T.J. (1985). Assessment in vitro and in vivo of muscle degradation in chronic skeletal muscle myopathy of alcoholism. Clinical Science 68, 693-700.

Maughan, R.J., Nimmo, M.A. (1984). The influence of variations in muscle fibre composition on muscle strength and cross sectional area in untrained males. Journal of Physiology (London) 351, 299-311.

Maughan, R.J., Watson, J.S., Weir, J. (1983). Strength and cross sectional area of human skeletal muscle. Journal of Physiology (London) 338, 37-49.

Max, S.R. (1984). Androgen-estrogen synergy in rat levator ani muscle: glucose-6-phosphate dehydrogenase. Molecular and Cellular Endocrinology 38, 103-107.

Max, S.R., Toop, J. (1983). Androgens enhance in vivo 2-deoxyglucose uptake by rat striated muscle. Endocrinology 113, 119-126.

Maxwell, J.D., Hodt, P., Taylor, W.H. (1984). A portable chair for testing isometric muscle strength. Lancet i, 18-19.

Maxwell, L.C., Faulkner, J.A., Hyatt, G.J. (1974). Estimation of number of fibres in guinea pig skeletal muscles. Journal of Applied Physiology 37, 259-264.

Melton, L.J., Riggs, B.L. (1985). Risk factors for injury after a fall. Clinics in Geriatric Medicine, 1, 525-539.

Merton, P.A. (1954). Voluntary strength and fatigue. Journal of Physiology (London) 123, 553-564.

Meyer, H.H., Rapp, M. (1985). Estrogen receptors in bovine skeletal muscle. Journal of Animal Science 60, 294-300.

Meyer, R.A., Brown, T.R., Kushmerck, M.J. (1985). Phosphorus nuclear magnetic resonance of fast and slow-twitch muscle. American Journal of Physiology 248 (Cell Physiology 17) C279-C287.

Milne, J.S., Maule, M.M. (1984). A longitudinal study of hand grip and dementia in older people. Age and Ageing 13, 42-48.

Möller, P., Bergström, J., Fürst, P., Hellström, K. (1980). Effect on ageing on energy rich phosphogens in human skeletal muscles. Clinical Science 58, 553-555.

Moritani, T., de Vries, H.A. (1980). Potential for gross muscle hypertrophy in older men. Journal of Gerontology 35, 672-682.

Moxham, J., Morris, A.J.R., Sprio, S.G., Edwards, R.H.T., Green, M. (1981). Contractile properties and fatigue of the diaphragm in man. Thorax 36, 164-168.

Müller-Höcker, J. (1990) Cytochrome *c* oxidase deficient fibres in the limb muscle and diaphragm of man without muscular disease: an age-related alteration. Journal of the Neurological Sciences 100, 14-21.

Murry, M.P., Gardner, G.M., Mollinger, L.A., Sepic, S.B. (1980). Strength of isometric contractions. Knee muscles of men aged 20-26. Physical therapy 60, 412-419.

Murry, M.P., Duthie, E.H., Gambert, S.R., Sepic, S.B., Mollinger, L.A. (1985). Age related differences in knee muscle strength in normal women. Journal of Gerontology 40, 275-280.

Narici, M.V., Bordini M., Cerretelli, P. (1991). Effects of ageing on human adductor pollicis muscle function. Journal of Applied Physiology 71, 1277-1281.

Newham, D.J. (1986). Nutritional status and skeletal muscle contractility. British Journal of Parenteral Therapy 7, 93-96.

Newham, D.J., Tomkins, A.M., Clark, C.G. (1986). Contractile properties of the adductor pollicis in obese patients on a hypocaloric diet for two weeks. American Journal of Clinical Nutrition 44, 756-760.

Newsholme, E.A., Leech, A.R. (1984). "Biochemistry for the Medical Sciences". Wiley, Chichester.

Newton, J.P., Yemm, R. (1986). Changes in the contractile properties of the human first dorsal interosseous muscle with age. Gerontology 32, 98-104.

Newton, J.P., Yemm, R., McDonagh, M.J.N. (1988). Study of age changes in the motor units of the first dorsal interosseous muscle in man. Gerontology 34, 115-119.

Nosek, T.M., Fender, K.Y., Godt, R.E. (1987). It is dipronated inorganic phosphate that depresses force in skinned skeletal muscle fibres. Science 236, 191-193.

Novak, L.P. (1972). Aging, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. Journal of Gerontology 27, 438-443.

Örlander, J., Kiessling, K-H., Larsson, L., Karlsson, J., Aniansson, A. (1978). Skeletal muscle metabolism and ultrastructure in relation to age in sedentary men. Acta Physiologica Scandinavica 104, 249-261.

Pate, E., Cooke, R. (1989). A model of cross bridge action: the effects of ATP, ADP, and Pi. Journal of Muscle Research and Cell Motility 10, 181-196.

Patrick, J.M., Bassey, E.J., Fentem, P.H. (1982). Changes in body fat and muscle in manual workers at and after retirement. European Journal of Applied Physiology 49, 187-196.

Paz, O. (1989). "The Monkey Grammarian", (H.R. Lane, Trans.) Peter Owen, London.

Pearson, M..B. Bassey, E.J., Bendall, M.J. (1985a). Muscle strength and anthropometric indices in elderly men and women. Age and Ageing 14, 49-54.

Pearson, M.B., Bassey, E.J., Bendall, M.J. (1985b). The effects of age on muscle strength and anthropometric indices within a group of elderly men an women. Age and Ageing 14, 230-234.

Phillips, P. (1986). Grip strength, mental performance and nutritional status as indictors of mortality risk among female geriatric patients. Age and Ageing 15, 53-56.

Phillips, S.K., Bruce, S.A., Woledge, R.C. (1991). In mice, the muscle weakness due to age is absent during stretching. Journal of Physiology (London) 437, 63-70.

Phillips, S.K., Bruce, S.A., Newton, D., Woledge, R.C. (1992). The weakness of old age is not due to failure of activation. Journal of Gerontology: Medical Sciences 47, M45-M49.

Phillips, S.K., Woledge, R.C. (1992). A comparison of isometric force, maximum power and isometric heat rate as a function of sarcomere length in mouse skeletal muscle. Pflugers Archiv 420, 578-583.

Phillips, S.K., Rook, K.M., Siddle, N.C., Bruce, S.A., Woledge, R.C. (1993a). Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clinical Science 84, 95-98.

Phillips, S.K., Wiseman, R.W., Woledge, R.C., Kushmerck, M.J. (1993b). The effects of metabolic fuel on force production and resting inorganic phosphate levels in mouse skeletal muscle. Journal of Physiology (London) 462, 135-146.

Phillips, S.K., Wiseman, R.W., Woledge, R.C., Kushmerck, M.J. (1993c). Neither changes in phosphorus metabolite levels, nor myosin isoforms can explain the weakness in aged mouse muscle. Journal of Physiology (London) 463, 157-167.

Phillips, S.K., Gopinathan, J., Meehan, K., Bruce, S.A., Woledge, R.C. (1993d). Muscle strength changes during the menstrual cycle in human adductor pollicis. Journal of Physiology (London), *in press.*

Puah, H.A., Bailey, C.J. (1985). Effect of ovarian hormones on glucose metabolism in mouse soleus muscle. Endocrinology 117, 1336-1340.

Quetelet, A. (1842). "A Treatise on Man and the Development of his Faculties." Chambers, Edinburgh.

Rance, N.E., Max, S.R. (1984). Modulation of the cytosolic androgen receptor in striated muscle by sex steroids. Endocrinology 115, 862-866.

Rejs, J.H.O. (1921). Uber die veranderung der kraft wahrend der bewegung. Pflugers Archiv 191, 234-257.

Riggs, B.L., Melton, L.J. (1992). The prevention and treatment of osteoporosis. New England Journal of Medicine 320, 620-627.

Ross, R.J.M., Buchanan, C.R. (1990). Growth hormone secretion: its regulation and the influence of nutritional factors. Nutritional Research Reviews 3, 143-162.

Ross, R.J.M., Miell, J.P., Buchanan, C.R. (1991). Avoiding autocannibalism. British Medical Journal 303, 1147-1148.

Rubinstein, L.J. (1960). Aging changes in muscle. In "Structure and Function of Muscle" (G. H. Bourne, Ed.), volume 2 pp 209-226. Academic Press, New York.

Rudman, D., Feller, A.G., Nagraj, H.S., Gergans, G.A., Lalitha, P.Y., Goldberg, A.F., Schleneker, R.A., Cohn, L., Rudman, I.W., Matteson, D.E. (1990). Effects of human growth hormone in men over 60 years old. New England Journal of Medicine 323, 1-6.

Rüegg, J.C. (1986). "Calcium in Muscle Activation - a Comparative Approach." Springer, Berlin.

Russell, D. McR., Leiter, L.A., Whitwell, J., Marliss, E.B., Jeejeebhoy, K.N. (1983a). Skeletal muscle function during hypocaloric diets and fasting: a comparison with standard nutritional assessment parameters. American Journal of Clinical Nutrition 37, 133-138.

Russell, D.McR., Prendergast, P.J., Darby, P.L., Garfinkel, P.E., Whitwell, J., Jeejeebhoy, K.N. (1983b). A comparison between muscle function and body composition in anorexia nervosa: the effect of refeeding. American Journal of Clinical Nutrition 38, 229-237.

Russell, D. McR., Walker, P.M., Leiter, L.A., Sima, A.A.F., Tanner, W.K., Mickle, D.A.J., Whitwell, J., Marliss, E.B., Jeejeebhoy, K.N. (1984a). Metabolic and structural changes in skeletal muscle during hypocaloric dieting. American Journal of Clinical Nutrition 39, 503-513.

Russell, D.McR., Atwood, H.L., Whittaker, J.S., Itakura, T., Walker, P.M., Mickle, D.A.J., Jeejeebhoy, K.N. (1984b). The effect of fasting and hypocaloric diets on the functional and metabolic characteristics of rat gastrocnemius muscle. Clinical Science 67, 185-194.

Rutherford, O.M., Jones, D.A., Newham, D.J. (1986). Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. Journal of Neurology, Neurosurgery and Psychiatry 49, 1288-1291.

Rutherford, O.M., Jones, D.A. (1992). The relationship of muscle and bone loss and activity levels with age in women. Age and Ageing 21, 286-293.

Scelsi, R., Marchetti, C., Poggi, P. (1980). Histochemical and ultrastructural aspects of m.vastus lateralis in sedentary old people (age 65 - 89 years). Acta Neuropathologica 51, 99-105.

Shafiq, S.A., Lewis, S.G., Dimino, L.C., Schuttea, H.S. (1978). Electron microscopic study of skeletal muscle in elderly subjects. In "Aging Vol.6 - Aging in Muscle." (G. Kalder, W.J. DiBattista, Eds.). Raven Press, New York.

Shaunak, S., Ang, L., Colston, K., Patel, S., Bland, M., Maxwell, J.D. (1987). Muscle strength in healthy, white and Asian subjects. Clinical Science 73, 541-546.

Shephard, R.J. (1969). "Endurance Fitness." pp 107-108. University of Toronto Press, Toronto.

Shizgal, H.M., Vasilevsky, C.A., Gardiner, P.F., Wang, W., Tuitt, D.A.Q., Branbent, G.V. (1986). Nutritional assessment and skeletal muscle function. American Journal of Clinical Nutrition 44, 761-771.

Sica, R.E.P., McComas, A.J. (1971). Fast and slow twitch units in a human muscle. Journal of Neurology, Neurosurgery and Psychiatry 34, 113-120.

Sica, R.E.P., Sanz, O.P., Colombi, A. (1976). The effects of ageing upon the human soleus muscle. Medicina (Buenos Aires) 36, 443-446.

Sinaki, M., McPhee, M.C., Hodgson, S.F., Merritt, J.M., Offord, K.P. (1986). Relationship between bone mineral density of the spine and strength of back extensors in healthy post menopausal women. Mayo Clinic Proceedings 61, 116-122.

Skelton, D.A., Young, A. (1993). Are the National Fitness Survey strength and power thresholds for performance of everyday tasks too high? Journal of Physiology (London). *In press.*

Smith, P., Heimer, G., Norgren, A., Ulmsten, U. (1990). Steroid hormone receptors in pelvic muscles and ligaments in women. Gynecologic and Obstetric Investigation (Basel) 30, 27-30.

Snedecor, G.W., Cochran, W.G. (1976). "Statistical Methods." (6th edition) The Iowa State University Press.

Stalberg, E., Borges, O., Ericsson, M., Essén-Gustavsson, B., Fawcett, P.R.W., Nordejo, L.O., Nordgon, B., Uhlin, R. (1989). The quadriceps femoris muscle in 20 - 77 year old subjects: relationship between knee extension torque, electrophysiological parameters, and muscle fibre characteristics. Muscle and Nerve 12, 382-389.

Steen, B., Bruce, A., Isaksson, B., Levin, T., Svanborg, A. (1977). Body composition in 70 year old males and females in Gothenberg, Sweden. A Population Study. Acta Medica Scandinavica Suppl. 611, 87-112.

Stevens, W. (1953). Final Soliloquy of the Interior Paramour. In "Selected Poems." Faber and Faber, London.

Stokes, M.J., Cooper, R.G., Edwards, R.H.T. (1988). Normal muscle strength and fatigability in patients with effort syndromes. British Medical Journal 297, 1014-1017.

Tanner, J.M. (1942). Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. Journal of Applied Physiology 2, 1-15.

Taylor, D.J., Crowe, M., Bore, P.J., Styles, P., Arnold, D.L., Radda, G.K. (1984). Examination of the energetics of ageing skeletal muscle using nuclear magnetic resonance. Gerontology 30, 2-7.

Tomlinson, B.E., Irving, D. (1977). The numbers of limb motor neurons in the human lumbosacral cord throughout life. Journal of the Neurological Sciences 34, 213-219.

Tomonaga, M. (1977). Histochemical and ultrastructural changes in senile human skeletal muscle. Journal of the American Geriatrics Society 25, 125-131.

Trounce, I., Byrne, E., Marzuki, S. (1989). Decline in skeletal muscle mitochondrial respiratory chain function: possible factor in ageing. Lancet ii, 637-639.

Tzanhoff, S.P., Norris, A.H. (1977). The effect of muscle mass and decrease on age-related BMR changes. Journal of Applied Physiology 43, 1001-1006.

Ufland, J.M. (1933). Einfluss des Lebensalters, Geschlechts, der Konstitution und des Berufs auf die Kraft ver schiedener Muskelgruppen. Arbeitsphysiologie 6, 653-663.

Ulmer, H-V. (1989). Energy Balance. In "Human Physiology." (R.F. Schmidt, G. Thews, Eds.) pp 618-619. Springer, Berlin.

Vandervoort, A.A., McComas, A.J. (1986). Contractile changes in opposing muscles of the human ankle joint with aging. Journal of Applied Physiology 61, 361-367.

Vandervoort, A.A., Kramer, J.F., Wharram, E.R. (1990). Eccentric knee strength of elderly females. Journal of Gerontology 45, B125-128.

Vaughan, L., Zurlo, F., Ravussin, E. (1991). Aging and Energy Expenditure. American Journal of Clinical Nutrition 53, 821-825.

Vermeulen, A. (1991). Clinical Review 24: Androgens in the aging male. Journal of Clinical Endocrinology and Metabolism 73, 221-224.

Westerblad, H., Allen, D.G. (1991). Changes of myoplasmic calcium concentration during fatigue in single mouse muscle fibres. Journal of General Physiology 98, 615-635.

Westerblad, H., Lee, J.A., Lannergren, J., Allen, D.G. (1991). Cellular mechanisms of fatigue in skeletal muscle. American Journal of Physiology 261, (Cell Physiol.30), C195 - C209).

Wickham, C.A.C., Walsh, K., Cooper, C., Barker, D.J.P., Margetts, B.M., Morris, J., Bruce, S.A. (1989). Dietary calcium, physical activity, and risk of hip fracture: a prospective study. British Medical Journal 299, 889-892.

Wiles, C.M., Young, A., Jones, D.A., Edwards, R.H.T. (1979). Relaxation rate of constituent muscle-fibre types in human quadriceps. Clinical Science 56, 47-52.

Winner, S.J., Morgan, C.J., Grimley-Evans, J. (1989). Perimenopausal risk of falling and incidents of distal fore arm fracture. British Medical Journal 298, 1486-1488.

Winter, E.M., Maughan, R.J. (1991). Strength and cross sectional area of the quadriceps in men and women. Journal of Physiology (London) 438, 175P.

Woledge, R.C., Curtin, N.A., Homsher, E. (1985). "Energetic Aspects of Muscle Contraction." Academic Press, London.

Young, A. (1984). The relative isometric strength of type I and type II muscle fibres in the human quadriceps. Clinical Physiology 4, 23-32.

Young, A. (1986). Exercise Physiology in geriatric practice. Acta Medica Scandinavica Suppl.711, 227-232.

Young, A., Edwards, R.H.T. (1977). Clinical investigation of muscle contractility. Rheumatology and Rehabilitation 16, 231-235.

Young, A., Stokes, M., Crowe, M. (1984). Size and strength of the quadriceps muscles of old and young women. European Journal of Clinical Investigation 14, 282-287.

Young, A., Stokes, M., Crowe, M (1985). The size and strength of the quadriceps muscles of old and young men. Clinical Physiology 5, 145-154.

Ziegler, T.R., Young, L.S., Manson, J.McK., Wilmore, D.W. (1988). Metabolic effects of recombinant human growth hormone in patients receiving parenteral nutrition. Annals of Surgery 208, 6-16.

[*From the Proceedings of the Physiological Society*, 8–9 *November* 1985
Journal of Physiology, 372, 9*P*, 1986]

Apparatus for measuring force of adduction of the thumb, and for measuring profiles of the hand in human subjects

By S. A. Bruce, S. K. Phillips and R. C. Woledge. *Department of Physiology, University College, Gower Street, London WC1*

Force is measured by a strain gauge bridge incorporating two wire gauges mounted on opposite sides of a brass ring. The force exerted by adduction of the thumb compresses this ring. The bridge circuit is compensated to render the bridge output insensitive to sideways forces applied to the ring. The ring is mounted in a brass rod, one end of which opposes thumb adduction at the base of the proximal phalanx. The other end is held in a Perspex hand splint so as to lie between the index and middle fingers. The splint prevents flexion of the fingers about the metacarpo-phalangeal joints, thus minimizing the contribution to the force recorded from the flexor muscles of the fingers. The flexor muscles of the thumb cannot contribute to the force because the points of attachment of their tendons are distal to the place at which force is recorded. Thus the force is due largely to the activity of the adductor pollicis, with a probable contribution from the first dorsal interosseus muscle.

The thickness of the hand was measured by the difference in the output of two linear potentiometers, the shafts of which were held by springs against the two surfaces of the hand. These potentiometers are held in a light frame which can be moved over the hand while its position is monitored by a third potentiometer. An X–Y plot of the thickness against the distance moved, as measured by the third potentiometer, is thus a profile of the hand. The signals were acquired on a digital oscilloscope (Nicolet 4094) with an X–Y mode. This oscilloscope was also used to integrate the areas of the profiles, with a view to estimating the cross-sectional areas of the muscles in the hand.

Some of the results obtained by these techniques will be communicated to the Society at this meeting (Bruce, Phillips & Woledge, 1985).

We wish to thank Dr J. Hutchinson for valuable assistance and advice. Financial support from Action Research for the Crippled Child and from the Medical Research Council is gratefully acknowledged.

REFERENCE

Bruce, S. A., Phillips, S. K. & Woledge, R. C. (1985). *J. Physiol.* **372**, 31*P*.

From

Volume 7 Special Supplement August 1988

Clinical Nutrition

P.12 THE EFFECT OF SUBNUTRITION ON VOLUNTARY MUSCLE FUNCTION TESTS. S.A. BRUCE, D. Newton, R.C. Woledge. Department of Medicine for the Elderly, Hastings and Department of Physiology, University College, London, United Kingdom.

It has been suggested that decline in muscle function in the absence of nerve and muscle diseases, may be a sensitive and specific indicator of subnutrition. A useful clinical measurement of muscle force should use voluntary rather than stimulated contractions and be related to cross-sectional-area (CSA) so that different subjects can be compared.

We have measured maximum voluntary contractions (MVC) of adductor pollicis muscle in eleven subnourished patients (age-rage 19-54, 6 males, 5 females) and related force to an anthropometric assessment of CSA of this muscle. We have compared the results with those obtained from 40 normally nourished subjects (age-range 19-53, 21 male, 19 female). The correlation between MVC and CSA ($r=0.91$) for the control subjects was stronger than that between grip-strength, measured with a hand-grip dynamometer, and arm muscle area, measured anthropometrically ($r=0.78$). The subnourished group though weak, did not differ from the controls ($p=0.2$) in respect of MVC/CSA. However, as previously reported with stimulated tests, relaxation rates were significantly slower in the subnourished patients ($p<0.001$) and it is suggested that this may be a simple bedside test which can be used to measure marginal subnutrition and follow the effectiveness of nutritional support.

Clinical Science (1989) 76, 637-641

Effect of subnutrition on normalized muscle force and relaxation rate in human subjects using voluntary contractions

S. A. BRUCE, D. NEWTON AND R. C. WOLEDGE

Department of Medicine for the Elderly, St Helen's Hospital, Hastings, Sussex, U.K., and Department of Physiology, University College London, London

(Received 29 June/17 October 1988; accepted 25 October 1988)

SUMMARY

1. Muscle weakness and wasting are well-known consequences of subnutrition, but there have been no published comparisons of these variables in a single muscle or muscle group. We report voluntary force measurements of adductor pollicis muscle in 11 subnourished patients normalized for their cross-sectional areas. We also report normalized relaxation rates of these contractions and the results are compared with those obtained in 40 healthy normally nourished subjects.

2. Normalized muscle force was no different in the subnourished group. However, relaxation rate was significantly slower than in the control group.

Key words: muscle function, normalized force, normalized relaxation rate, subnutrition.

Abbreviations: CAT, computer-assisted tomography; CSA, cross-sectional area; MRR, maximum relaxation rate; MVC, maximal voluntary contraction.

INTRODUCTION

Muscle wasting during periods of undernutrition is well recognized [1], but recently specific functional changes (abnormal force–frequency relationship, slow relaxation rate and increased fatiguability during a 30 s stimulated tetanus) have been described in the adductor pollicis muscles of patients who were chronically subnourished secondary to a variety of gastrointestinal disorders [2]. Subsequently, similar changes were described in obese patients after 2 weeks of a 1674 kJ diet followed by 2 weeks fasting [3], and it was claimed that the changes in muscle function were more sensitive indicators of nutritional status than standard assessment techniques. In the same study it was reported that these changes were reversed after 2 weeks refeeding [3], and this finding was confirmed in six severe anorexia nervosa patients [4]. On refeeding, the anorexic patients also showed improvement in maximal voluntary contractions (MVC) and maximal stimulated forces. In a subsequent study [5] improvement in muscle function with improved nutritional status was demonstrated without any significant change in muscle bulk as assessed by arm muscle area. This observation, and the speed of the observed changes, suggests that improvements in muscle function may precede recovery of bulk and therefore lead one to expect a different relationship between force and cross-sectional area (CSA) in normally nourished and in subnourished subjects. However, to date no direct comparison of these two variables for a single muscle or muscle group appears to have been attempted in subnourished patients.

We have therefore measured MVC and CSA of adductor pollicis of 11 subnourished patients and compared the results with those obtained from 40 normally nourished healthy subjects. We have also measured normalized relaxation rates after a brief MVC and fatigue during a MVC sustained for 30 s.

Correspondence: Dr S. A. Bruce, Department of Physiology, University College London, Gower Street, London WC1E 6BT.

METHODS

Subjects

Forty normally nourished healthy subjects (age range 17–53 years, mean 28 years, 21 male, 19 female) were selected from staff and students at University College London to give as wide a range as possible for height and frame size. Results for 20 of these subjects have been presented in a preliminary communication [6].

Eleven patients who were known to be chronically less than 90% of ideal body weight for height and frame size were tested (age range 19–54 years, mean 29 years, six

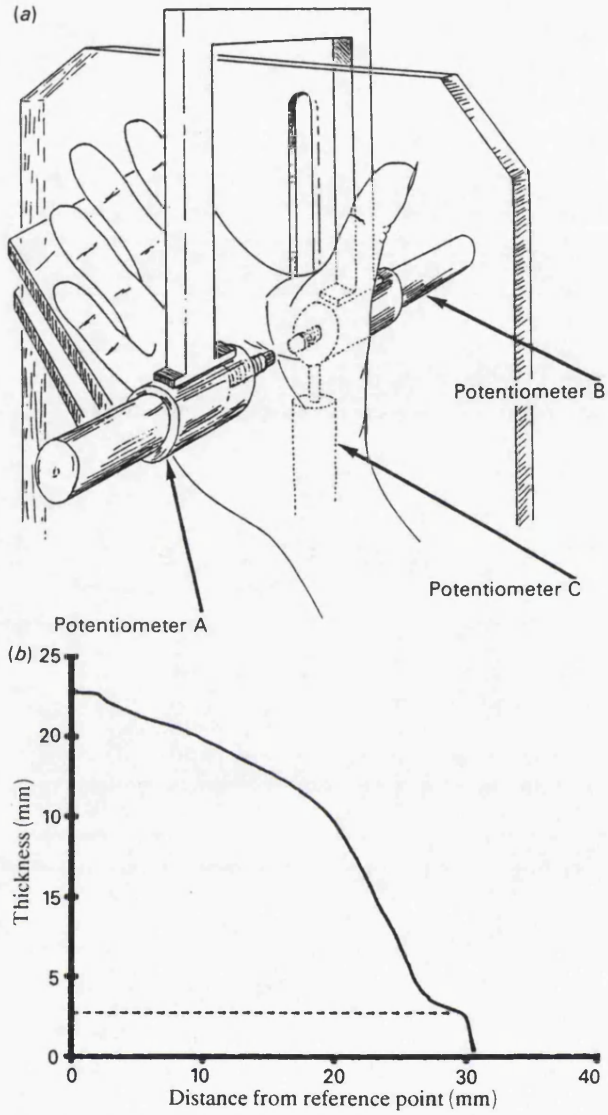


Fig. 1. (*a*) Apparatus for estimating CSA of adductor pollicis. Hand thickness was measured by the difference between the outputs of potentiometers A and B, and distance from the starting point (see the text) by the output of potentiometer C. The resulting X–Y plot is shown in (*b*). (*b*) Profile of the hand as measured by the apparatus shown in (*a*). The area above the broken line is taken to represent the CSA of adductor pollicis. The area below the broken line represents skin and subcutaneous fat.

males, five females). Eight of these had Crohn's disease, one had ulcerative colitis, one short-bowel syndrome and one pulmonary tuberculosis. At the time of testing their percentage ideal body weights ranged from 76.4 to 89% (mean 83.5%). Two of these patients were on steroids at the time they were tested. Patients with specific muscle diseases, osteomalacia or thyroid disease were excluded.

All subjects gave informed consent verbally and the project received approval from the ethical committees at University College London, Hastings Health Authority and Guy's Hospital.

Force measurement

MVC of the adductor pollicis was measured using a strain gauge bridge circuit. The gauge was mounted in the centre of a small brass plate which was seated in a brass cylinder. A rod, which opposed thumb adduction at the base of the proximal phalanx, ran down inside the cylinder and depressed the plate when force was applied. The system was insensitive to sideways forces applied to the cylinder. The other end of the cylinder was applied to a ballbearing mounted in a Perspex hand splint so as to lie between the index and middle fingers. The splint inhibited flexion of the fingers about the metacarpo-phalangeal joints. Contribution to the recorded force from the flexor muscles of the fingers was thus reduced though not completely eliminated. The point of opposition of adduction of the thumb was chosen because it is close to the attachment of the adductor pollicis muscle and because it is proximal to the attachments of the flexor muscles of the thumb. The force measured was therefore largely due to activity of adductor pollicis and a contribution from first dorsal interosseous.

Each subject's hand and forearm were warmed in hot water (40°C) for 5 min and they were then asked to perform nine 2 s MVCs, within a period of about 3 min. Twenty of the control subjects and nine of the subnourished were then asked to perform an MVC sustained for 30 s.

The subjects were allowed to watch the screen of the Nicolet 3091 portable oscilloscope on which data were collected, and encouraged verbally. Results from subjects tested during our preliminary study [6] were obtained using a different transducer [7]. The results obtained from the two transducers were directly comparable after appropriate calibration.

Measurements for the subnourished patients were made at the bedside but data could also be transferred for analysis on to the Nicolet 4094 oscilloscope or on to a personal computer. Maximal relaxation rate (MRR) was measured using a differentiating program available on this oscilloscope or Nicolet PC31 computer, program and normalized by the maximum force exerted [8] and had the units s^{-1} (equivalent to percentage force loss in 10 ms).

CSA

The apparatus for measuring CSA is shown in Fig. 1(*a*). The profile of the hand was measured with the thumb fully abducted. The plane of the measurement bisected the angle between the metacarpal bones of the thumb and index finger up to the point between the bases of these bones. The thickness of the hand along this plane was measured by the difference in the outputs of two linear potentiometers, the shafts of which were held by springs against the two surfaces of the hand. The potentiometers were held in a light frame which could be moved over the hand while its position was monitored by a third potentiometer. This apparatus was also used in the preliminary study [6]. An X–Y plot of thickness against distance moved thus represents a profile of the hand (Fig. 1*b*). Three profiles were obtained for each subject, the

subject being asked to remove the hand from the apparatus between each measurement. These profiles were integrated after allowing for skin thickness (Fig. 1*b*). An anatomical dissection of a cadaver hand through this plane confirmed that the results of these measurements should approximate to the CSA of adductor pollicis together with part of first dorsal interosseous.

The area measurement could be made at the bedside using Gaussian quadrature integration but specimen records were kept for transfer either to the Nicolet 4094, which has an integration program, or on to a personal computer. Areas could be measured on computer using an extended Nicolet PC31 program.

RESULTS

Force/CSA

The coefficient of variation for the force measurements on each subject was 5% or less for the control group and for all but one of the subnourished group. The mean co-efficient of variation for the area measurements on any one subject was 5.1% in both groups.

We have found the area measured by this method to be well correlated ($r = 0.937$) with measurements of muscle CSA obtained from computer-assisted tomography (CAT) and n.m.r. images through the same plane (Fig. 2). The estimated CSA obtained from our hand profiles appears to underestimate the actual muscle CSA by approximately 40%. This is partly because some of the muscle is proximal to the bases of the metacarpal bones and is therefore not included in our CSA measurements. There is also a small compressing effect of the springs holding the potentiometers against the two surfaces of the hand. This underestimate does not affect our conclusions which are based on comparing relationships between force and CSA and not on the absolute value of their ratio.

The results of force and CSA measurements for the 40 normal subjects and the 11 subnourished patients are shown in Fig. 3. The regression line and 95% confidence limits for the control observations are shown. The regression line passes through the origin within the confidence limits and it can be seen that all but two of the observations from the subnourished patients are evenly scattered about it. These two observations are discussed below.

Force/height

Fig. 4 shows force plotted against height for 20 of the controls (with the regression line for these observations) and the 11 subnourished patients. It can be seen that the subnourished patients are generally weaker relative to their height than the controls. The significant correlation between force and height seen in the control group ($r = 0.73$) is absent in the subnourished group. This is partly because of the smaller range of heights, but is probably mostly because of the variable degree of subnutrition in this group.

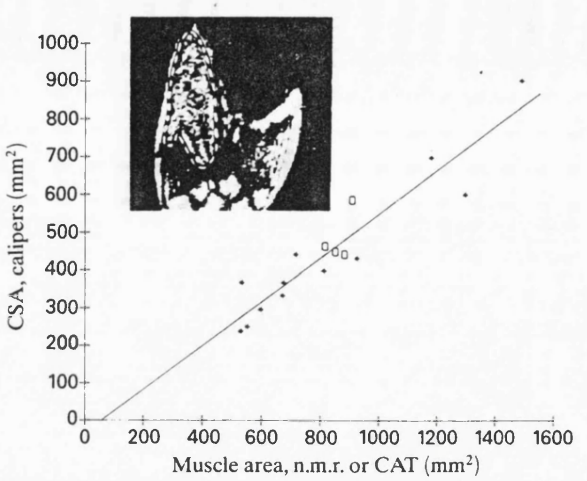


Fig. 2. Relationship between muscle area measured from n.m.r. (*, $n = 12$) or CAT (□, $n = 4$) images and CSA as measured by the method described in the text. The area measured is shown on the example of an n.m.r. image (insert). The unbroken line is the regression line: $y = 0.58x - 33$.

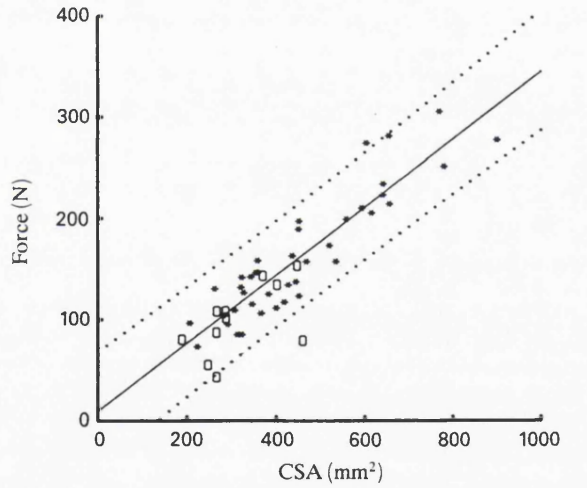


Fig. 3. Relationship between force and CSA of adductor pollicis of normal subjects (*, $n = 40$) and subnourished patients (□, $n = 11$). The unbroken line is the regression line for the normal subjects and the dotted lines show the 95% confidence limits for single observations on normal subjects (correlation co-efficient $r = 0.907$).

MRR

MRR was measured for 28 of the control group and eight of the subnourished patients. The mean coefficient of variation for measurements of relaxation rate on control and subnourished subjects was 13.7%. The normalized MRR in the control group was 6.8 ± 0.216 s^{-1} (mean ± SEM, range 4.9–9.4 s^{-1}). In the subnourished patients the value was 5.2 ± 0.336 s^{-1} (range 4.0–6.7 s^{-1}). Thus relaxation was significantly slower in this group ($P < 0.001$).

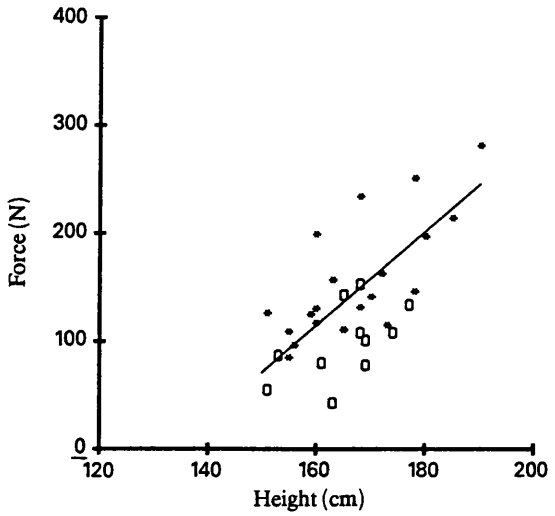


Fig. 4. Relationship between force of adductor pollicis and height of normal subjects (*, $n=20$) and subnourished patients (□, $n=11$). The unbroken line is the regression line for the normal subjects.

Fatigue

There was no significant difference between the 20 control subjects and nine subnourished patients. The mean fall of force for all subjects and patients was 25% ± 12% (mean ± SEM).

DISCUSSION

Force/CSA

Although measurement of isometric force from the adductor pollicis muscle is a well-established research and clinical technique [9, 10], we believe this is the first attempt to correlate force measurements from this muscle with CSA. This information is essential to compare voluntary activity in a muscle between subjects and good correlations have previously been obtained with the quadriceps muscle group [11–13]. However, this group contains multipennate muscles, which makes the comparison of force/CSA measurements with other muscles difficult. It also obscures the interpretation of data when changes in muscle bulk have occurred because increase in muscle bulk of a mature muscle, due to hypertrophy, leads to a change in the angle of pennation of the fibres and therefore the effective lever ratio [14]. It seems likely that loss of muscle secondary to subnutrition or ageing would have a similar effect. Adductor pollicis is a more nearly parallel-fibred muscle (S. A. Bruce, D. Newton & R. C. Woledge, unpublished work). Our modification of the technique for force measurement minimizes the differences in lever ratio between individuals because the point of opposition of the force at the base of the proximal phalanx of the thumb is closer to the attachment of the muscle than the more conventional interphalangeal joint [10]. These factors contribute to the better correlation between force and CSA achieved by our technique than those published for quadriceps [11–13]. The forces observed in this study are higher than have been previously reported for adductor pollicis partly because the lever ratio is small but also because there is some contribution from long flexor muscles of the fingers and because very strong subjects were deliberately selected for the control group.

Muscle function and nutritional status

Our results confirm that subnourished subjects are weak relative to their height, which was chosen as an indicator of body build, but show that the weakness is generally in proportion to muscle bulk. Observations from two of our patients with Crohn's disease fell outside the 95% confidence limits for the control observations (Fig. 3). One of these patients was on long-term steroids; the other had a history of alcohol abuse. Both steroid therapy [15] and alcohol [16] are known to cause myopathies which might have affected the results, although there was no clinical evidence of specific muscle disease in either patient. The coefficient of variation of the force observations from the second of these two patients was 8.4%, suggesting that her contractions may not have been maximal. Even including these two observations the subnourished group did not significantly differ from the controls ($P=0.2$). This suggests that the most important effect of subnutrition on muscle is loss of bulk consequent on its homoeostatic function as a store of protein [1]. The difficulties in interpreting earlier studies of muscle function and nutritional status have recently been reviewed [17]. Since that review, further studies [5, 18] have reported slow relaxation rates in adductor pollicis muscle-stimulated contractions tested in subnourished surgical patients, confirming that this is the most consistently abnormal normalized muscle variable in subnourished patients. Reported changes in the force–frequency relationship [2–5, 18] are probably largely explained by the prolonging of relaxation [17]. Our finding that relaxation rate measured in voluntary contractions is also demonstrably slower in subnourished patients should make the test more widely available and more readily tolerated.

The MRR of our control subjects was slower by approximately 25%, than that previously published for stimulated relaxation rates [17]. A large part of this difference is probably due to asynchronous activation of motor units during voluntary contraction. A numerical simulation of this asynchrony was carried out using a differentiated force record from one of our control subjects. The record was averaged in a moving window of 80 ms width. This depressed the peak value of fall of force by 27%, suggesting that this explanation is likely to be correct.

Our results suggest that force generated during MVC is unlikely to be a useful measurement in the diagnosis or follow-up of subnourished patients as the major change is on muscle bulk which is non-specific. This is in contrast to the indirect inference, from results of submaximal stimulated contractions, in the work cited above that subnutrition has a specific effect on the ability of muscle

protein to develop force, perhaps through changes in calcium kinetics [19]. However, relaxation rate may well be a useful additional test in demonstrating marginal subnutrition and in assessing the efficacy of re-feeding regimens in subnourished patients.

ACKNOWLEDGMENTS

This project is funded by South-East Thames Regional Health Authority (Locally Organized Research Scheme). We are most grateful to Dr G. Sladen for his encouragement and for enabling us to study his patients, and to Dr M. Wilson for writing the extension to the PC31 computer program.

REFERENCES

1. Daniel, P.M., Pratt, O.E. & Spargo, E. (1977) The metabolic homeostatic role of muscle and its function as a store of protein. *Lancet*, **ii**, 446–448.
2. Lopes, J., Russell, D.M., Whitwell, J. & Jeejeebhoy, K.N. (1982) Skeletal muscle function in malnutrition. *American Journal of Clinical Nutrition*, **36**, 602–610.
3. Russell, D.M., Leiter, L.A., Whitwell, J., Marliss, E.B. & Jeejeebhoy, K.N. (1983) Skeletal muscle function during hypocaloric diets and fasting: a comparison with standard nutritional assessment parameters. *American Journal of Clinical Nutrition*, **37**, 133–138.
4. Russell, D.M., Prendergast, P.J., Darby, P.L., Garfinkel, P.E., Whitwell, J. & Jeejeebhoy, K.N. (1983) A comparison between muscle function and body composition in anorexia nervosa: the effect of refeeding. *American Journal of Clinical Nutrition*, **38**, 229–237.
5. Brough, W., Horne, G., Blount, A., Irving, M.H. & Jeejeebhoy, K.N. (1986) Effects of nutrient intake, surgery, sepsis and long term administration of steroids on muscle function. *British Medical Journal*, **293**, 983–988.
6. Bruce, S.A., Phillips, S.K. & Woledge, R.C. (1986) Isometric force in maximum voluntary contractions related to an estimate of the cross-sectional area of adductor pollicis in the human subject. *Journal of Physiology (London)*, **372**, 31*P*.
7. Bruce, S.A., Phillips, S.K. & Woledge, R.C. (1986) Apparatus for measuring force of adduction of the thumb, and for measuring profiles of the hand in human subjects. *Journal of Physiology (London)*, **372**, 9*P*.
8. Wiles, C.M., Young, A., Jones, D.A. & Edwards, R.H.T. (1979) Relaxation rate of constituent muscle-fibre types in human quadriceps. *Clinical Science*, **56**, 47–52.
9. Merton, P.A. (1954) Voluntary strength and fatigue. *Journal of Physiology (London)*, **123**, 553–564.
10. Edwards, R.H.T., Young, A., Hosking, G.P. & Jones, D.A. (1977) Human skeletal muscle function: description of tests and normal values. *Clinical Science and Molecular Medicine*, **52**, 283–290.
11. Maughan, R.J., Watson, J.S. & Weir, J. (1983) Strength and cross-sectional area of human skeletal muscle. *Journal of Physiology (London)*, **338**, 37–49.
12. Chapman, S.J., Grindrod, S.R. & Jones, D.A. (1984) Cross-sectional area and force production of the quadriceps muscle. *Journal of Physiology (London)*, **353**, 53*P*.
13. Young, A., Stokes, M. & Crowe, M. (1984) Size and strength of the quadriceps muscles of old and young women. *European Journal of Clinical Investigation*, **14**, 282–287.
14. Binkhorst, R.A. & van't Hof, M.A. (1973) Force–velocity relationship and contraction time of the rat fast plantaris muscle due to compensatory hypertrophy. *Pflugers Archiv*, **342**, 145–158.
15. Kendall-Taylor, P. & Turnbull, D.M. (1983) Endocrine myopathies. *British Medical Journal*, **287**, 705–708.
16. Martin, F.C. & Peters, T.J. (1985) Assessment *in vitro* and *in vivo* of muscle degradation in chronic skeletal muscle myopathy of alcoholism. *Clinical Science*, **68**, 693–700.
17. Newham, D.J. (1986) Nutritional status and skeletal muscle contractility. *British Journal of Parenteral Therapy*, **7**, 93–96.
18. Chan, S.T.F., McLaughlin, S.J., Ponting, G.A., Biglin, J. & Dudley, H.A.F. (1986) Muscle power after glucose–potassium loading in undernourished patients. *British Medical Journal*, **293**, 1055–1056.
19. Russell, D.M., Atwood, H.L., Whittaker, J.S., Itakura, T., Walker, P.M., Mickle, D.A.G. & Jeejeebhoy, K.N. (1984) The effect of fasting and hypocaloric diets on the functional and metabolic characteristics of rat gastrocnemius muscle. *Clinical Science*, **67**, 185–194.

Quarterly Journal of Experimental Physiology (1989), 74, 359–362
Printed in Great Britain

EFFECT OF AGE ON VOLUNTARY FORCE AND CROSS-SECTIONAL AREA OF HUMAN ADDUCTOR POLLICIS MUSCLE

S. A. BRUCE, D. NEWTON AND R. C. WOLEDGE*†

*Department of Medicine for the Elderly, St Helen's Hospital, Hastings and *Department of Physiology, University College London, Gower Street, London WC1E 6BT*

(MANUSCRIPT RECEIVED 13 JANUARY 1989, ACCEPTED 13 FEBRUARY 1989)

SUMMARY

Muscle weakness accompanies ageing but its causes are still uncertain. We report maximum voluntary force measurements of adductor pollicis muscle, normalized for cross-sectional area, in twenty-three elderly subjects. Normalized force was lower in the elderly compared with a group of fifty-five young adult subjects by 27±4 % (S.E.M.). This shows that atrophy alone is not the cause of the weakness of old age.

INTRODUCTION

It is a commonplace observation that skeletal muscle strength declines with age. However, despite repeated observations over the past 150 years it remains controversial whether the decrease in muscle strength is simply due to the decrease in muscle bulk, which also occurs, or whether there is an additional specific decrease in the ability of ageing muscle to produce force. In order to determine the relative contributions of atrophy and specific changes one must normalize force measurements by comparing them with those of bulk for the same muscle or group of muscles: the ratio of maximum voluntary force (MVF) to cross-sectional area (CSA) should not change with muscle atrophy. In their study of young, adult and aged mice, Brooks & Faulkner (1988) did find a specific decrease in maximum tetanic force for extensor digitorum longus (EDL) and soleus muscles in the aged mice (although the change only achieved significance for EDL). Similar comparisons in human quadriceps (Young, Stokes & Crowe, 1984, 1985) produced contradictory results. This may be partly because a specific change is harder to detect when a large amount of atrophy has occurred. One cause of atrophy, disuse, is less likely to affect distal upper limb muscles than proximal lower limb muscles, such as quadriceps, but there does not appear to have been a study comparing force and bulk in the former type of muscle. We have therefore studied the thumb adductor muscle (adductor pollicis). This is a relatively parallel-fibred muscle in which the relation between bulk and force might be correspondingly more straightforward than in muscles examined previously.

METHODS

Twenty-three healthy elderly subjects (fourteen females and nine males) aged 76 to 94 years, mean age 81·3 years, were recruited from a general practitioner's age–sex register and from those attending a Day Centre. Results from the elderly were compared with those from a group consisting of fifty-five healthy subjects (twenty-eight females and twenty-seven males) aged 18 to 54 years, mean age 29 years, who were recruited

† To whom reprint requests should be addressed.

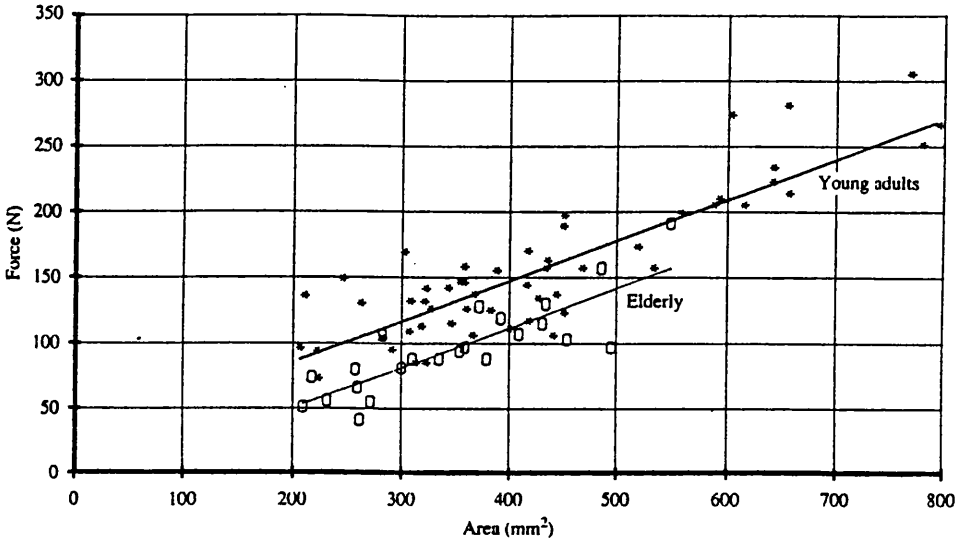


Fig. 1. Relation between isometric force of thumb adduction and cross-sectional area of adductor pollicis for elderly (0) and young adult (*) subjects. The regression lines are shown.

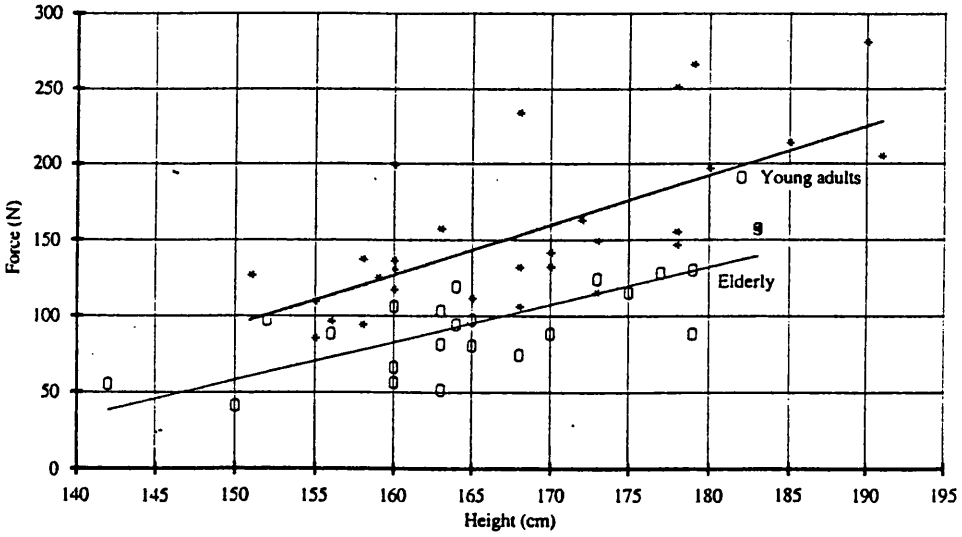


Fig. 2. Relation between isometric force of thumb adduction and subject's height for the same group of elderly subjects (0) and thirty of the young adults (*). The regression lines are shown.

from staff and students at University College London to give a wide range of height and frame size. Subjects with pain or stiffness of movements of the thumb or specific wasting of the hand muscles were excluded as were those with cardiovascular, generalized neuromuscular or thyroid disease and those taking regular medication likely to affect muscle function or motivation. MVF and CSA of adductor pollicis were measured as described by Bruce, Newton & Woledge (1989). Results are expressed as means±S.E.M.

RESULTS

The relationship between force and cross-sectional area for the fifty-five young adult subjects and the twenty-three elderly subjects is shown in Fig. 1. Significant correlations between MVF and CSA are found for both groups (young adults: $r = 0{\cdot}883$, $P < 0{\cdot}001$; elderly: $r = 0{\cdot}840$, $P < 0{\cdot}001$). The regression line for the elderly is significantly below that for the young adult group ($P < 0{\cdot}001$). The mean ratio of MVF/CSA for the elderly is 73±4 % of that for the young adults. Significant correlations are also found for the relation between force and height (Fig. 2) in the two groups (young adults: $r = 0{\cdot}688$, $P < 0{\cdot}001$; elderly: $r = 0{\cdot}732$, $P < 0{\cdot}001$) and the ratio of force to height observed for the elderly is 63±7 % of that for the young adults.

DISCUSSION

Our comparison of MVF with CSA shows that with age there is a specific decrease (by 27±4 %) in the ability of the human adductor pollicis to produce force. The data for force *versus* height show a larger decrease in the ratio of these variables (37±7 %). This is in good accord with previous studies (Grimby & Saltin, 1983). The fact that the decline is greater (though not significantly greater) than that in MVF/CSA is compatible with atrophy also contributing to the weakness of old age. It may be that in other muscle groups, atrophy makes a bigger contribution to the loss of force and the specific change in force is, therefore, harder to detect. Young *et al.* (1984, 1985) did find evidence for a specific force loss with ageing in the quadriceps of men but not of women. We note that the correlations between MVF and CSA in both their studies are lower than ours; this may be because the relation between force and CSA is more complex in the multipennate quadriceps muscle group than in adductor pollicis (Bruce *et al.* 1989).

The cause of the atrophy associated with age is not well established, there being evidence for both loss of motor units (Grimby & Saltin, 1983) and decrease in fibre size (Essén-Gustavsson & Borges, 1986). Neither is the mechanism for the specific loss of ability to produce force understood. There are four possibilities. The first is a reduced ability to activate the muscles. This could not be the mechanism in the mouse where maximum tetanic force was measured (Brooks & Faulkner, 1988) and is testable in humans using interpolated twitches (Merton, 1954). The second possibility is a change in gross muscle architecture; this could reflect changes in lever ratio or pennation angle and would be testable by measuring maximum power output which would be unchanged in this case. Muscle architecture could also be changed by replacement of muscle by non-muscle tissue which would lead to an overestimate of muscle CSA by our method. An increased prominence of fat cells and connective tissue and the presence of lipofuscin has been described in ageing muscle (Jennekens, Tomlinson & Walton, 1971). However evidence from ^{31}P nuclear magnetic resonance (Taylor, Crowe, Bore, Styles, Arnold & Radda, 1984), showing that there is no diminution in muscle metabolites with ageing, is against the

reduction in normalized force resulting from replacement of muscle with non-muscle tissue. Thirdly, there may be a change in the ability of actin and myosin to interact (testable by measuring force during shortening), and fourthly, a change in the predominant myosin isozyme present, which would be reflected in a change in fibre type composition. A preferential loss of fast-twitch fibres has been reported in some studies of ageing muscle (Grimby & Saltin, 1983). However, although slow-twitch fibres do have a somewhat lower normalized force a much larger change in relative fibre type composition than has been observed would be required to account for the reduction in MVF/CSA.

Financial support from South East Thames Regional Health Authority is gratefully acknowledged.

REFERENCES

BROOKS, S. V. & FAULKNER, J. A. (1988). Contractile properties of skeletal muscles from young, adult and aged mice. *Journal of Physiology* **404**, 71–82.

BRUCE, S. A., NEWTON, D. & WOLEDGE, R. C. (1989). Effect of subnutrition on normalized muscle force and relaxation rate in human subjects using voluntary contractions. *Clinical Science* **76** (in the Press).

ESSÉN-GUSTAVSSON, B. & BORGES, O. (1986). Histochemical and metabolic characteristics of human skeletal muscle in relation to age. *Acta physiologica scandinavica* **126**, 107–114.

GRIMBY, G. & SALTIN, B. (1983). The ageing muscle. *Clinical Physiology* **3**, 209–218.

JENNEKENS, F. G. I., TOMLINSON, B. E. & WALTON, J. N. (1971). Histochemical aspects of five limb muscles in old age. *Journal of the Neurological Sciences* **14**, 259–276.

MERTON, P. A. (1954). Voluntary strength and fatigue. *Journal of Physiology* **123**, 553–564.

TAYLOR, D. J., CROWE, M., BORE, P. J., STYLES, P., ARNOLD, D. L. & RADDA, G. K. (1984). Examination of the energetics of aging skeletal muscle using nuclear magnetic resonance. *Gerontology* **30**, 2–7.

YOUNG, A., STOKES, M. & CROWE, M. (1984). Size and strength of the quadriceps muscles of old and young women. *European Journal of Clinical Investigation* **14**, 282–287.

YOUNG, A., STOKES, M. & CROWE, M. (1985). The size and strength of the quadriceps muscles of old and young men. *Clinical Physiology* **5**, 145–154.

From "Third Vienna Muscle Symposium."
(G. Freilinger, M. Deutinger, Eds.). Blackwell-MZV, Vienna, 1992

Prediction of the Length Force Relation of Adductor Pollicis Muscle from its Internal Structure

S.A. Bruce, S. Johnson, S.K. Phillips, R.C. Woledge

Department of Physiology, University College London

Introduction

Muscles are generally regarded as functionally homogenous consisting of an assemblage of sarcomeres all of the same length - a sufficient number in parallel to give the force needed and a sufficient number in series to give the required range and velocity of shortening.

Some muscles however undergo length changes large relative to the fibre length. If they were homogenous this would mean that tension would be near optimum only over a small part of the working range. Adductor pollicis is such a muscle. A possible method of building a muscle in which force can be kept fairly uniform through a wide range of movements is to have regions with optima at different muscle lengths. To discover if this is in fact the situation in adductor pollicis we have made observations on cadaver hands.

Methods

Two fixed cadaver hands were dissected. We are presenting results from one of these.

Adductor pollicis was divided into twenty-nine bundles as far as possible following natural lines of cleavage. Twelve bundles were from transverse head and seventeen from oblique head (In both our specimens the two heads were clearly divisible).

Measurements were made of the coordinates of the origin and insertion of each bundle with respect to an arbitrary reference point. Sarcomere length was measured at three places along each fibre bundle by diffraction of laser light. These three values were averaged. The total length of each bundle and muscle fibre length were measured, tendon length thus being obtained. After removal of as much tendon as possible bundles were dried over silica gel and the dry weight measured. These data was put into a computer model using Microsoft Excel. The following calculations were made for a range of thumb positions covering those that would be achieved in vivo:

1. Sarcomere length assuming that it would be uniform along each fibre and that the tendon length is fixed i.e. that the tendon is non-compliant.
2. Isometric force assuming that the relationship between isometric force and sarcomere length is the same for human muscle as it has been found to be in mouse muscle in vitro (Phillips, 1988) and that force is proportional to cross- sectional area.
3. The torque produced in the thumb by the isometric force. This takes account of the fact that the bundles pull on the thumb at various angles. For this calculation we assumed

that the carpo-metacarpal joint acts like a universal joint capable of rotation in any direction but not of sliding.

Results and Discussion

The calculated sarcomere lengths are shown for a variety of thumb positions in fig 1. In this and subsequent figures the ordinate represents the position of the hand as it passes through a sequence of positions, key points of which are illustrated in the drawing underneath. The thumb is progressively lowered while being moved from side to side thus covering the full range of possible length changes for adductor pollicis.

We found that all twelve bundles in the transverse head are functionally homogenous, that is, their sarcomere lengths vary by no more than +/- 0.3 micrometres between one bundle and another over the full range of the movements studied. The results were therefore grouped together by averaging the sarcomere lengths.

The oblique head was inhomogenous - the seventeen bundles could be divided into a functionally homogenous groups and the results for each were averaged as shown in fig. 1 (groups BB-GG). One of these groups (EE) which consists of two bundles had sarcomere lengths which are similar to those of the transverse head (AA) in all hand positions. The remaining five groups differ from one another quite considerably both in sarcomere length and in the way this varies with hand position. In general the more oblique parts of the oblique head have shorter sarcomere lengths in most hand positions. These results suggest that there is functional specialisation between the transverse and oblique head, and within the oblique head itself.

Fig. 2 shows force in each group of fibre bundles as a function of hand position. It can be seen that across the whole range of hand positions there is always one section of adductor pollicis muscle which is exerting its maximum force. There is clearly a tendency for the different sections of the muscle to compensate for each other. To express the extent of this compensation quantitatively we must take into account the relative sizes of the different bundles and the angles at which they pull on the thumb. We have therefore calculated the torque that each bundle exerts on the thumb during an isometric contraction. The results are shown in fig. 3. For this figure we have summed the torques produced by each bundle within both the transverse and oblique heads and also show the total torque produced by the whole muscle. In this addition the torques have been treated as scalar quantities. Strictly vectorial addition should have been used but we expect this refinement to have only a minor effect. The total torques produced by the transverse and oblique heads are similar in spite of the large difference in their size (the oblique head is two and a half times larger than the transverse head). In hand positions four and six where the oblique head torque is low because the sarcomeres are shorter than their optimum length the transverse head is producing its greatest torque. In positions one, three and five the transverse head is relatively ineffective because the sarcomeres are well beyond their optimum length but in these positions the oblique head exerts a torque near to its optimum. Only in position seven are both sections of the muscle exerting well below their optimum torque. This is because around this position nearly all sections of the muscle have sarcomere lengths greater than optima. Note however that even in this position one section of the oblique head (GG) exerts its optimum force (fig 2). The results of these compensations is that total torque exerted by the whole of adductor pollicis is relatively constant over the

wide range of possible movements. We suspect that in positions five and seven significant torque in the thumb in the same direction as that produced by adductor pollicis can be produced by first dorsal interosseous which is usually supplied by the same branch of the ulnar nerve.

Conclusion

Our measurements have shown that adductor pollicis is definately not a functionally homogenous muscle. There is an extremely wide range of sarcomere lengths within it, in some thumb positions covering almost the full range of possible sarcomere lengths. This wide range is found within the oblique part of the muscle. We suggest that this can be considered a functionally advantageous arrangement allowing relatively constant torque to be produced over a wide range of thumb positions.

Acknowledgements. Financial assistance of South East Thames Regional Health Authority and also Lederle Laboritories is gratefully acknowledged.

Reference

Phillips, S.K.: Ph.D.Thesis, London University 1988

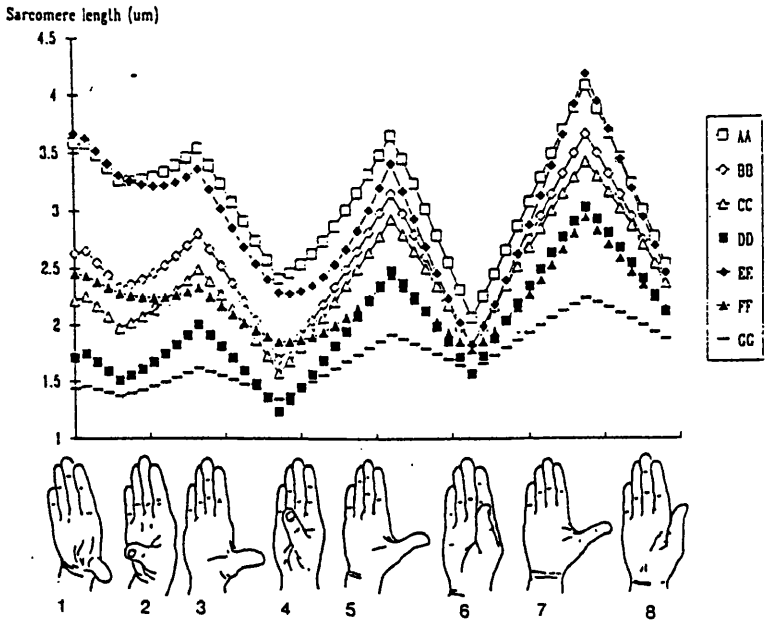


Fig. 1. Calculated sarcoma lengths for the range of thumb position shown. (AA = transverse head, BB-GG = oblique head).

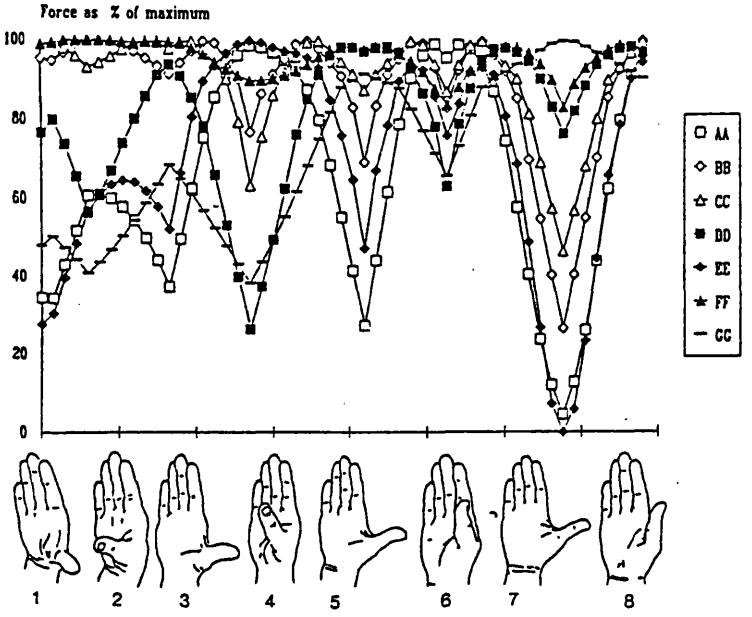


Fig. 2. Calculated force for the range of thumb positions shown. (AA = transverse head, BB-GG = oblique head).

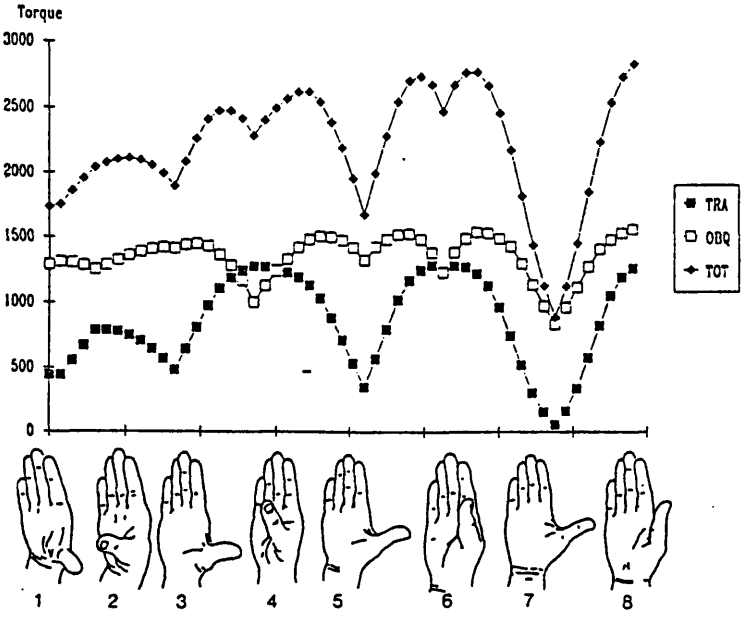


Fig. 3. Torque (N.m) exerted on the thumb for the range of positions shown by all the bundles from the transverse (TRA), and oblique (OBQ) heads and whole (TOT) adductor pollicis muscle.

Journal of Gerontology: MEDICAL SCIENCES
1992, Vol. 47, No. 2, M45–49

The Weakness of Old Age Is Not Due to Failure of Muscle Activation

Suzanne K. Phillips,[1] Stuart A. Bruce,[2] David Newton,[1] and Roger C. Woledge[1]

[1]Department of Physiology, University College London.
[2]Department of Medicine for the Elderly, St. Helen's Hospital, Hastings, East Sussex.

Maximum voluntary force and cross-sectional area (MVF and CSA) of the human adductor pollicis muscle were compared in groups of young (19–55 years, mean = 28, n = 53) and elderly (74–90 years, mean = 80, n = 39) subjects, of both sexes. Despite the elderly subjects being in good health and active outdoors, they were considerably weaker than the young subjects, their MVF/CSA being 26 ± 3% (mean ± SEM) lower. It was found that both young and elderly subjects could fully activate their muscles. Therefore the muscle weakness of old age does not appear to be due to reduced activation and must be caused by another mechanism, possibly biochemical in nature.

MOST studies of muscle strength and aging in humans (e.g., 1–5), including longitudinal studies (5), show a decline in strength with aging. This is partly explained by a reduction of muscle mass, or atrophy (3,5,6,7), but there is also evidence for a reduction in maximum isometric force per cross-sectional area (CSA) of muscle with aging, both in humans (4,8,9), in mice (10,11), and in rats (12). We are interested here in the mechanism by which force/CSA is reduced.

To compare individuals of different sizes and to determine whether there is a reduced force/CSA with aging, the CSA of the muscle fibers must be known. This is simple and routine in experiments on isolated muscle preparations from small animals, in which the relation of force/CSA is established and predicted by Huxley's 1957 model (13) of muscle contraction. In vivo measurements of both maximum voluntary force (MVF) and fiber CSA are subject to errors because of lever systems related to the muscle groups studied. For example, force measurements of the quadriceps muscle are usually taken at the ankle, which is some distance from the muscle insertion. Muscles generally have a complex pennate fiber arrangement, which means that the CSA of the muscle is not the same as the summated CSA of all the fibers. Perhaps for these reasons measurements of MVF and CSA in young human subjects are often found to be rather weakly correlated (r = .51 for females and r = .59 for males (14), r = .53 for females (15) and r = .015 for males (9)). The exception seems to be the adductor pollicis muscle, which is almost parallel fibered, i.e., the fiber length is a large proportion of muscle length (16); it is easily accessible for CSA measurements, giving a strong correlation coefficient (r = .926) (17).

We have previously reported that the MVF/CSA for this muscle that can be achieved by a group of elderly male and female subjects is less than that by a group of young subjects (4). This finding is in contrast to a study using the quadriceps muscle (15), in which it was found that elderly women were weaker but that the weakness was proportional to a reduction in CSA. Most of our elderly subjects were recruited from a social services day center. That they were known to social services implies a degree of frailty, although we excluded those with clinical disability. We now report measurements of MVF/CSA on a group of healthy, active, elderly individuals.

The simplest explanation for the production of a low MVF/CSA in the elderly is that not all the muscle is fully activated either because of a lack of subject motivation or reflex inhibition, either of which is known to cause muscle weakness (18,19). We have therefore tested for this in elderly subjects with low MVF/CSA measurements using electrical stimulation.

METHODS

Subjects. — Young subjects between 19 and 55 years (mean age 28 ± 1.1 years, n = 53, 26 male and 27 female) were recruited from staff and students of University College London. The average height for young male subjects was 1.72 ± .02 m, weight 72.7 ± 2.4 kg, whereas the females were 1.60 ± .01 m tall and weighed 57.9 ± 1.7 kg (mean ± *SEM*).

Elderly subjects were recruited from three sources: (a) from retired staff of University College London (still active in their respective fields) and their relatives; (b) from a fitness club in London, and (c) from a bowling club in Hastings. Altogether we studied 39 healthy elderly subjects (22 male and 17 female) between 74 and 90 years of age (mean age 80 ± .7). The height of the elderly male subjects was 1.71 ± .02 m, weight 64.1 ± 3.4 kg, while the females were 1.57 ± .02 m and weighed 58.1 ± 1.5 kg. A questionaire modified from a Department of Health & Social Security questionnaire (20) was used to access both health and activity levels of the elderly subjects. These were analyzed by the geriatrician S.A. Bruce, and on this basis subjects were selected as being fully active outdoors (20). Subjects with pain or stiffness of movements of the thumb or specific wasting of the hand muscles were excluded as were those with cardiovascular, generalized neuromuscular or thyroid disease, or those regularly taking medication likely to affect muscle function or motivation.

The project was approved by the ethical committees at University College London and Hastings Health Authority.

Force and CSA measurements. — Measurements of MVF and CSA were made on all 53 young and 39 elderly subjects. CSA measuring apparatus and method have been described previously (21). The thickness of the hand in the plane that bisects the adductor pollicis muscle is measured by the difference in outputs from two linear potentiometers which are moved over the skin. This hand thickness is measured from just above the metacarpal base to the web between thumb and index finger, and this distance is measured by a third potentiometer. An X-Y plot of thickness against distance gives a profile of the hand, the area of which is measured. The web skin fold is not included in the area as this contains no muscle, just skin and subcutaneous fat. We have improved our apparatus for measuring force, since, as we previously noted (21), our original apparatus recorded some contribution from the long flexors of the fingers. In the present experiments subjects were requested to hold their thumb flat in the plane of the palm of the hand. The force transducer which is mounted on an angled metal bar was wedged in between the bases of the proximal carpal bone of the thumb and the metacarpal bone of the index finger. The fingers and interphalangeal joint of the thumb were kept maximally extended throughout the measurements, and the subjects were requested to squeeze the bar as hard as possible against the metacarpal of the index finger. The protocol was otherwise as previously described (21). For each subject the MVF is a mean of up to 9 maximum voluntary contractions and the CSA is a mean of 3–4 measurements.

Testing for full activation. — As well as MVF and CSA measurements, the last 8 young (3 female and 5 male) and the last 4 elderly subjects (2 female and 2 male) studied were also tested for full muscle activation. This small sample of the total number of subjects was considered to be adequate because the results obtained are significant. In view of this and the fact that the test is uncomfortable, we did not feel that it was ethically justified to recruit more subjects, especially elderly.

Twitch interpolation was used to test for full activation. This is a well-established technique (22) which relies on the principle that the size of the twitch response that is recorded from a muscle after single electrically stimulated shocks applied to the motor nerve, depends on the degree of concomitant activation in the muscle. The maximal twitch height is recorded when there is no voluntary force being produced; as the proportion of voluntary force is increased, the superimposed twitch height decreases toward zero, as the muscle becomes fully activated. The technique gives reproducible results in clinical and experimental settings (19) and is more acceptable to subjects than the alternative way of establishing full activation (which is by comparison of voluntary with maximally stimulated tetanic contractions).

Statistics. — Regression lines were calculated for each group by the least squares method. The 99% confidence limits are for the population mean, and regression lines were compared using analysis of covariance (23).

Results

MVF and CSA measurements are shown in Figure 1 and summarized in Table 1. For each subject MVF was highly reproducible, resulting in a coefficient of variation of $< 5\%$ for up to 9 contractions. The measurements were made by three different investigators. Our method of measuring CSA has previously been shown to be highly correlated with, but not equal to, the true cross-sectional area of adductor pollicis (21). Systematic differences were found in the measurements of CSA, but not force, between the investigators. Scaling factors were obtained by comparing measurements of CSA made on the same subjects by different investigators.

To position the thumb correctly on our force transducer, a small deflection is produced. Therefore, twitch height at 0% MVF could not always be reliably recorded. Twitch height for each subject is therefore presented as a proportion of the twitch height at 20% of MVF (normalized twitch height).

Significant correlations between MVF and CSA were found for both groups. The correlation coefficient was higher for the young subjects ($r = .96, p < .001$) than for the elderly subjects ($r = .71, p < .001$). The regression line for the elderly is significantly different to that for the young subjects ($F < .01$).

Table 1. A Summary of MVF and CSA Data for Young and Elderly Male and Female Subjects

		n	MVF (N) (mean ± *SEM*)	CSA (mm) (mean ± *SEM*)	Age (yrs) (mean ± *SEM*)
Young	Females	27	61.0 ± 2.1	439.9 ± 18.9	26.6 ± 1.4
	Males	26	81.6 ± 3.4	612.7 ± 24.9	29.6 ± 1.6
	All	53	71.1 ± 2.4	524.6 ± 19.5	28.0 ± 1.1
Elderly	Females	17	40.0 ± 2.7	401.1 ± 27.2	80.8 ± 0.7
	Males	22	55.0 ± 3.8	555.6 ± 30.8	79.9 ± 1.1
	All	39	48.5 ± 2.7	488.3 ± 24.2	80.3 ± 0.7

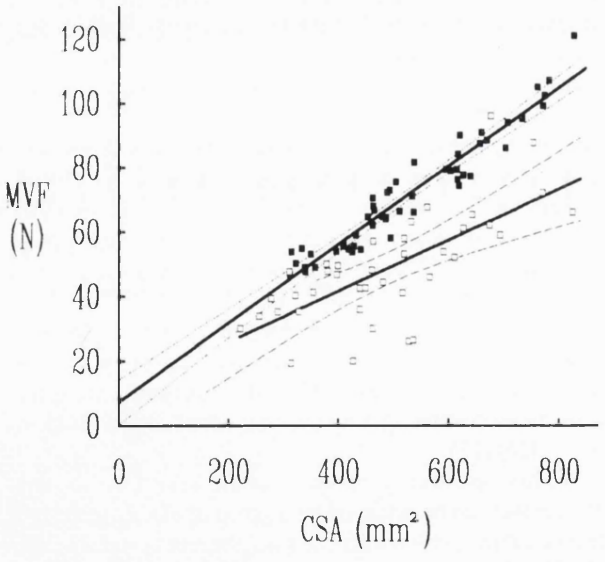


Figure 1. The relationship between MVF and CSA of the adductor pollicis muscle in young (■) and elderly (□) subjects. The regression lines for both the young and elderly are shown by heavy solid lines. The 99% confidence limits of the population regression line for each group are also shown, except where they cross (young, fine dotted line, and elderly, fine dashed line).

Results from the twitch interpolation experiments on 8 young subjects are shown in Figure 2. Normalized twitch height is plotted against the degree of concomitant voluntary activation expressed as % of MVF. The relationship between twitch height and voluntary force is curvilinear, as previously shown for quadriceps muscle in young subjects (19). The data have therefore been transformed to a linear scale by plotting [normalized twitch height]$^{0.66}$ against %MVF. It can be seen that the regression line passes through zero at 100% MVF within the 99% confidence limits (23) showing, as expected, that full activation of the muscle can be achieved by young subjects.

Data for one of our four elderly subjects are not shown because her MVF/CSA was the same as for the young subjects and therefore does not contribute to the testing of the hypothesis below. Twitch interpolation showed her to be able to fully activate her muscle. The results for the three weak elderly subjects are shown in Figures 3a and 3b and have been plotted in two ways corresponding to the following two hypotheses:

(a) that elderly subjects can fully activate their muscles. Hypothesis (a) is tested by plotting the linearized results of the elderly subjects in the same way as for the young subjects i.e., normalized twitch height is plotted against the degree of concomitant voluntary activation expressed as % of MVF of each individual (Fig. 3a). As the regression line again passes through zero at 100% MVF within the 99% confidence limits, this hypothesis, of full activation, is compatible with our results.

(b) that the reduction in MVF/CSA in elderly subjects is due to the inability to fully activate.

To test this hypothesis we have to replace the measured MVF by that predicted from the muscle CSA when fully activated. This predicted force value can be obtained from the regression between MVF and CSA for young subjects if hypothesis (b) is correct. When the experimental points are plotted in this way (Fig. 3b), they are clearly different from those for the young subjects, the regression line crossing zero at approximately 60%, not 100%. Thus, it seems that all the muscle is activated at 60% of the predicted MVF. Therefore hypothesis (b) is not compatible with our results.

DISCUSSION

There are a number of factors that could cause the decrease in MVF/CSA with aging. It was the aim of this study to investigate one of these factors, i.e., activation, in a group of healthy, active elderly with a low MVF/CSA.

The MVF produced by the elderly was 26 ± 3% (mean ± *SEM*) less than that predicted from their CSA using the regression line for the young subjects. This result is the same as that in our previous study (4), which was of smaller groups. In the present study the results from the young subjects show less scatter, probably because the varying

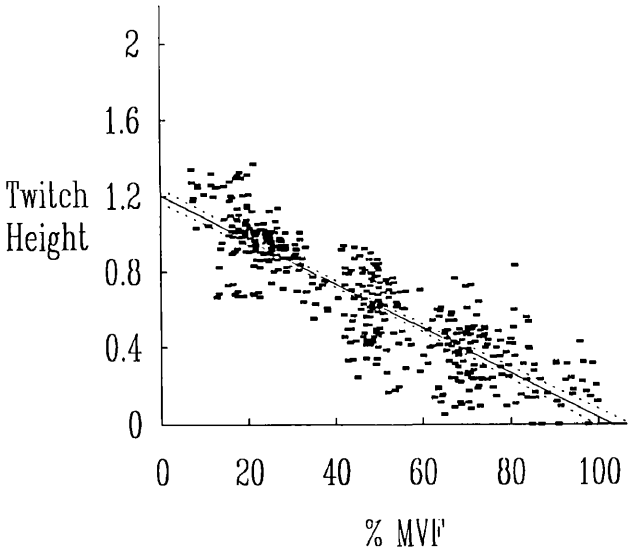


Figure 2. The relationship between [normalized twitch height]$^{0.66}$ and %MVF from 8 young subjects. Regression line (−) and 99% confidence limits (- - -) of the population regression line are shown.

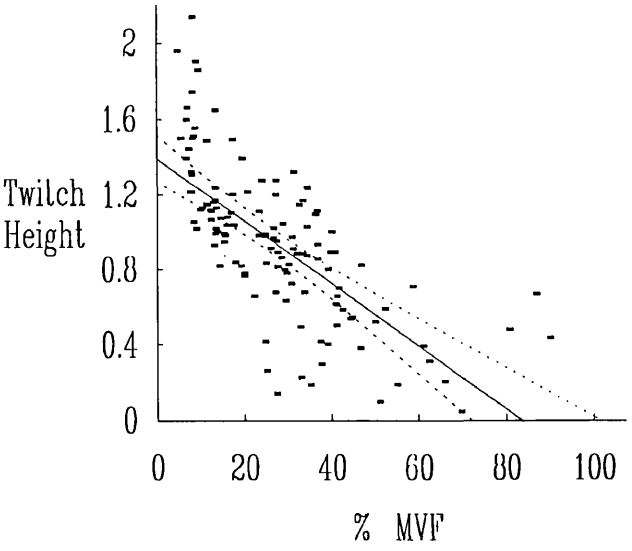


Figure 3a. The relationship between [normalized twitch height]$^{0.66}$ and %MVF from 3 elderly subjects with low MVF/CSA measurements.

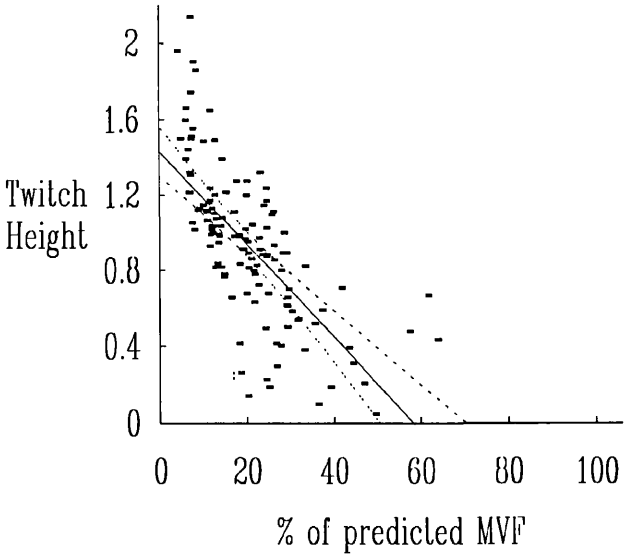


Figure 3b. The relationship between [normalized twitch height]$^{0.66}$ and predicted %MVF (see text) for the same 3 elderly subjects. Regression line (−) and 99% confidence limits (- - -) of the population regression line are shown.

contribution from finger flexors has been eliminated (4). In contrast, the results from the elderly subjects show a much greater scatter, several achieving forces/CSA comparable with the younger subjects. There was no correlation between age and the ratio of MVF/CSA within the elderly group and no difference in this ratio between males and females. We attribute the greater variability to the fact that these subjects were fitter than our previous group and included individuals who, despite their chronological age, do not appear biologically aged. In this study the elderly were selected as fully independent out of doors by means of a fitness questionnaire. There is evidence that fitness is an indicator of physiological reserve and therefore of biological as opposed to chronological age (24). We also feel that greater variability in the results from elderly subjects may account for some of the difficulty previously encountered in demonstrating differences in MVF/CSA measurements between young and elderly subjects. In Young and colleagues' study of quadriceps (15), lower correlation coefficients were obtained than in our studies. The interpretation of changes in CSA for this highly pennate muscle may be more difficult than with the more parallel fibered adductor pollicis (21).

However, the greater variability in the elderly subjects could be due to varying degrees of activation in this group, with only those whose MVF/CSA was similar to the young subjects achieving maximal activation. We studied the whole relation of twitch height against different levels of voluntary force, as was done by Merton (22), rather than merely trying to observe the twitch size at MVF. Our reasons are that a maximum isometric contraction is not a steady baseline, and it is therefore difficult to determine the presence or not of superimposed twitches near to MVF. Measurements are, therefore, more reliable at low %MVF. The results from our twitch interpolation experiment exclude an important possible cause of weakness by showing that even those elderly with reduced MVF/CSA measurements were fully activated during a maximal voluntary contraction. This is in agreement with Vandervoort and McComas (3), who found by twitch interpolation, at MVF only, that most elderly subjects could fully activate their ankle muscles, although it is unclear whether these individuals had a reduced MVF/CSA.

This negative result indicates that the force reduction is due to factors other than activation. One possibility is an overestimation in the measurement of contractile material. However, we have shown that our method of measuring CSA of the adductor pollicis is known to correlate well with measurements taken from NMR or CAT scan images of this muscle in young subjects (21). It is not likely that the adductor pollicis muscle of elderly subjects contains a sufficiently greater proportion of fat or connective tissue compared to that of young subjects to account for a 26% reduction in MVF/CSA. Orlander et al. (25) found no increase in lipid droplets, as a percentage of cell volume, with age in vastus lateralis of men. Connective tissue does not make up a large proportion of normal muscle, only about 1% in 3-month-old rat muscle (26); therefore even a doubling of this amount would make only an insignificant difference to the CSA. Also, work on isolated muscle from young and elderly mice has shown a decrease in isometric and shortening force with aging but no reduction in the force during active stretch (11). There is also evidence that this may occur in human muscle (27). This directly contradicts the hypothesis that the force reduction is due to less contractile material per CSA, as in this case stretch force would also be proportionally lower.

In some studies (28,29) it has been reported that type II muscle fibers are stronger than type I fibers. Type II fiber atrophy has been associated with aging (6,30) and this could therefore contribute to the finding of a lower MVF/CSA. However, adductor pollicis force would be virtually unaffected if such a change occurred, because this muscle consists almost entirely of type I fibers (31).

Alternatively there may be a chemical change within the muscle. Perhaps there is a raised intracellular phosphate or lower intracellular pH, conditions which are known to cause muscle weakness in isolated young animal muscle (32,33). One in vivo study on human muscle using ^{31}P NMR has shown no difference in muscle metabolites with aging (34). However, the variation between subjects was quite large and may be masking differences between the young and elderly which, though small, would be sufficient to reduce force.

We have previously argued that the reduction in MVF/CSA is unlikely to account for all the weakness of old age, and that atrophy also occurs (4). The atrophy is probably multifactorial, with both loss of fiber number and reduction in fiber size taking place (6,15,30). It has recently been shown that fiber atrophy may also have a biochemical basis in that reduced muscle carnitine, which is known to occur with aging (35), results in a reduction in fiber size (36). In young subjects this is reversible when muscle carnitine returns to a normal level (36). The fact that both reduction in MVF/CSA and fiber atrophy may have a biochemical basis raises the possibility that at least a proportion of the muscle weakness that occurs with old age might possibly be amenable to pharmacological reversal.

In normal daily activity the adductor pollicis muscle will be used both dynamically and isometrically. This muscle is very important for gripping or holding on to objects that will mainly require submaximal isometric contractions, and this is reflected in the fibers which are type I, fatigue resistant. Using handrails as support and to help in climbing stairs, etc. may become increasingly important as one becomes more elderly. However, with aging and the accompanying muscle atrophy and reduced force/CSA, older subjects will have to use a higher proportion of their adductor pollicis MVF or even their entire MVF to produce the same force as a young subject. Young (37) has stressed the problem of weak quadriceps muscle with aging resulting in elderly subjects having difficulties in rising from a sitting position.

The mechanism responsible for the muscle weakness that occurs with aging is not known. However, it is not due to failure of muscle activation. More work is needed to find the cause of this weakness in order to prevent or reverse its disabling effect on the elderly population.

ACKNOWLEDGMENTS

Financial support for this study from South East Thames Regional Health Authority is gratefully acknowledged. We would like to thank Shirley Rice, Rashbal Ghattaora, and Aziz Sheikh for collecting data for some of the experiments.

Address correspondence to Dr. S. K. Phillips, Department of Physiology, University College London, Gower Street, London, WC1E 6BT, U.K.

References

1. Quetelet A. Sur l'homme et le developpement de ses facultes, vol. 2. Paris: Bachelier, Imprimeur-Libraire, 1835.
2. Burke WE, Tuttle WW, Thompson CW, Janney CD, Weber RJ. The relation of grip-strength and grip-strength endurance to age. J Appl Physiol 1953;5:628–30.
3. Vandervoort AA, McComas AJ. Contractile changes in opposing muscles of the human ankle joint with aging. J Appl Physiol 1986;61:361–7.
4. Bruce SA, Newton D, Woledge RC. Effects of age on voluntary force and cross-sectional area of human adductor pollicis muscle. Qtr J Exp Physiol 1989;74:359–62.
5. Kallman DA, Plato CC, Tobin JD. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J Gerontol Med Sci 1990;45:M82–8.
6. Grimby G, Saltin B. The ageing muscle. Clin Physiol 1983;3:209–18.
7. Essen-Gustavsson B, Borges O. Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiol Scand 1986;126:107–14.
8. Klitgaard H, Mantoni M, Schiaffino S, et al. Function, morphology and protein expression of ageing skeletal muscle: a cross-sectional study of elderly men with different training backgrounds. Acta Physiol Scand 1990;140:41–54.
9. Young A, Stokes M, Crowe M. The size and strength of the quadriceps muscles of old and young men. Clin Physiol 1985;5:145–54.
10. Brooks SV, Faulkner JA. Contractile properties of skeletal muscles from young, adult and aged mice. J Physiol 1988;404:71–82.
11. Phillips SK, Bruce SA, Woledge RC. The muscle weakness due to age is absent during stretching. J Physiol 1991;437:63–70.
12. Klitgaard H, Marc R, Brunet A, Vandewalle H, Monod H. Contractile properties of old rat muscles: effect on increased use. J Appl Physiol 1989;67:1401–8.
13. Huxley AF. Muscle structure and theories of contraction. Prog Biophys 1957;7:233–318.
14. Maughan RJ, Watson JS, Weir J. Strength and cross-sectional area of human skeletal muscle. J Physiol 1983;338:37–49.
15. Young A, Stokes M, Crowe M. Size and strength of the quadriceps muscles of old and young women. Eur J Clin Invest 1984;14:282–7.
16. Bruce SA, Johnson S, Phillips SK, Woledge RC. Prediction of the length force relation of adductor pollicis muscle from its internal structure. Proc. 3rd Vienna Muscle Symposium, June 1990. (In press).
17. Bruce SA, Phillips SK, Woledge RC. Isometric force in maximum voluntary contractions related to an estimate of the cross-sectional area of adductor pollicis in the human subject. J Physiol 1985;372:31.
18. McComas AJ, Kereshi S, Quinlan J. A method for detecting functional weakness. J Neurol Neurosurg Psychiatry 1983;46:280–2.
19. Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. J Neurol Neurosurg Psychiatry 1986;49:1288–91.
20. Wickham CAC, Walsh K, Cooper C, Barker DJP, Margetts BM, Morris J, Bruce SA. Dietary calcium, physical activity, and risk of hip fracture: a prospective study. Br Med J 1989;299:889–92.
21. Bruce SA, Newton D, Woledge RC. Effect of subnutrition on normalized muscle force and relaxation rate in human subjects using voluntary contractions. Clin Sci 1989;76:637–41.
22. Merton PA. Voluntary strength and fatigue. J Physiol 1954;123:553–64.
23. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, IA: The Iowa State University Press, 1976; Chapters 6 & 14.
24. [No author given]. Intensive care for the elderly (Editorial). Lancet 1991;337:209–10.
25. Orlander J, Kiessling K-H, Larsson L, Karlsson J, Aniansson A. Skeletal muscle metabolism and ultrastructure in relation to age in sedentary men. Acta Physiol Scand 1978;104:249–61.
26. Alnaqeeb MA, Al Zaid NS, Goldspink G. Connective tissue changes and physical properties of developing and ageing skeletal muscle. J. Anat. 1984;139:677–89.
27. Vandervoort AV, Kramer JF, Wharram ER. Eccentric knee strength of elderly females. J Gerontol Biol Sci 1990;45:B125–8.
28. Young A. The relative isometric strength of type I and type II muscle fibres in the human quadriceps. Clin Physiol 1984;4:23–32.
29. Grindrod S, Round JM, Rutherford OM. Type 2 fibre composition and force per cross-sectional area in the human quadriceps. J Physiol 1987;390:154.
30. Lexell J, Taylor CC, Sjostrom M. What is the cause of ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15 to 83 year old men. J Neurol Sci 1988;84:275–94.
31. Round JM, Jones DA, Chapman SJ, Edwards RHT, Ward PS, Fodden DL. The anatomy and fibre type composition of the human adductor pollicis in relation to its contractile properties. J Neurol Sci 1984;66:263–72.
32. Brandt PW, Cox RN, Kawai M, Robinson T. Regulation of tension in skinned muscle fibres. Effect of cross-bridge kinetics on apparent Ca^{+2}-sensitivity. J Gen Physiol 1982;79:997–1016.
33. Edman KAP, Mattiazzi AR. Effects of fatigue and altered pH on isometric force and velocity of shortening at zero load in frog muscle fibres. J Musc Res Cell Motility 1981;2:321–34.
34. Taylor DJ, Crowe M, Bore PJ, Styles P, Arnold DL, Radda GK. Examination of the energetics of aging skeletal muscle using nuclear magnetic resonance. Gerontology 1984;30:2–7.
35. Costell M, O'Connor JE, Grisolia S. Age-dependent decrease of carnitine content in muscle of mice and humans. Biochem Biophys Res Commun 1989;161:1135–43.
36. Spagnoli LG, Palmieri G, Mauriello A, Vacho GM, D'Iddio S, Giorcelli G, Corsi M. Morphometric evidence of the trophic effect of L-carnitine on human skeletal muscle. Nephron 1990;55:16–23.
37. Young A. Exercise physiology in geriatric practice. Acta Med Scand [suppl] 1985;711:227–32.

Received February 26, 1991
Accepted September 17, 1991

Strength and cross-sectional area of adductor pollicis muscle in men and women

S.A. Bruce, S.K. Phillips and R.C. Woledge

Department of Physiology, University College, Gower Street, London WC1E 6BT

In their analysis of data from human quadriceps muscle Winter & Maughan (1991) used regression analysis to show a difference between men and women in the force produced for a given cross-sectional area (CSA). This difference had not been shown when mean force/CSA measurements had been compared.

In our previously published data for adductor pollicis (Bruce *et al.* 1989) the correlation between force and CSA was much stronger than for quadriceps. This suggests that any sex difference in muscle function could be resolved more clearly with this muscle. We therefore analysed data for adductor pollicis from 23 males (19–53 years) and 28 females (22–42 years) (Fig. 1). Approval was granted by UCL Ethical Committee.

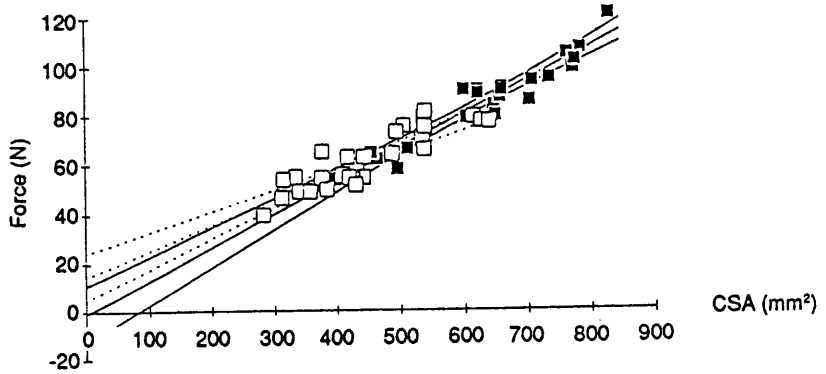


Fig. 1. Force and CSA of the adductor pollicis muscle in male (■) and female (□) subjects and regression lines with 95% confidence limits (male, continuous line; female, dotted line).

This shows no significant difference between male and female subjects. There is again a stronger correlation between force and CSA for both groups ($r = 0.96$, male and $r = 0.89$, female) than with Maughan *et al.* data for quadriceps (0.59 and 0.51 respectively). Using this same regression analysis on the data of Maughan *et al.* (1983) we confirm the difference between males and females. However, there is very little overlap of CSA measurements between the two groups in their study. The confidence limits are much wider than for adductor pollicis and there is a large positive intercept of both regression lines on the y axis. This large intercept, which is not seen with adductor pollicis, suggests that the difference between males and females in quadriceps may be due to factors other than differences in crossbridge function.

We gratefully acknowledge support from S.E. Thames Regional Health Authority.

REFERENCES

Bruce, S.A., Newton, D. & Woledge, R.C. (1989). *Clin. Sci* **76**, 637–641.
Maughan, R.J., Watson, J.S. & Weir, J. (1983). *J. Physiol.* **338**, 37–49.
Winter, E.M. & Maughan, R.J. (1991). *J. Physiol.* (in the Press).

Force and cross-sectional area of adductor pollicis muscle in post-menopausal women, with and without hormone replacement therapy

S.K. Phillips, S.A. Bruce, R.C. Woledge and N. Siddle*

*Department of Physiology, University College, Gower Street. *Department of Obstetrics & Gynaecology, University College Hospital, Huntley Street, London WC1*

With the menopause, when oestrogen levels are low, bone loss occurs at a rapid rate. Hormone replacement therapy (HRT) is known to prevent this bone loss which reduces the risk of fractures in old age. The force produced, by a given cross-sectional area (CSA) of the quadriceps muscle, was found to be lower in women with osteoporosis compared to those without (Jones & Rutherford, 1990). We studied the effect of HRT on the adductor pollicis muscle force and CSA in post-menopausal (PM) women. We compared a group of women on HRT (10 ± 2 years PM) with a group having had no treatment (13 ± 2 years PM) and a control group of premenopausal subjects. The study was approved by the UCL Ethical Committee.

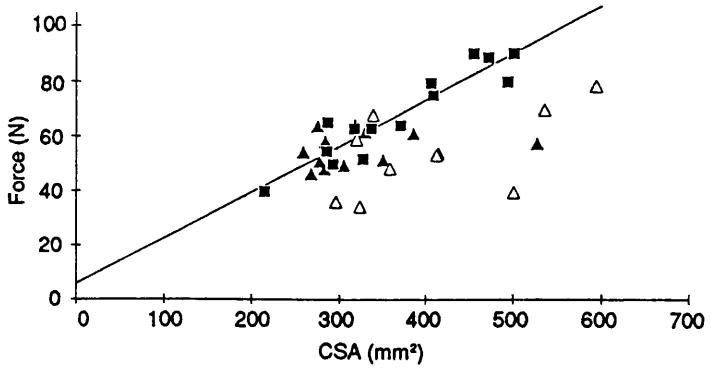


Fig. 1. Force and CSA. Control (aged 32 ± 2.4 (mean ± S.E.M.)), ■; HRT (aged 57 ± 2.6), ▲; and non HRT (aged 62 ± 1.8), △. The regression line is for the controls ($r = 0.93$).

Figure 1 shows that the observations from women on HRT fall about the regression line for the controls. There was no significant difference between the mean force/CSA for the control group and the HRT group, even though the mean age of the HRT group was much greater. In contrast, observations from the group without HRT generally fell below the controls and the mean force/CSA was significantly below that of the control group ($P < 0.001$) and of the HRT group ($P < 0.01$). Without HRT the force/CSA was 27% lower than the control value and this is a similar reduction to that seen in the very elderly (75–90 years) (Bruce *et al.* 1989). In women, this muscle weakness associated with old age seems to be linked to the decline in oestrogens at the menopause.

Supported by the S.E. Thames Regional Health Authority & Wyeth laboratories.

REFERENCES

Bruce, S.A., Newton, D. & Woledge, R.C. (1989). *Q. J. Exp. Physiol.* **74**, 359–362.

Jones, D.A. & Rutherford, O.M. (1990). *J. Physiol.* **423**, 84*P*.

From

Age and Ageing
Volume 21 (Supplement No 1)
1992

HIP FRACTURE PATIENTS HAVE WEAK HAND MUSCLES 31

SA BRUCE, R GHATTAORA, SK PHILLIPS, A SHEIKH & RC WOLEDGE

Department of Physiology, University College, Gower Street, London WC1E 6BT.

Maximum voluntary force (MVF) per cross sectional area (CSA) of quadriceps muscle declines even more in osteoporotic than in normal women >50 years of age (Jones & Rutherford 1990, J. Physiol. 423, 84P). If disuse were an important factor one might expect hand muscles to be relatively spared. We measured MVF and CSA of the adductor pollicis muscle for 53 young, 39 elderly and 23 elderly hip fracture patients (Table 1.).

Table 1. Summary of results (mean±sem) for both sexes.

	n	Age (yrs)	Force (N)	CSA (mm^2)	Height (m)	%MVF Loss
Yng.	F 27	27±1	61±2	440±1	1.59±0.02	-1±2
	M 26	30±2	82±3	613±2	1.71±0.02	0±1
Eld.	F 17	81±1	40±3	401±2	1.57±0.03	26±5
	M 22	80±1	55±4	556±3	1.74±0.02	27±3
Hip	F 18	83±1	27±2	299±1	1.60±0.01	39±5
	M 5	76±1	32±2	357±2	1.67±0.03	36±4

MVF strongly correlates with CSA in the young (r= 0.96). This regression line was used to predict MVF from CSA and to calculate the % loss of MVF. There was a significant %MVF loss in the elderly group (P<0.001) and the %MVF loss in the hip fracture patients was greater than that of the elderly group (P<0.02). We also find more muscle atrophy in the hip fracture group; the mean CSA was lowest in this group even though there was no difference in the mean height of the groups. This shows that the muscle weakness associated with osteoporosis, like that in with normal ageing is a general process effecting men as well as women. Weak muscles are likely to be an important additional risk factor for bone fractures.

ACUTE AND CHRONIC CARDIOVASCULAR EFFECTS OF CAFFEINE IN NORMOTENSIVE ELDERLY SUBJECTS 32

RA HAIGH, GD HARPER, and JF POTTER

University Department Medicine for Elderly, Leicester General Hospital, Leicester LE5 4PW

The acute cardiovascular effects of caffeine were studied after abstention and loading in elderly normotensive subjects.
Methods: 8 normotensive, non obese, subjects (mean age 74 yrs) were studied in a double blind randomised crossover trial. After 48 hrs caffeine abstention and 6 hrs fasting, supine and erect systolic (SBP) and diastolic (DBP) BP(mmHg), pulse (PR), plasma renin activity (PRA), noradrenaline (NA), adrenaline (A) and caffeine levels were recorded before and for 2 hrs after 250mg oral caffeine or placebo. The acute response was reassessed after taking 250mg caffeine /day for 5 days. Areas under curve were compared with paired t-tests.

Results:

	BASELINE			CHANGE FROM BASELINE	
	A	P	C	A vs P	A vs C
Sup SBP	143	143	137	11.9 ***	9.8 **
DBP	81	79	75	5.8 *	4.1
PR	72	71	69	1.5	0.4
Er SBP	147	145	138+	8.5 ***	6.9 *
DBP	91	89	82+	5.8 *	0.8
PR	85	83	82	0.2	-1.7
Caff.(mg/l)	0	0	.7	5.5 ***	-0.2
PRA (µg/l/h)	.39	.48	.63+	0.14 **	-0.05
A (nmol/l)	.31	.30	.34	0.10	0.11
NA (nmol/l)	1.6	1.9	1.9	-0.03	-0.4

(***p<0.0001 **p<0.01 *p<0.05 +p<0.01 A vs C)
A = Acute, P = Placebo, C = Chronic

Conclusion: In elderly normotensives, acute caffeine ingestion leads to a rise in supine and erect BP, but no change in PR. Chronic intake attenuates the acute pressor response. The rise in PRA after caffeine was abolished by chronic use although basal PRA increased after loading.

AN AUDIT OF AMIODARONE USE IN THE ELDERLY 33

G C MORRIS, H G M SHETTY, and K WOODHOUSE(*)

(*)University Department of Geriatric Medicine, Cardiff Royal Infirmary, Newport Road, Cardiff

Amiodarone is an effective antiarrhythmic drug but its use is limited by potentially serious side effects and therefore should only be prescribed to patients with a clear cut indication. In order to examine the usage of Amiodarone in elderly patients we audited the case notes of 46 patients discharged taking Amiodarone during the period of January 1989 to January 1991.

In 3 cases we were unable to define the indication for use of Amiodarone. Of the 43 remaining cases it was felt that Amiodarone was used appropriately in 31(72%):-

The effects of ageing on muscle strength in men and women

K.M. Rook, S.K. Phillips, S.A. Bruce and R.C. Woledge.

Department of Physiology, University College, Gower Street, London WC1

The force per cross sectional area (CSA) of the muscles of men and women after the age of 75 years is approximately 30 % lower than young men and women (20–40 years) (Bruce *et al.* 1989). Neither the cause of this weakness nor the time course by which it proceeds is known. The present study set out to investigate the age-related changes in F/CSA of the adductor pollicis muscle in men and women between the ages of 17 and 90 years. Approval was given by UCL Ethical Commitee.

Maximum voluntary force of the adductor pollicis was measured using a force transducer mounted on a metal bar placed between the bases of the proximal carpal bone of the thumb and the metacarpal bone of the index finger. CSA was determined by measuring the thickness of the hand in the plane that bisects the adductor pollicis muscle by the difference in output from two linear potentiometers which are moved over the skin. For each subject the force is a mean of up to 9 maximum voluntary contractions and the CSA is a mean of 3–4 measurements.

The time course of the decrease in force/CSA in men and women is very different. In women the decrease begins after the menopause (average age 50 years), whereas in men the decrease begins at about 60 years of age. The post-menopausal women (41–85 years) (who were not taking hormone replacement therapy (HRT)) have a reduced force/CSA similar to that of men over 75 years of age. In contrast women receiving HRT are as strong as pre-menopausal women (Phillips *et al.* 1991). At the time of the menopause there is a dramatic reduction in oestrogen levels (McKinlay, 1989). Since women on HRT (which consists largely of oestrogen administration) show no loss of strength, it is likely that oestrogen in some way prevents the reduction in force/CSA associated with the menopause.

A corresponding hormone in men to provide this function is possibly testosterone. Evidence suggests free testosterone levels start to decline in men at about 60 years of age (McKinlay, 1989), which is consistent with the time course of reduced force/CSA shown in the present study. This suggests that reduced testosterone levels in men might be responsible for the reduced force/CSA associated with old age.

Supported by the S.E. Thames Regional Health Authority.

REFERENCES

Bruce, S.A., Newton, D. & Woledge, R.C. (1989). *Qtr. J. Exp. Physiol.* **74**, 359–62.

McKinlay, J.B. (1989). In *Progress In Clinical Research* vol. **320**, ed. Hammond, C.B., Haseltine, F.P. & Schiff, I., pp. 163–192. Alan R. Liss Inc., New York.

Phillips, S.K., Woledge, R.C., Bruce, S.A. & Siddle, N. (1992). *J. Physiol.* **446**, 364*P*.

Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy

S. K. PHILLIPS*, K. M. ROOK*, N. C. SIDDLE†, S. A. BRUCE‡ and R. C. WOLEDGE*

Department of Physiology, University College London, London, U.K., †Department of Obstetrics and Gynaecology, University College Hospital, London, U.K., and ‡Department of Medicine for the Elderly, St Helen's Hospital, Hastings, Sussex, U.K.

(Received 22 May/22 July 1992; accepted 5 August 1992)

1. The time-course of the age-related decline in specific muscle force (maximum voluntary force per cross-sectional area) in men and women was determined by measuring the maximum voluntary force and cross-sectional area of the adductor pollicis muscle in 273 subjects aged 17–90 years (176 men, 30 pre-menopausal women and 67 peri- or post-menopausal women who were not receiving hormone replacement therapy).

2. To determine whether the loss of specific muscle force is hormone-dependent in women, we studied a further 25 women, aged 42–72 years, who were receiving hormone replacement therapy.

3. There was no significant difference in specific force between young men and pre-menopausal women. Around the time of the menopause there was a dramatic decline in specific force in women which was prevented by the use of hormone replacement therapy. In men the weakness started later (around the age of 60 years) and the decline in specific force was more gradual, reaching the level seen in post-menopausal women after the age of 75 years.

4. The protective effect of hormone replacement therapy on muscle strength is likely to be an important contributory factor to its proven action in preventing osteoporotic fractures. The dramatic peri-menopausal decline in muscle strength is a likely explanation for the known increases in falls and Colles' fractures around the time of the menopause.

INTRODUCTION

The muscle weakness associated with ageing has two components. There is weakness due to muscle atrophy [1–3], but a specific weakness of the remaining muscle of around 20% has also been shown by comparing maximum force with muscle cross-sectional area (CSA) in the adductor pollicis of young and elderly human subjects [4] and the hindlimb muscles of young and aged mice [5, 6].

The overall weakness is of the order of 40% and its time-course has been investigated [2, 3, 7]. Comparing measurements of grip-strength in male subjects reported over the past 150 years, it has been suggested that the onset of the weakness may now be occurring later, implying that environmental factors are capable of significant influence [8]. However, neither when the age-related decrease in specific force begins nor the time course by which it proceeds is known. Neither has the time course of the onset of muscle weakness in women previously been compared with that in men. We therefore report measurements of maximum voluntary force (MVF) and CSA in both men and women aged 17–90 years.

The cause of the specific loss of force is also unknown. We have tested the hypothesis that, in women, hormonal factors might contribute. This is suggested by the observations that patients with osteoporotic fractures have been shown to have specific muscle weakness [9, 10], and that bone loss can be prevented by hormone replacement therapy (HRT). We have therefore compared the results obtained in peri- and post-menopausal women not taking HRT with measurements of MVF and CSA from a further group of women on HRT (aged 42–72 years).

Preliminary accounts of this work have been presented to the Physiological Society [11–13].

METHODS

Subjects

Subjects were recruited from students, current staff and retired staff of University College London, pensioners of the Royal Hospital, Chelsea, London, a sports centre in London, a bowling club in Hastings, Sussex, and the menopause clinic at the Elizabeth Garrett Anderson Hospital, London. Altogether 298 subjects between the ages of 17 and 90 years were tested (176 men, 30 pre-menopausal

Key words: ageing, hormone replacement therapy, menopause, muscles.

Abbreviations: CSA, cross-sectional area; MVF, maximum voluntary force.

Correspondence: Dr S.K. Phillips, Department of Physiology, University College London, Gower Street, London WC1E 6BT, U.K.

women, 67 peri- or post-menopausal women who were not receiving HRT and 25 women aged 42–72 years who were receiving HRT).

Subjects were excluded if they: (1) had pain or stiffness of movements of the thumb, (2) had clinically evident wasting of hand muscles, (3) had generalized cardiovascular or neuromuscular disease, or (4) were regularly taking medication likely to affect muscle function or motivation.

The women on HRT (combined sequential oestrogen/progestin, or oestrogen alone in the five women who had had a hysterectomy) had been on therapy between 1 and 25 years (7.8 ± 1.3 years, mean $\pm$ SEM, $n = 25$) and all except two had started peri-menopausally, one of these was 16 years post-menopausal, the other seven years post-menopausal, and they had received HRT for the last 9 and 5 years, respectively. The indications for HRT were menopausal symptoms or prophylaxis against osteoporosis.

Of the subjects not on HRT, five had received treatment a year or more ago for a short time (between 1 and 6 months); all these subjects were 5–17 years post-menopausal.

None of the subjects had had other treatment for osteoporosis. Subjects completed a simple activity questionnaire.

MVF and CSA measurements

MVF of the adductor pollicis of the right hand was measured using a force transducer mounted on a metal bar placed between the bases of the proximal carpal bone of the thumb and the metacarpal bone of the index finger [14]. CSA was determined by measuring the thickness of the hand in the plane that bisects the adductor pollicis muscle by the difference in output from two linear potentiometers which were moved over the skin [15]. For each subject the MVF was a mean of four to nine maximum voluntary contractions and the CSA was a mean of two to four measurements. In this series mean coefficients of variations for each subject were 3.5% for MVF and 7.5% for CSA.

All subjects gave their informed consent. The study was approved by the ethical committees of University College London, University College Hospital and Hastings Health Authority.

Statistical analysis

Unpaired Student's t-tests were used to test for significant differences between data.

RESULTS

Fig. 1 shows MVF plotted against CSA for men aged 17–60 years and pre-menopausal women aged 22–45 years. MVF and CSA were strongly correlated in both groups (men: $n = 148$, $r = 0.83$; pre-menopausal women: $n = 30$, $r = 0.79$) and neither the regression lines nor the mean MVF/CSA values were significantly different. When the data for these subjects were pooled r was 0.86 ($P < 0.001$).

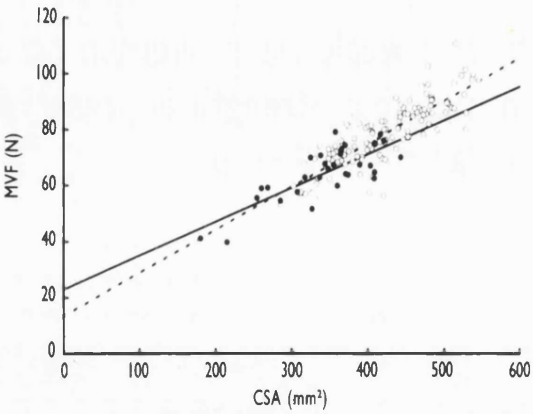


Fig. 1. Relationship between MVF and CSA in men aged 60 years and under (○) and pre-menopausal women aged 45 years and under (●). The regression lines for men (----) and women (——) are also shown. The regression line for men and women combined is not shown, but the equation for the line is $y = 12 + x0.16$.

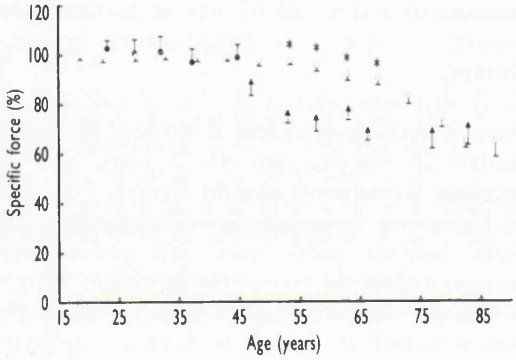


Fig. 2. Relationship between specific force and age for three groups of subjects: men (○), pre-menopausal women (●) and peri- or post-menopausal women (▲). Specific force is expressed as a percentage of the mean value for subjects aged 45 years and under. The points shown are means and SEMS; n ranges between 4 and 18 (mean = 12, men), 4 and 9 (mean = 6, pre-menopausal women) and 5 and 15 (mean = 10, peri- and post-menopausal women). Statistical significance: $^*P < 0.02$ comparing men and women.

Decline in MVF/CSA with age

In order to determine the time-course of the decline in specific muscle strength we plotted mean MVF/CSA for men and women in age groups spanning about 5 years (Fig. 2). This again emphasized the absence of any difference between men and women up to the time of the menopause. Thereafter there was a dramatic decline in strength in women followed by little change, whereas in men there was

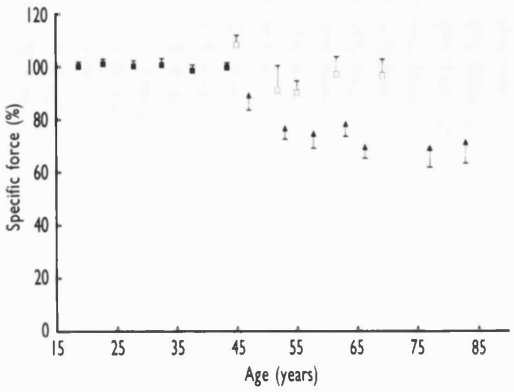


Fig. 3. Relationship between specific force and age in both men and pre-menopausal women aged 45 years and under (■), peri- or post-menopausal women (total 67) not on HRT (▲) and peri- or post menopausal women (total 25) on HRT (□). Specific force is expressed as a percentage of the mean value for subjects aged 45 years and under. Means and SEMS are shown; *n* ranges between 12 and 22 (mean = 18, men and pre-menopausal women), 4 and 15 (mean = 10, peri- and post-menopausal women not on HRT) and 4 and 6 (mean = 5, post-menopausal women on HRT).

a gradual decline which started much later (Fig. 2). For each of the four age groups between 53 and 68 years of age, the MVF/CSA for women was significantly lower than that for men of the same age group (Fig. 2). Only after the age of 75 years did the MVF/CSA produced by men and women once again reach the same level.

MVF/CSA with and without HRT

Fig. 3 shows the effect of HRT on specific force with age. Specific force is plotted in age groups spanning about 5 years. Data from men and pre-menopausal women were pooled, there being no significant difference between their specific forces, in order to simplify the presentation of the data.

To directly compare women on HRT with those who were not, we had to match the groups for age. Comparing subjects between 49 and 73 years of age gave the same mean age of 60 years, the same mean length of time post-menopause (11 years) and same average age at the time of menopause (48 years). There was no significant difference between these two groups in height (no HRT: 1.63 ± 0.01 m, $n = 35$; HRT: 1.62 ± 0.02 m, $n = 21$) or weight (no HRT: 66.7 ± 2.0 kg, $n = 35$; HRT: 62.0 ± 2.8 kg, $n = 21$). None of the women in these two groups was a trained athlete or dancer and there was no difference in their activity scores. However, MVF/CSA was very different between the two groups: those not on HRT were significantly weaker (0.140 ± 0.005 N/mm^2, $n = 35$, $P < 0.001$) than those on HRT (0.176 ± 0.006 N/mm^2, $n = 21$). The MVF/CSA of the pre-menopausal group (0.190 ± 0.004 N/mm^2, $n = 30$) was not different from that of the group on HRT.

DISCUSSION

The time course of the age-related decline in skeletal muscle MVF/CSA in men and women is very different. In men, MVF/CSA is maintained until the age of about 60 years, after which it declines. In women there is a dramatic reduction in MVF/CSA around the time of the menopause. This may elucidate the previously unexplained results of Winner *et al.* [16] showing a peri-menopausal increase in falls and Colles' fractures. Muscle weakness is associated with falls [17] and intuitively the association seems particularly likely when the onset of the weakness is rapid.

The fact that the reduction in MVF/CSA seen in very elderly women (>75 years) has actually occurred in the peri-menopausal years suggests a sex-hormone-dependent change. We tested this by examining the MVF/CSA of post-menopausal women receiving HRT and found that the menopausal decrease in specific force was prevented. The fact that HRT protects against loss of muscle strength as well as bone loss [18, 19] suggests an important additional role for this treatment in the prevention of osteoporotic fractures.

The mechanism whereby hormonal changes result in loss of specific muscle force in ageing female muscle, which can be prevented by HRT, is speculative. We have previously shown that the specific decrease in force seen in very elderly subjects is not due to failure of activation [14]. In the mouse model the decreased maximum force/CSA seen in muscles from aged animals can be restored by applying a rapid stretch during the contraction [6]. This phenomenon is thought to result from a change in an equilibrium, at the level of the cross-bridges, between high- and low-force states. When the muscle is being rapidly stretched all the cross-bridges exert the same maximum force whichever state they are in at the onset of stretch [6, 20]. Similar behaviour, that is decreased isometric force which can be restored by stretch, is also seen in fatigued muscle [21] and can be brought about experimentally by increasing intracellular P_i [22] or lowering H^+ concentration (pH) [23]. Observations so far suggest that there are no significant changes in P_i or pH in aged mouse [23a, 24]. However, it remains a possibility that hormonal influences could alter the sensitivity of the cross-bridges to such metabolites or that some other factor affects the cross-bridge reducing force development with ageing. Our current results show that in women oestrogen is able to prevent the action of this unknown factor.

The corresponding hormonal influence in men might be androgens or the relationship between androgens and oestrogen. Free testosterone levels decline in men from around 60 years of age [25,

26], which is consistent with the time course in reduction in MVF/CSA shown in the present study. This decrease in free testosterone is probably due to decreased Leydig cell mass and function [26]. The administration of testosterone to older men (>50 years) causes a general increase in muscle mass and strength but has no effect on young men, whereas castration is known to cause a reduction in muscle mass and strength [8]; the effect on MVF/CSA has not been studied. In normal men, the peripheral aromatization of androgens is an important source of oestrogens. It is not clear what happens to the levels of oestrogens with age in men [25] and both androgens and oestrogens should be estimated in any study to investigate the possible role testosterone might play in maintaining MVF/CSA in men.

As well as oestrogen replacement preventing menopausal bone loss in women [18, 19], testosterone replacement therapy has been shown to restore bone mass in osteoporotic men [27]. It is not known if these are direct actions of the respective hormones on bone [27]. It is an intriguing possibility that the primary abnormality may be a hormone-related loss of specific muscle strength and that bone loss is secondary to this muscle weakness.

ACKNOWLEDGMENTS

We are grateful to Ms J. Hull of the Elizabeth Garrett Anderson Hospital for her help in recruiting peri- and post-menopausal women. The financial assistance of South East Thames Regional Health Authority, Research into Ageing and Wyeth Laboratories is gratefully acknowledged.

REFERENCES

1. Essen-Gustavsson, B. & Borges, O. Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiol. Scand. 1986; **126**, 107–14.
2. Kallman, D.A., Plato, C.C. & Tobin, J.D. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J. Gerontol. 1990; **45**, M82–8.
3. Vandervoort, A.A. & McComas, A.J. Contractile changes in opposing muscles of the human ankle joint with aging. J. Appl. Physiol. 1986; **61**, 361–7.
4. Bruce, S.A., Newton, D. & Woledge, R.C. Effects of age on voluntary force and cross-sectional area of human adductor pollicis muscle. Q. J. Exp. Physiol. 1989; **74**, 359–62.
5. Brooks, S.V. & Faulkner, J.A. Contractile properties of skeletal muscles from young, adult and aged mice. J. Physiol. (London) 1988; **404**, 71–82.
6. Phillips, S.K., Bruce, S.A. & Woledge, R.C. In mice, the muscle weakness due to age is absent during stretching. J. Physiol. (London) 1991; **437**, 63–70.
7. Narici, M.V., Bordoni, M. & Cerretelli, P. Effect of aging on human adductor pollicis muscle function. J. Appl. Physiol. 1991; **71**, 1227–81.
8. Larson, L. Aging in mammalian skeletal muscle. In: Pirozzolo, F.J. K Maletta, G.J., eds. The aging motor system. New York: Praeger, 1982: 60–98.
9. Bruce, S.A., Ghattaora, R., Phillips, S.K., Sheikh, A. & Woledge, R.C. Hip fracture patients have weak hand muscles. Age Ageing 1992; **21** (Suppl. 1), P12.
10. Jones, D.A. & Rutherford, O.M. Effect of ageing and osteoporosis on the force-generating capacity of the quadriceps muscle in women. J. Physiol. (London) 1990; **423**, 84P.
11. Bruce, S.A., Phillips, S.K. & Woledge, R.C. Strength and cross sectional area of adductor pollicis muscle in men and women. J. Physiol. (London) 1992; **446**, 226P.
12. Rook, K.M., Phillips, S.K., Bruce, S.A. & Woledge, R.C. The effects of ageing on muscle strength in men and women. J. Physiol. (London) 1992; **452**, 25P.
13. Phillips, S.K., Bruce, S.A., Woledge, R.C. & Siddle, N.C. Force and cross-sectional area of adductor pollicis muscle in post-menopausal women, with and without hormone replacement therapy. J. Physiol. (London) 1992; **446**, 364P.
14. Phillips, S.K., Bruce, S.A., Newton, D. & Woledge, R.C. The weakness of old age is not due to failure of muscle activation. J. Gerontol. 1992; **47**, M45–9.
15. Bruce, S.A., Newton, D. & Woledge, R.C. Effect of subnutrition on normalised muscle force and relaxation rate in human subjects using voluntary contractions. Clin. Sci. 1989; **76**, 637–41.
16. Winner, S.J., Morgan, C.A. & Grimley-Evans, J. Perimenopausal risk of falling and incidence of distal forearm fracture. Br. Med. J. 1989; **298**, 1486–8.
17. Wickham, C., Cooper, C., Margetts, B.M. & Barker, D.J.P. Muscle strength, activity, housing and the risk of falls in elderly people. Age Ageing 1989; **18**, 47–51.
18. Lindsay, R., Aitken, J.M., Anderson, J.B., Hart, D.M., MacDonald, E.B. & Clarke, A.C. Long-term prevention of postmenopausal osteoporosis by estrogen. Lancet 1976; **1**, 1038–41.
19. Smith, R. Osteoporosis: cause and management. Br. Med. J. 1987; **294**; 329–32.
20. Lombardi, V. & Piazzesi, G. The contractile response during steady lengthening of stimulated frog muscle fibres. J. Physiol. (London) 1990; **431**, 141–71.
21. Curtin, N.A. & Edman, K.A.P. Effects of fatigue and reduced intracellular pH on segment dynamics in 'isometric' relaxation of frog muscle fibres. J. Physiol. (London) 1989; **413**, 159–74.
22. Elzinga, G., Steinen, G.J.M. & Versteeg, P.G.A. Effect of inorganic phosphate on length responses to changes in load in skinned rabbit psoas muscle. J. Physiol. (London) 1989; **415**, 132P.
23. Curtin, N.A. Force during stretch and shortening of frog sartorius muscle: effects of intracellular acidification due to increased carbon dioxide. J. Muscle Res. Cell Motil. 1990; **11**, 251–7.
23a. Phillips, S.A., Wiseman, R.W., Woledge, R.C. & Kushmerick, M.J. Neither changes in phosphorus metabolite levels nor myosin isoforms can explain the weakness in aged mouse muscle. J. Physiol. (In press).
24. Taylor, D.J., Crowe, M., Bore, P.J., Styles, P., Arnold, D.L. & Radda, G.K. Examination of the energetics of aging skeletal muscle using nuclear magnetic resonance. Gerontology 1984; **30**, 2–7.
25. McKinlay, J.B. Prog. Clin. Res. 1989; **320**, 163–92.
26. Vermeulen, A. Clinical review 24: androgens in the aging male. J. Clin. Endocrinol. Metab. 1991; **73**, 221–4.
27. Marcus, R. Skeletal ageing: understanding the functional and structural basis of osteoporosis. Trends Endocrinol. Metab. 1991; **2**, 53–8.