Muscle Fatigue

The Scientific Basis of Medicine

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Black-and-white
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<Opening titles>

<Edwards to camera>

A skeletal muscle is said to be fatigued when it fails to sustain the required force. Fatigue can be demonstrated in an isolated frog muscle and it can, of course, be observed in a patient or even in a normal subject after continual activity. With my colleagues at the Royal Postgraduate Medical School, I've been interested in studying the physiological and metabolic basis of muscular fatigue in man, and in order to begin, I should start with the factors controlling muscular contraction and these are shown here.

<Edwards refers to series of diagrams and slides and narrates over them, interspersed with talk to camera>

The motor pathway from the brain to the muscle involves the spinal cord and the peripheral nerves. Then a transfer of information through the neuromuscular junction from the motor nerves to the muscle itself. The processes involved in contraction and the force generated depend on the recruitment of muscle fibres, and this recruitment is governed by information which travels back to the spinal cord and further up – sensory pathways within the brain, and this together constitutes a very complex series of server mechanisms which give the fine, co-ordinated muscular contractions that we know so well. Now, in fact, another subtle factor which controls and influences the way in which a patient may recognise how or not his muscles are working normally depends on the adequacy of performance, and these involve visual feedbacks, feedback through other sensory pathways to the brain and possibly other psychological influences in which the subject or patient judges whether or not the performance is appropriate for what his needs are.

<*To camera*> Now neurologists and necrophysiologists, in the past, have for many years studied muscle function, very effectively studying neuromuscular transmission, nerve conduction velocity and the electrical properties of the muscle itself. But, it occurred to us, that since fatigue and the closely allied symptom of muscle weakness are in themselves symptoms based on failure of generating an appropriate force within the muscles, that it would be worthwhile developing methods for assessing muscle function which were based primarily on the measurement of muscle force.

Now, I shall begin by showing some new tests that are useful for assessing muscle function at the bedside, and then to take the matter further and study muscle function at a cellular level, first by measuring metabolic production with the thermal probe which we have developed at Hammersmith, and then further to study the structure and the chemical changes within the muscle by sampling the muscle with a needle biopsy technique which we've recently introduced here.

Now let us turn to the clinical assessment of muscle function. <*Slide*> A clinical grading scale was introduced sometime during the last war when disturbances of neuromuscular function due to injury were unfortunately very common and in order to follow the severity of the resulting weakness and the course of recovery, this particular scale was introduced.

<Slide>

0 no contraction
1 flicker or trace of contraction
2 active movement with gravity eliminated
3 active movement against gravity
4 active movement against gravity and resistance
5 normal power

And as you see, it covers the very broad range from no contraction, through active movements with gravity eliminated, and active moments against gravity to normal power. But these are rather broad categories and this does not give a very precise indication of muscle power <*to camera*> and if comparisons are to be made on different occasions and by different observers, it is necessary for us to have more precise, quantitative test for muscle function which can be added into the usual clinical examination. These I'd like to show you now.

00:04:51:06

<Edwards to camera: he stands beside a patient lying supine on an examining table>

Neurologists have for many years found it useful to time how long the subject can hold a limb up above the couch as a test of the function of the hip flexors. I'll show you. <*To patient*> Can you hold your leg up at 45 degrees and hold it up there for as long as possible, please?

<*To camera*> Now, from studies on the large number of normal men and normal women, Fessel and colleagues have recently found that the lower limit for normal men for this procedure is 60 seconds and for women 30 seconds.
<*To patient*> That'll do now, thank you very much indeed.

<*To camera*> The other test that has been recently quantitated and in which we are finding similar results, in fact, at Hammersmith is to time how long the subject can hold his head off the couch <*Edwards raises patient's head at angle of about 45 degrees from couch*>. <*To patient*> Keep it there now for as long as possible, please. The fact is that this can be kept up in a normal man for at least 90 seconds and in a female for at least 30 seconds. <*To patient*> Now, I think, that'll do for now, thank you very much indeed.

<*To camera*> Now, of course, this test depends a lot on motivation on part of the subject and we have felt that it is worthwhile to have a way of quantitating the force of contraction of the muscles that have been tested in this way, in order to see whether any poor performance could be due to muscle weakness at the start. Of course, this type of test is useful only to confirm normality and, in fact, if the patient has results which fall within the normal range, then they can be reassured, but if they do not have normal results, then it is necessary to take this further with more detailed study, which I'll be coming along to.

<Edwards demonstrates clinical force dynamometer>

But this little instrument here is a clinical force dynamometer which we've recently developed for use at Hammersmith on our patients complaining of muscle weakness or fatigue. You'll see here that it comprises a metal bellows, which is oil filled, and it's connected to a pressure gauge, and then with this little dial on the upper surface of it, it's possible to see the maximum force that is generated in contact between the examiner's hand and the part of the body to which it is being applied. It's a very simple tool, but we've found it useful in checking some of the results in clinical tests like this.

Let me demonstrate how it's being used. First thing to remember, in using this, is that it is the maximum force that is necessary to overcome a resisted movement on the part of the patient that is being recorded. So, I'll ask the subject to hold the head up and then keep it there. Don't let me press it down. There we are, thank you. The force necessary to overcome neck flexion in this healthy subject was 11 kilograms. Now, this is a simple tool and it can be used to measure muscle function in a number of different places, but one thing that must be remembered again is that standard anatomical sites must be used, not only because of the variation from time to time and the way in which different observers may use the tool, but because the force exerted on the lever and the force recorded here varies according to the position on the limb. In order to study these things in more detail, however, it is necessary to investigate the function of a single muscle in a great deal more detail than has been possible in this sort of bedside test […]

<Edwards narrates over diagram>

[…] and there are a number of muscles in the body which can be studied but we have chosen to study the quadriceps muscle. This is because it is an important muscle for physical activities in everyday life and it is frequently affected in proximal myopathies. Further advantages, which will become evident in the remainder of my lecture, is that this muscle is large enough and free of important blood vessels and nerves to allow probes to be inserted and for small samples to be taken by a needle biopsy technique without risk.

<Edwards to camera and then refers to series of diagrams and narrates over them. Interspersed with talk to camera>

Let me show you how we study the quadriceps. The subject sits in an adjustable chair. The pelvic girdle is attached with a seatbelt and the force of contraction is measured at the ankle when the subject makes an effort to extend the knee and the force is measured with a strain gauge. Now, in a contraction in which there is no movement, this is called an isometric contraction and this type of contraction is associated with an exchange of energy from the chemically stored energy into force,

<*to camera*> and since there is no external work done, all the energy appears as heat. And I shall be showing how this heat can be measured and what we can learn from this.

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But first, let us look at the relationship between the force of contraction and the time for which a contraction can be held. Obviously, it's common experience that the higher the force, the shorter time for which it can be held. Now, Rohmert in Germany studied this in a great deal of detail some years ago and brought out what might be called a law. <*Next diagram*> This is his curve here which in a graph relates the endurance time to the contraction force, and the contraction force is expressed as a percentage of the maximum force possible in a voluntary contraction. Rohmert delineated this law from over 6000 measurements in 13 different muscle groups in 38 normal subjects. Well, we have tested the same thing in the quadriceps muscle in a group of sedentary individuals and in a group of athletes, and broadly speaking the results agree with Rohmert, possibly the athletes have a better endurance, perhaps because of improved motivation on their part and perhaps because of changes in their muscle. But, the point I want to make from this is that the time for which a contraction can be held depends on two things <*to camera*>: first is the standard on which the force of contraction has been established and that is the maximum contraction force, and this has to be determined with some precision and this may not be possible always in patients. The second thing is that the endpoint of the long sustained isometric contraction demands quite a lot of motivation and determination on part of the subject, and a considerable amount of variation is possible, particularly in patients as regards to the endpoint of such a contraction and I'll be showing how we can be making objective assessments of this endpoint.

Well, first of all, let us consider the force of a maximum voluntary contraction. Now, it is very difficult for us to determine how exactly the muscle should be contracting maximally. For one reason, muscle may be weak because it has lost muscle fibres or, alternatively, it may be weak because the force generated by each individual fibre is, in fact, lower than normal, or, as may well be the case in a number of conditions, a

mixture of both. Well, we have found a useful relationship which is helpful in determining whether a patient has a normal power in the quadriceps or not by relating <*next diagram*> the force of a maximal voluntary contraction with the body weight. We've studied a number of young children and adults and found a very highly significant relationship between the force of a maximum voluntary contraction and body weight. Clearly, if a patient is capable of generating a normal power in voluntary effort, then this is encouraging and can be used to reassure the patient that there is no objective evidence of weakness. <*To camera*> But, of course, if the patient is unable to generate a sufficiently normal force then it's necessary to look further and I shall be describing ways now of assessing whether the force of maximum voluntary contraction is indeed maximal. And the key to doing this is really the use of a thermal probe and with this we measure the maximum metabolic heat production in the muscle. Let me show the instrument now.

<Edwards narrates over shot of probe>

The probe itself is made of nylon and has a thermistor at its tip and has to be inserted into the muscle first after inserting a cannula under local anaesthesia. And then the probe is pushed down the cannula into the muscle until its end projects some 5 to 10 millimetres beyond the end of the cannula and its tip is some 30 to 50 millimetres deep to the skin surface, deep within the muscle. Now this probe was designed by Dr David Hill and myself at Hammersmith and made by Mr Michael MacDonald in the school workshop. It is sensitive to a thousandth of a degree centigrade and has been the instrument that we've used for the measurements of metabolic heat production that I shall describe.

<Edwards to camera>

Now, the idea behind doing this is to see whether the rate of heat production in a contraction – in a maximum voluntary contraction – is as great as that in a maximum electrically stimulated contraction. Now you might say immediately, why not simply see whether the force generated in a maximum stimulated contraction and a maximum voluntary contraction are the same? Well, I have to admit, from rather

painful personal experience, that maximum tetanic stimulation of the femoral nerve is rather painful and this is not something that is practical for clinical purposes or for very many investigations, though I would say that the force is, in fact, equal in a maximum voluntary and maximum stimulated contraction when the femoral nerve was supermaximally stimulated. And the heat measurements were, in fact, the same in both instances, but let me show you some records obtained with this instrument.

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<Edwards refers to diagrams and narrates over them, interspersed with talk to camera>

Here is the record of the force measurement in a voluntary contraction during a contraction lasting about 15 seconds. The temperature in the muscle increased steadily during the contraction and the slope of this rise in temperature is the rate of rise of temperature and indicates the metabolic heat production in the muscle.

In an electrically stimulated contraction not all the muscle is, in fact, activated because it has been found to be practical to stimulate only about half the muscle bulk through saline-soaked electrode pads placed on front of the thigh. This is not particularly painful and it is possible by this way to have sufficient muscle working maximally so that there is a uniform heat generation in the region of the probe; and the thermal record again shows the rate of rise of temperature and the rate of heat production in the muscle.

<*To camera*> Well, let me show you the results of a formal comparison between the rate of rise of temperature in stimulated and voluntary contractions in a group of normal subjects and patients. <*Next diagram*> Here is the rate of rise of temperature in degrees centigrade a minute in a voluntary contraction and this is contrasted with the same in an electrically stimulated contraction. This is a line of equality. The results in normal subjects, starting with fresh muscle, are shown here as solid dots; and then after a period of repeated contractions, the muscle force fell off and the rate of heat production in the muscle declined, but notice that even when the muscle was

fatigued in this way, the rate of heat production in the voluntary contraction was closely similar to that in a maximum stimulated contraction in the normal subjects, both with fresh and fatigue muscle.

In the case of the patients who had fresh muscle in this instance, the results are shown here and again the results agreed very well that voluntary contractions and stimulated contractions have the same rate of heat production. <*To camera*> So from this it can be concluded that it is possible to activate a muscle maximally under voluntary effort and this is something that a number of patients are capable of doing soon.

Now let's look at the clinical implication of this a little further. <Next diagram> Here I've plotted the same graph: this is the rate of heat production <*indicates y-axis*> voluntary contraction and this <*indicates x-axis*> is stimulated contraction. Here is the normal range for the maximum metabolic heat production from a number of studies in normal subjects, and the range goes from 0.6 to 1.2°C a minute. Now, if a patient is capable of achieving the same rate of heat production in two types of contraction then it indicates that the control mechanisms for muscular contraction and the metabolic processes involved in muscular contraction are working normally. If, however, the patient is unable to have a sufficiently large contraction under voluntary effort and thereby finds that the rate of heat production in voluntary contraction is less than that in a stimulated contraction, then this would indicate some impairment of the neuromuscular control mechanisms involved in contraction, either because of impaired neuromuscular transmission or involvement of the multi pathways in some way or for psychological reasons. And these are matters which have to be looked into further, by, in the case of impaired neuromuscular transmission if this is suspected, repetitive nerve stimulation or pharmacological tests for these are conventional neurological tests now.

The other possibility seen from this study is that the rate of heat production in the voluntary contraction and the stimulated contraction may, indeed, be the same, but it may be lower than normal; and this is something that we have seen and it suggests the possibility that either the muscle in the patient is behaving in a way analogous to

the fatigued muscle in a normal subject or, that for reasons to do with the mobilisation of energy supply mechanisms within the muscle, that the maximum metabolic rate in the muscle in the patient is actually lower than normal. And these are open to investigation further, particularly using the needle biopsy method to sample the muscle.

<*To camera*> Now, the key to investigating these further is indeed to look at the chemistry, but before leaving the myofilament measurements, it's perhaps worth pointing out that although these are still in the experimental stage, we have been able to make the thermal probe much smaller.

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<Edwards narrates over shot of thermal probe>

And here is shown the new development which is a screened thermocouple needle, which is small enough now that it's really little larger than the EMG needle, concentric needle electrode, which is conventionally used in studying patients with neuromuscular disorders. And with this needle it's been possible for us to study the maximum heat production in some of the small muscles of the hand.

<Edwards to camera>

Well, the key to looking further at the factors involved in muscle fatigue is to sample muscle at the end of a sustained submaximal isometric contraction. And I propose to make a short digression at this point to show you some of the ways in which needle biopsy can be used to study muscle, and in order to do this, I'll show you some excerpts from a film that we made recently for this purpose.

<Film with narration, unspecified narrator>

The idea of obtaining small samples of human muscle with a needle is not new. Duchenne in his original description of pseudohypertrophic dystrophy, which he

published in 1868, describes a needle for obtaining muscle samples for histology. The needle biopsy technique was neglected for nearly a century until reintroduced by Bergström in Sweden for the purpose of measuring muscle electrolytes. There are three parts to Bergström's needle: a trocar, an inner cutting cylinder and the needle proper. The trocar is used only to remove the sample from the needle after use. A simple manipulation moves the inner cutting cylinder and opens the window near the end of the needle. Tissue bulging into this window is guillotined and retained in the needle as it is withdrawn from the muscle.

<Edwards to camera, holding a Bergström's needle >

In fact, this is rather a large needle and it has to be inserted under local anaesthesia. This is what is done: the skin and subcutaneous tissues are anaesthetised with Xylocaine and then an incision is made with a sharp pointed surgical blade. This incision need only be some 4 or 5 millimetres long. The muscle is not anaesthetised because for two reasons really. One, is that the muscle doesn't have the same sort of pain endings as skin and the sensation that is experienced is one of deep pressure not of a sharp pain such as would be experienced with injury to the skin or subcutaneous tissue. The second thing is that local anaesthetic itself interferes with the electrical properties of muscle and the procedure would therefore interfere with what we are, certainly in the dynamic studies, attempting to measure.

Now, the procedure itself is not unduly unpleasant. I myself have had nine biopsies and as many as thirty biopsies have been experienced by individuals, and the experiences, that's the pain, only lasts some 1 to 2 seconds at the time of the biopsy and then there is a sensation of stiffness such as might accompany or follow unaccustomed or severe exercise, and this stiffness, like that following stiffness in sport, usually clears up in a few days afterwards. Providing that there's no tendency to bleeding, there is no risk attached to this, or at least very little risk attached to this procedure.

Well, I'd like to now show you the study of muscle metabolism in a normal volunteer and we shall take samples in quick succession: one at the start, one during and one at the end of a sustained isometric contraction taken to fatigue.

<Film with narration by Edwards>

Each sample will be rapidly frozen by plunging the needle into isopentane cooled in liquid nitrogen. A thermistor probe has already been inserted to record the temperature deep in the quadriceps muscle. The probe can be seen on the right of the three skin incisions made in preparation for the biopsies. After a biopsy at rest, the muscle contracts at a constant force. The subject holds the force signal on the oscilloscope screen in front of him to a target line. A second biopsy is performed at 20 seconds and then the same force is held for as long as possible. The subject's face shows signs of mounting effort and eventually the target force can no longer be held because of the intense feeling of muscular fatigue. A third biopsy is then taken to indicate muscle metabolism at fatigue. Despite three biopsies in less than 90 seconds, the muscle is not particularly tender and there are no signs of a haematoma. Three days after this study, the subject ran 6 miles without discomfort.

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<Edwards to camera, then refers to series of graphs and slides and narrates over them. Interspersed with talk to camera>

Let's see the record from this study. <*Graph*> Here is the force record and here the temperature record; an isometric contraction held at 48% of the force of a maximal voluntary contraction. After a biopsy at rest, the subject held the force to the target, as you saw, and then after 20 seconds he released the force briefly for a biopsy and then held the same force until he could hold it no more. This is what we now call fatigue and then at the end at this point, a third biopsy was taken, and then during this period there was a rise in temperature, steady rise in temperature, and the rise amounted to nearly half a degree centigrade.

<*To camera*> The immediate energy source for muscle contraction is adenosine triphosphate, ATP. <*Slide*> This is re-synthesised continuously by the breakdown of phosphorylcreatine; and by anaerobic glycolysis – that is the breakdown of glycogen in the absence of oxygen; and further in dynamic exercise and in many other circumstances when oxygen is applied to the muscle, the most important source of energy is the generation of ATP by oxidation of carbohydrate and free fatty acids.

<*To camera*> But in isometric exercise – we know this from pressure measurements that we have made from deep within the muscle – the muscle force increases the pressure deep within the muscle to the extent that it occludes the muscle circulation with the result that no oxygen can be supplied during the period of the contraction and therefore the energy supplying the actions has to be anaerobic. So, the studies that I've been showing you are really designed to test the integrity of anaerobic energy supply mechanisms. Another result of the occlusion of the circulation during contraction is the fact that the heat is retained in the muscle and hence the observed rise in temperature.

<*Next graph*> Let me show the changes in muscle chemistry which occurred in the study that you've seen on film. Here are the muscle contents of ATP, phosphorylcreatine and lactate in muscle biopsies taken at the start some time during the contraction and at the end of the contraction. I'm showing here the results not only of the study that you have seen but those of similar studies in 4 other normal subjects in whom the middle biopsy was set at some other time during the contraction, so that we can see the general time course of these chemical reactions. The time axis has been expressed in terms of the overall endurance time, that is from the time to fatigue, in order to allow comparison between the results in different subjects.

Notice that the ATP level fell only slightly, even at fatigue. Phosphorylcreatine fell fairly steadily down during the contraction, and at fatigue was at a very low level. Lactate rose steadily during the contraction to a high level and, in fact, in molar terms the rise in lactate was just about the same as the fall in phosphorylcreatine and the fall in ATP. The fall in ATP plus the fall in phosphorylcreatine together is called the

phosphagen depletion; phosphagen is an old name but a very useful one to describe the short-acting energy supply mechanisms in muscle <*to camera*>.

Now, I'd like now to turn to the energy supplying mechanisms in studies in patients. And the patients were studied in a very similar way except that we didn't take samples during the contraction. One other modification was that since the forces generated in the isometric contractions in the patients were not always as great as those in normal subjects, we had to be quite sure that the muscle was behaving as a closed system and therefore we inflated a cuff around the thigh to a pressure sufficient to occlude the circulation, thus ensuring anaerobic conditions in the muscle.

00:29:54:08

<*Next diagram*> Well, these are the results from studies in 11 normal subjects and 5 patients. These patients came complaining of muscle weakness and fatigue, and subsequent investigation showed that they had either rheumatoid arthritis or had weakness or fatigue due to unfitness or some psychological reason, but on detailed investigation of muscle structure by needle biopsy – in needle biopsy samples, in fact – their muscle structure was normal. Notice that the ATP, phosphorylcreatine and lactate in the resting muscle was the same in the patients as in the normal subjects. Also at fatigue, the fall in ATP and the fall in phosphorylcreatine was much the same in the patients as in the normal subjects, and similarly the rise in lactate was the same.

Now, as I say, these were the results in patients who had histologically normal muscle. <*To camera*> And the finding of the same chemical composition in the muscle at fatigue, both in the patient groups and the normal subjects, indicates that the patients were at least capable of driving their muscles to the same extent as the normal subjects at fatigue, and further that the energy supply mechanisms had been working normally.

<Next *slide*> Now, let me turn now to a further consideration of the energy supply mechanism during contraction. The ATP is, as I said, the main source of energy, but

this has to be re-synthesised from the breakdown of phosphorylcreatine and by anaerobic glycolysis. The key substance in this is ADP, in fact, as this dictates the breakdown of phosphorylcreatine, and further is the trigger for anaerobic glycolysis, and, incidentally, if oxygen-available ADP is the trigger for initiating oxidative metabolism too.

<*To camera*> Now, it's not feasible to measure the active or free component of the ADP which acts as this trigger and, at present, it is convenient and, in fact, all that is possible at the moment, to use the overall fall in phosphorylcreatine and ATP as the indicator of the trigger and to see whether the rise in lactate as the indicator of the contribution of anaerobic glycolysis is, in fact, appropriate. <Next graph> And we therefore found for studies in patients, it's convenient to relate the rise in lactate production, here shown on the ordinate with the phosphagen depletion in contractions similar to those that you've just seen. Now, in this are shown the lines indicating the ratio of lactate production to oxygen depletion. The solid line is the mean value for a number of normal subjects and the shaded area indicates Pearson lines 2 standard deviations to the mean.

Now, I'm going to show with individual symbols the results from individual patients with metabolic myopathies. First, notice that patients with hyperthyroid myopathy, these had values which fell within the normal range. Patients with hypothyroid myopathy had values which tended to be low and this indicated some impairment of anaerobic glycolysis in relation to the phosphagen depletion, which we are taking as the indication, the internal standard in a sense, of the muscle action of the muscle activity. In a patient who had McArdle's syndrome – this is characterised by an absence of myophosphorylase, the key enzyme necessary for breaking down glycogen – there was no rise in lactate during the contraction despite phosphagen depletion. And it was interesting to find another two patients with alcoholic myopathy who had a reduced lactate production in relation to the phosphagen depletion, and this has been seen previously and these illustrate well this partial impairment in anaerobic glycolysis seen in these patients.

<*To camera*> Well, the question is what is the nature of this partial impairment of anaerobic glycolysis? Is this something which affects all the muscle fibres uniformly or is this, in some way, reflecting a change in the structure of the muscle caused by the disease? Well, this is something which demands a look into the structure of the muscle and how it is affected by disease. We have used needle biopsy samples to investigate this and it's possible to do fairly precise quantitative, morphological studies on needle biopsy samples and to study muscle histochemistry.

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Well, if a needle biopsy sample is stained for myophosphorylase, this important enzyme for anaerobic glycolysis, it is seen here that the fibres here are not uniformly stained <*photomicrograph*>. There are, in fact, different populations of muscle fibres in human muscle, some with a high glycolytic activity and these are highly active for myophosphorylase, hence the dark staining, and there are others which have a lower activity and these are rather less well stained. Incidentally, in the patient with McArdle's disease, there was no staining for myophosphorylase in any of the muscle fibres. Well, in practice, it's more convenient to type the muscle fibres in human muscle, as in animal muscles too, using a stain for myosin ATPase. This is the stain which correlates well with the speed of contraction with the muscle, and in this way it's been found that human muscles comprise of two main populations of fibres: one type of fibre which stains rather strongly for myosin ATPase and these are the fast-twitch glycolytic fibres, and these are shown in cross-section here <*next photomicrograph*>. These are the darkly stained fibres. There are another population of fibres which are less well stained; these have a lower myosin ATPase activity and correspond with the slow-twitch red fibres with a high oxidative capacity and a rather lower glycolytic activity. Notice that the fibres here are approximately equal in size.

Now, a number of studies have been carried out in animals and in man, particularly the studies of Saltine and Gollnick in Sweden and the USA which have looked into the way in which these different muscle fibre populations are recruited. Fibres with a low glycolytic activity, the so-called type 1 fibres, are recruited at low threshold for forces which are rather low and have to be sustained for a long time. Also, they are

used in long-sustained cycling or running exercise. The fibres with a high glycolytic activity, the fast fibres, are recruited at higher threshold and are necessary for sustaining high forces for shorter periods of time and for making very large efforts in dynamic exercise.

<*Next photomicrograph*> Well, in disease, the muscle structure that we saw most commonly in our patients with metabolic myopathies were muscles in which the type 2 fibres were atrophied as shown here. Notice that the pale-stained type 1 fibres are about the same size as in the normal muscle, but that the type 2 fibres, darkly stained, are smaller. And the question arises as to whether or not the partial reduction in overall glycolytic activity is simply a reflection of the impaired glycolysis in a smaller muscle bulk of this particular fibre, or whether it is a phenomenon diffusely affecting all muscle fibres? And the other question <*to camera*> is whether or not the fibres are atrophied because of disuse because they are fibres which are normally brought into use at a higher threshold for intense muscular activities or whether there is some more subtle reason? Well, these are matters which are currently under investigation and at the moment there is no particular clear answer. But, for us to look further into the interpretation of chemical changes during contraction, it is necessary for us to study the chemistry of individual muscle fibres and this is something which we are doing now at Hammersmith with Dr David Jones, who is our biochemist, and in order to show you how we propose to proceed, I think I'd like to show you now a short section of a film that we made in order to illustrate the dissection of individual muscle fibre fragments from needle biopsy samples. This is rather a tedious procedure and takes rather a long time but what I'm going to show you now is an edited version.

00:39:14:23

<Edwards narrates over film>

Here is a freeze-dried needle biopsy sample of human muscle and you'll see that dissection gradually allows the separation of the fibres into fibre bundles. The fibres are about 2 millimetres or 3 millimetres long – they're best – sometimes considerably

shorter unfortunately. The process of dissection gets them down to bundles of individual fibres. Then you'll see a single fibre being lifted off on a human hair. Now, what follows is the typing of these individual fibres from small fragments taken from the end of each of these large fragments, and this is something which Mrs Caroline Maunder, the histochemist who works with us, does using a myosin ATPase stain <*to camera*>. Fibres of either type 1 or type 2 are then grouped and then analysed using the microanalytical enzymatic techniques that we use for analysing whole muscle biopsy samples. Well, in this way, it is hoped that it will be possible to investigate further the effects of altered muscle composition in disease on the way in which energy supply mechanisms are involved in generating force. Well, I mentioned the generation of force and the energy supply mechanisms – what of the contractile machinery within the muscle itself?

<Edwards narrates over electron micrograph and slides, interspersed with talk to camera>

This is a longitudinal section of muscle and an electron micrograph showing the characteristic broad striations, the dark bands constituting the myosin molecules and the light bands, the actin molecules. These fibres interdigitate and the process of generating force is through the formation of cross-bridges between them. Now, this is the basis of the Huxley theory of muscular contraction, and here this is a static view of the molecular machinery of skeletal muscle. You see the thick myosin filaments and the thin actin filaments. And the thin actin filaments are held together by the Z line as they are so-called, the transverse bands which hold the muscle fibrils together. Well, the actual dynamics of muscular contraction are well understood from studies in animal muscle, but there is still much to be learned about the way in which the cross-bridges are formed through the activating influence of calcium ions, the formation of cross-bridges and the breakage and the involvement of ATP and the supply of ATP for this process in human muscle <*to camera*> and also how this is affected in disease.

There is still much to be learned in this respect. And if I may now summarise what I've been saying; we have come in this lecture from the assessment of muscle function at the bedside and two studies at a cellular level.

<Slide>

Muscle function

1 Performance time

2 Force – clinical dynamometer

3 Force – strain gauge

But let's begin with a summary of the muscle function studies. The simplest thing to do is to simply measure the time for which a muscle contraction can be sustained, and I've suggested holding the leg at 45 degrees as this is a well-known test, in fact, and can be made fairly quantitative, similarly holding the head of the couch can be useful, but this can be checked by measuring the force of contraction of the muscles using the new clinical dynamometer that we've developed and this may prove to be quite a useful adjunct in clinical neuromuscular examinations. And finally, more detailed studies of muscle, and here we're using the quadriceps muscle as a model, involve measurements of force with a strain gauge.

<*Next slide*> Well, the next aspect that I covered was muscle heat production and the development of a thermal probe for measuring the maximum metabolic rate in voluntary and electrically stimulated contractions. If the rate of heat production in a voluntary contraction is less than that in a maximally stimulated contraction, it suggests that the control mechanisms for contraction, perhaps, are inadequate due to neurological reasons or because of failure of drive for psychological reasons and these will have to be looked into further. On the other hand, if muscle heat production is normal, this can be used as a reassurance that the control mechanisms and the metabolic processes in muscle are, in fact, behaving normally. And finally, there's the possibility that muscle heat production is reduced in both types of contraction and that this may indicate either some process analogous to fatigue in normal muscle or that there is an impairment in the maximum metabolic rate of the tissue.

<*Next slide*> Finally, the needle biopsy technique has been used to help us investigate muscle structure and chemistry and this has proved to be valuable both in giving a, say, picture of the structure and the histochemistry of the muscle and the electron microscopy of the muscle, but also in indicating objectively the state of the muscle at a time when the patient is fatigued, when the muscle is unable to sustain force. And we have found that in a group of patients that this has been very similar to that in normal subjects, indicating their ability to drive their muscles to the same extent as normal subjects at fatigue.

<*To camera*> And we've seen also the situation in patients, in whom for reasons to do with their metabolic myopathies and possibly to the fact that the muscle has had an alteration in its structure, that there is evidence of an impaired glycolysis, and that I've given you a view into the future as to how we propose and, in fact, are continuing at present to investigate this problem further.

Well, in this lecture if I haven't given you any simple, straightforward answers, I think it must be because this is not a simple, straightforward problem. Yet, I hope I've been able to show you some of the formidable problems that are being faced and how we now are developing tools which will help us to solve them.

<End credits>