FATIGUE OF LONG DURATION IN HUMAN SKELETAL MUSCLE AFTER EXERCISE

By R. H. T. EDWARDS,* D. K. HILL, D. A. JONES*
AND P. A. MERTON†

*From the Jerry Lewis Muscle Research Centre, Royal
Postgraduate Medical School, Du Cane Road, London W12 0HS,
and the Physiological Laboratory, Cambridge†*

SUMMARY

1. After severe muscular contraction in man recovery of force is largely complete in a few minutes, but is not wholly so for many hours. The long-lasting element of fatigue is found to occur primarily for low frequencies of stimulation (e.g. 20/sec), and is much less pronounced, or absent, at high frequencies (80/sec). The twitch force is an unreliable measure of the state of fatigue.

2. The long-lasting element of fatigue is not due to depletion of high-energy phosphate nor is it due to failure of electrical activity as recorded from surface electrodes. It is probably the result of an impairment of the process of excitation-contraction coupling. Its practical importance for man could be significant as an explanation of the subjective feelings of weakness following exercise.

INTRODUCTION

It has been known for some years that prolonged stimulation of isolated muscle, particularly under anaerobic conditions, may result in an almost total loss of the mechanical response even though the action potential remains near normal and the contractile mechanism (as tested by a caffeine contracture) is unimpaired. This effect, which has been attributed to a failure of excitation-contraction coupling, reverses only very slowly (Eberstein & Sandow, 1963; Mashima, Matsumara & Nakayama, 1962; Grabowski, Lobsiger & Lüttgau, 1972). In this paper evidence is presented which suggests that this type of fatigue occurs in human muscle after a variety of forms of physical activity. A preliminary account of the work has already been presented (Edwards, Hill, Jones & Merton, 1974).

* Present address: Department of Human Metabolism, University College Hospital Medical School, University Street, London WC1E 6JJ.

METHODS

The experiments were made on eight normal adult males aged 28–60 yr.

The adductor pollicis was studied in experiments both at Cambridge and Hammersmith using a dynamometer based on that of Merton (1954). A strain gauge was attached by an inextensible link to a loop around the interphalangeal joint of the thumb. The hand was secured in supination with the fingers slightly flexed, the thumb abducted and its metacarpophalangeal and interphalangeal joints both fully extended. The ulnar nerve was supramaximally stimulated at the wrist with 50 μsec pulses up to 80 V.

Contractions of the quadriceps femoris were studied with the subject seated in an adjustable straight-back chair with the knee flexed to 90° (Tornvall, 1963). The pelvis was secured by a seat belt, and the ankle was connected to a strain gauge by a strap. For electrical stimulation two flexible saline-soaked electrodes (13 cm square) were applied proximally and distally to the anterolateral thigh. Stimulation was with 50 μsec pulses up to 70 V. Electrical stimulation produced contractions of up to 60 % of a maximal voluntary contraction, but the voltage was normally adjusted to give only 15–30 %. It has previously been shown that results obtained by submaximal stimulation give a reliable estimate of the function of the whole muscle (Edwards, Hill & McDonnell, 1973; Edwards, 1975; Edwards, Young, Hosking & Jones, 1977).

The control of muscle temperature is not a problem when studying a large muscle such as the quadriceps, but when dealing with a small distal muscle this does become an important matter. Tests with a thermocouple showed that even with a room temperature of 20 °C the temperature of the adductor pollicis may be as low as 29 °C. Experiments were therefore always preceded by 10 min immersion of the hand and forearm in a water bath at 44 °C, which brought the muscle to about 35 °C.

The effects of prolonged isometric contractions on adductor pollicis were studied with the circulation arrested by a cuff around the upper arm inflated to 200 mmHg. In some experiments the contractions were elicited by a succession of periods of stimulation at a frequency of 20/sec, separated by periods of aerobic recovery. In others the muscle was fatigued by sustaining a force of about half the maximum voluntary contraction until the discomfort could no longer be tolerated, followed by rest for about 20 sec to relieve the discomfort with ischaemia continued, then repeated contraction at the same force (or as much as could be produced) again to the point of endurance, and so on until practically no further contraction was possible.

In the quadriceps the fatigue effect was produced by voluntary contractions only. In one series these were isometric contractions at the greatest force that could be maintained following the same type of sequence as with the adductor pollicis, that is with brief periods to relieve the discomfort but with ischaemia maintained, and continuing until the muscle could scarcely be made to contract either by voluntary effort or by electrical stimulation. In two experiments samples of muscle were obtained by the needle biopsy technique (Bergström, 1962; Edwards, 1971) for chemical analysis of ATP and phosphorylcreatine (PC) (Edwards, Jones, Maunder & Batra, 1975).

To ascertain whether the observed changes occurred after exercise which was not so severe as to cause almost total loss of force, studies were carried out to determine the time course of recovery of the quadriceps following stepping exercise or exercise on a bicycle ergometer.

Further experiments were performed on five subjects to compare the electromyogram of the adductor pollicis before and after fatiguing voluntary contractions of

the kind described. The surface e.m.g. was recorded from silver electrodes 0·8 cm diameter, one placed over the belly of the adductor pollicis and the other on the tip of the index finger.

RESULTS

Contraction force increases steeply as stimulation frequency is increased in the range 10–30/sec, and the curve levels off at higher frequencies. The results for the quadriceps and the adductor pollicis are very similar (Fig. 1 and Edwards *et al.* 1977). For testing the muscle before and after fatigue the twitch was recorded (but proved an unreliable index – see
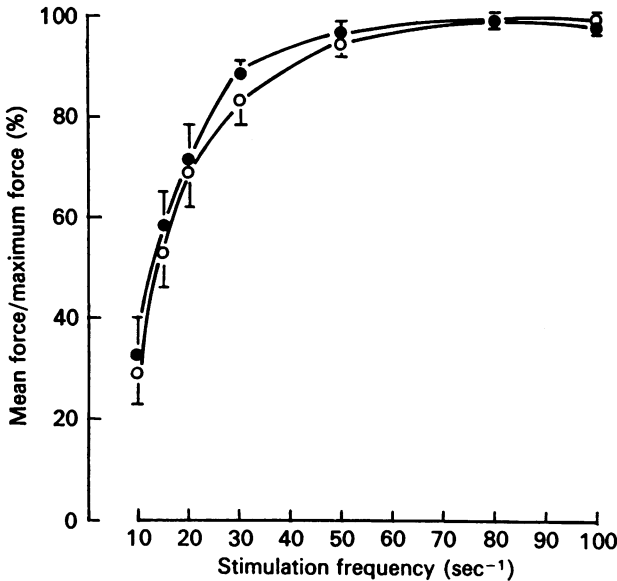

Fig. 1. Force generated in the adductor pollicis and quadriceps muscles by stimulating at different frequencies. ●, quadriceps; ○, adductor pollicis. Vertical bars indicate + or − 2 s.e. of mean (ten subjects).

below) and also tetani of 1–2 sec duration at two frequencies: (*a*) well below the 'plateau' of force; generally 20/sec, and (*b*) on the 'plateau', at a frequency in the range 50–100/sec.

The force generated by a twitch and by stimulating at 20 and 100/sec was measured during a series of fatiguing contractions in the adductor pollicis. The muscle was stimulated at 20/sec with the hand made ischaemic by a cuff inflated around the arm. After 50 sec the cuff was released and at successive 5 sec intervals the muscle received a single twitch, a 1 sec tetanus at 20/sec and a 1 sec tetanus at 100/ sec. Fifty sec after the end of the previous fatiguing tetanus the cuff was reinflated and the

muscle again stimulated for 50 sec. This procedure was repeated 17 times (Fig. 2) and it was clear that the twitch and the 20/sec tetani were more severely affected by the fatiguing regime than was the tetanus at 100/sec.
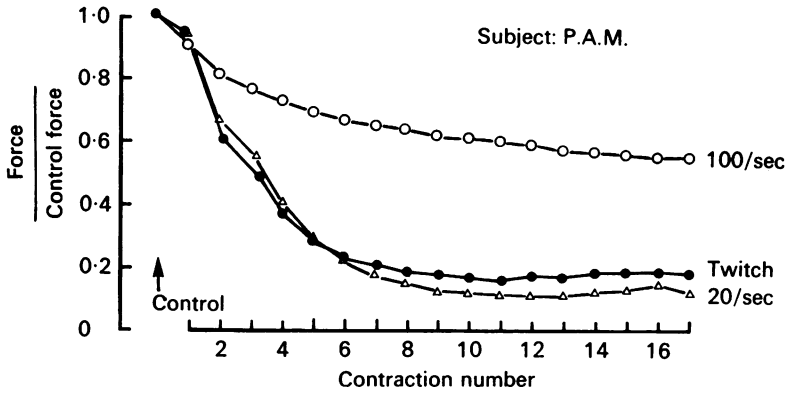

Fig. 2. Changes in relative peak tension developed in twitch and 1 sec tetani at 20 and 100/sec in adductor pollicis when tested after fatiguing contractions elicited by motor nerve stimulation at 20/sec for 50 sec alternating with 50 sec recovery intervals. Muscle blood supply was arrested with a cuff during each contraction but was unimpeded during the recovery intervals.
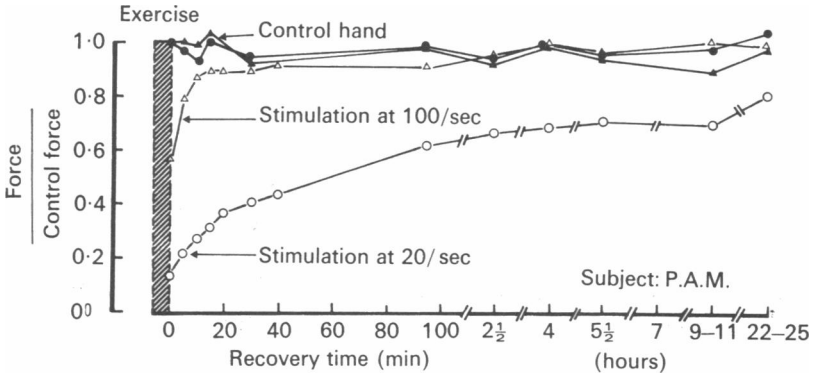

Fig. 3. Recovery from fatigue caused experimentlly as in Fig. 2. Note that whereas the force of 1 sec tetani at 100/sec increases in the first 20 min to a value which is close to that in the control (unfatigued) hand, that at 20/sec takes many hours to recover.

In the fresh muscle at the start of the experiment the tetanic force at 20/sec was 68 % that at 100/sec while after the 17th fatiguing contraction it was reduced to 12 %.

Recovery was followed using 1 sec test tetani at intervals over the following 24 hr. In the first 30 min there was a rapid recovery of force at 100/sec to about 90 % of the initial fresh value (Fig. 3). It is not clear,

however, at what time the muscle was fully recovered since values for the unstimulated hand showed a fluctuation of between 5 and 10% during the 24 hr period.
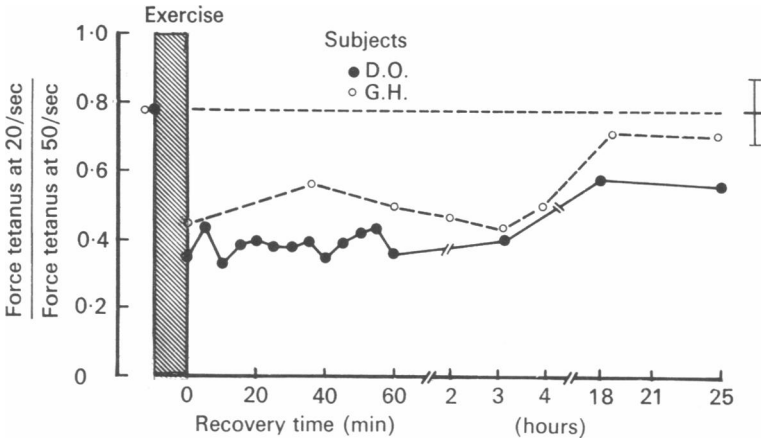

Fig. 4. Recovery of low frequency force fatigue after three maximum isometric contractions of the quadriceps muscle sustained to fatigue under conditions of local circulatory arrest. Horizontal dotted line gives the ratio of tetani at 20 and 50/sec for 26 fresh normal subjects. Vertical bar indicates ± 2 s.d.
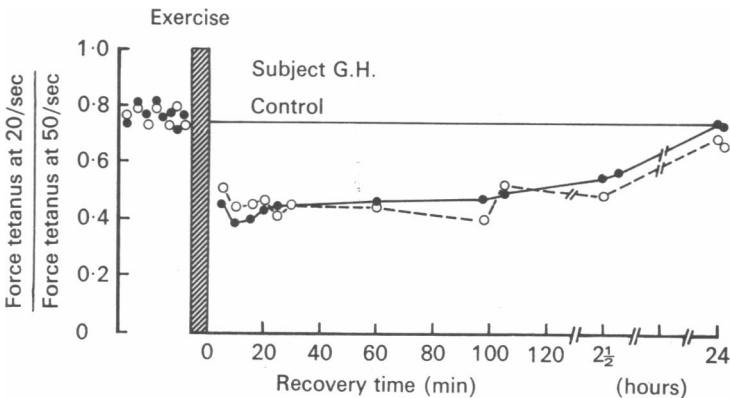

Fig. 5. Recovery of the ratio of forces in 5 sec tetani at 20 and 50/sec in the quadriceps muscle after stepping exercise at approximately 250 watts for 15 min. ●, right leg; ○, left leg. The 'control' line is the ratio for the subject determined before the start of the exercise.

The possibility that the results were a consequence of an increase in stimulus threshold of the nerve was eliminated by increasing the stimulus voltage to check that it remained supramaximal throughout.

Studies on the quadriceps muscle showed that a similar form of fatigue can occur both as the result of voluntary isometric contractions (Fig. 4)

and of dynamic exercise: the subject stepped on and off a low chair for 15 min (Fig. 5). Electrically stimulated contractions at 20 and 50/sec were recorded. Note that the ratio of the forces decreased markedly. The same features of fatigue were found in another subject who exercised on two occasions on a bicycle ergometer. On the first occasion his power output was progressively increased by 17 W every minute until he could continue no longer. In the second study the subject exercised for 60 min
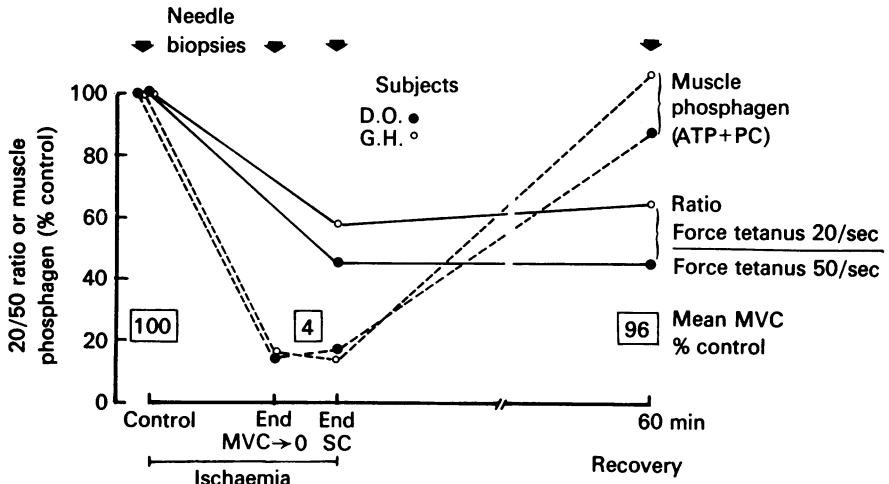

Fig. 6. Changes in muscle phosphagen (ATP + PC) content, MVC and ratio of forces of tetani at stimulation frequencies of 20 and 50/sec (MVC → 0 = maximum voluntary contraction sustained until no further force can be voluntarily generated, SC = attempt to cause muscle to contract by stimulation at 20 sec^{-1}). Control values for the variables studied are those determined before the start of the series of fatiguing contractions.

at a rate equivalent to 60 % of his maximal oxygen intake. The ratio for the forces of tetani elicited by low and high frequency stimulation of the quadriceps fell significantly on both occasions and recovered over the next 1½ hours.

In two subjects needle biopsies were obtained before the start, immediately at the end of a series of maximum voluntary contractions and finally after 60 min recovery. The force of the maximum voluntary contraction was reduced to 0 and to 8 % of the normal values in the two subjects and the muscle content of 'phosphagen' (ATP + PC) was reduced to about 10 % of the normal value. After 60 min, recovery of the maximum voluntary contraction force and tissue phosphagen content was virtually complete, while the ratio of the forces obtained by stimulating at 20 and 50/sec remained depressed (Fig. 6).

In a series of experiments on the adductor pollicis in which fatigue was

produced by repeated prolonged voluntary contractions under ischaemic conditions, no change in the shape or amplitude of the surface recorded action potential was seen when these were sampled during tetanic trains at 20 and 100/sec at times when there was significant loss of force at the lower frequency. This suggests that the preferential loss of force at low frequencies is not a consequence of changes in the electrical properties of the muscle or the neuromuscular junction.

DISCUSSION

A description has been given of a long-lasting form of fatigue which is manifest preferentially at low frequencies of stimulation. It is not attributable to a depletion of high energy phosphate, nor to a failure of the muscle action potential. The disproportionate loss of force at low frequency would be expected if there was a reduction in the amount of contractile activation produced by the passage of an action potential. At high frequencies the effect would be smaller because then the total, summated, level of activation approaches the saturation level and a change in the amount of activation per pulse would have a smaller, or negligible, net effect.

Following a series of fatiguing contractions there is a rapid recovery of high frequency tetanic force (Fig. 3), but it is difficult to say at what time recovery is complete. This is because with a human muscle preparation there are changes over a period of hours as the result of slight alterations in the position of the hand in the apparatus, and possible fluctuation in blood hormone and electrolyte levels which may influence muscle function. There is the possibility, therefore, that there may also be a slow recovery phase with tetani at high frequencies but what can be stated with certainty, is that slow recovery is very much more evident with the low frequency contractions. To emphasize the difference between high and low frequencies and to avoid complications as the result of not knowing quite what value to use for the control force, we have expressed many of the results as the ratio of the forces obtained at the two test frequencies. Although the high frequency tetani recover rapidly (Fig. 3) this occurs in a matter of minutes and is not sufficiently rapid to account for the different time courses of the tetani at 20 and 100/sec shown in Fig. 2. Test tetani were made within 18 sec of the end of the fatiguing tetanus thus permitting only very minimal recovery. The peak force in a twitch is only about one tenth of the tetanic force. This means that the mechanical response is bound to be critically sensitive to a change in the amount of activation per pulse. In a fresh muscle the activation per pulse can vary over a wide range, as is shown by the phenomenon of post-tetanic

potentiation, or staircase potentiation, the effects may be large correspond-
ing perhaps to a doubling of activation per pulse. So, with a coupling
mechanism which can be so variable in its 'efficiency' even under normal
conditions, it is not surprising to find an impairment as a consequence of
severe exercise. On the other hand the slowness of the recovery would
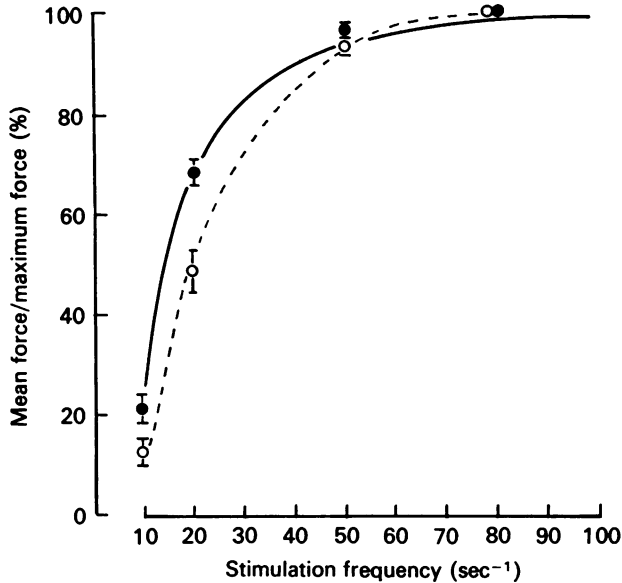not be anticipated.

Fig. 7. Long lasting effects of ischaemic fatigue on the force/frequency
relations of the adductor pollicis in five subjects. Results are the mean
± S.E. of mean. ●, fresh muscle; ○, 1½–2 hr after ischaemic fatigue. Con-
tinuous line taken from data for adductor pollicis in Fig. 1.

If this is the correct interpretation it might be expected that the long-
term fatigue effect would be at least as prominent for twitches as for low
frequency tetani. In many experiments (not reported here) this indeed
proved to be the case, but in others it was not so: it has seemed better
to restrict this account to what has been strictly repeatable. The incon-
sistency is probably connected with the remarkable variability of the
single twitch in mammalian muscle, referred to above.

Some experiments have shown a significant loss of force for high fre-
quency stimulation (80/sec) as a long term effect of severe exercise. The
reduction, when it occurs, is always less than for lower frequency stimula-
tion (20/sec). The time course of the onset and recovery of high frequency
fatigue is not the same as for low frequency fatigue: it develops to its
maximum 1–2 hr after the end of the fatiguing contraction and then
disappears before the low frequency force is restored. This suggests that

the origin of high frequency fatigue is not the same as for low frequency type.

In man the practical consequences of the form of long-term fatigue described here may be significant. The firing frequency for motor units in sustained voluntary contraction (say more than 10 sec duration) is generally no more than 30/sec (Freyschuss & Knutsson, 1971; Marsden, Meadows & Merton, 1971; Grimby & Hannerz, 1977) and in the submaximal contractions involved in most of everyday activities the frequency is probably in the range 10–20/sec. The present results (Fig. 7) show that the force at such frequencies may be reduced to about one half for several hours after severe physical activity. This means that the performance of a given task will require the recruitment of a larger number of motor units and/or an increase in the mean firing frequency of the motor nerves. Whether such compensation can be perceived and contribute to the subjective feeling of effort has yet to be investigated.

It has been suggested that the cause of fatigue described here (that is, impaired excitation-contraction coupling) may be present at all times, or produced by minor exertion, in certain forms of disease (for example, myasthenia gravis, Botelho, 1955; primary hypokalaemic periodic paralysis, Engel & Lambert, 1969). It has also been suggested that the efficiency of coupling may be modified by drugs (e.g. diazepam, Lundin & Robert, 1974; dantrolene sodium, Ellis & Bryant, 1972). It may perhaps be dependent on normal variations in hormonal or other blood constitutents, it may vary with differing fibre type patterns. Further studies are indicated.

REFERENCES

BERGSTRÖM, J. (1962). Muscle electrolytes in man. *Scand. J. clin. Lab. Invest.* suppl. 68.

BOTELHO, S. Y. (1955). Alterations in muscle tension without similar changes in electrical activity in patients with myasthenia gravis. *J. clin. Invest.* **34**, 1403–1409.

EBERSTEIN, A. & SANDOW, A. (1963). Fatigue mechanisms in muscle fibres. In *The Effect of Use and Disuse on Neuromuscular Function*, pp. 515–526. Prague: National Academy of Czechoslovakia.

EDWARDS, R. H. T. (1971). Percutaneous needle biopsy in diagnosis and research. *Lancet* ii, 593–596.

EDWARDS, R. H. T. (1975). Muscle fatigue. *Postgrad. Med. J.* **51**, 137–143.

EDWARDS, R. H. T., HILL, D. K. & McDONNELL, M. (1973). Metabolic heat production and relaxation rate of electrically stimulated contractions of the quadriceps muscle in man. *J. Physiol.* **231**, 81–83P.

EDWARDS, R. H. T., HILL, D. K., JONES, D. A. & MERTON, P. A. (1974). Fatigue of excitation-contraction coupling after prolonged stimulation of human muscle. Abstract No. 778 of the International Physiological Congress. New Delhi: I.U.P.S.

EDWARDS, R. H. T., JONES, D. A., MAUNDER, C. & BATRA, G. J. (1975). Needle biopsy for muscle chemistry. *Lancet* i, 736–740.

EDWARDS, R. H. T., YOUNG, A., HOSKING, G. P. & JONES, D. A. (1977). Human skeletal muscle function: description of tests and normal values. *Clin. Sci. molec. Med.* **52**, 283–290.

ELLIS, K. O. & BRYANT, S. H. (1972). Excitation-contraction uncoupling in skeletal muscle by Dantrolene Sodium. *Naunyn-Schmiedebergs Arch. exp. Path. Pharmac.* **274**, 107–109.

ENGEL, A. G. & LAMBERT, E. H. (1969). Calcium activation of electrically inexcitable muscle fibers in primary hypokalemic periodic paralysis. *Neurology, Minneap.* **19**, 851–858.

FREYSCHUSS, U. & KNUTSSON, E. (1971). Discharge patterns in motor nerve fibres during voluntary effort in man. *Acta physiol. scand.* **83**, 278–279.

GRABOWSKI, W., LOBSIGER, E. A. & LÜTTGAU, H. CH. (1972). The effect of repetitive stimulation at low frequencies upon the electrical and mechanical activity of single muscle fibres. *Pflügers Arch. ges. Physiol.* **334**, 222–239.

GRIMBY, L. & HANNERZ, J. (1977). Firing rate and recruitment order of toe extensor motor units in different modes of voluntary contraction. *J. Physiol.* **264**, 865–879.

LUNDIN, D. P. & ROBERT, F. (1974). The action of Diazepam on human skeletal muscle. *Europ. Neurol.* **11**, 345–352.

MARSDEN, C. D., MEADOWS, J. C. & MERTON, P. A. (1971). Isolated single motor units in human muscle and their rate of discharge during maximal voluntary effort. *J. Physiol.* **217**, 12–13P.

MASHIMA, H., MATSUMARA, M. & NAKAYAMA, Y. (1962). On the coupling relation between action potential and mechanical response during repetitive stimulation in frog sartorius muscle. *Jap. J. Physiol.* **12**, 324–336.

MERTON, P. A. (1954). Voluntary strength and fatigue. *J. Physiol.* **123**, 553–564.

TORNVALL, G. (1963). Assessment of physical capabilities with special reference to the evaluation of maximal voluntary isometric muscle strength and maximal working capacity. *Acta physiol. scand.* **58**, suppl. 201.