# **Skeletal Muscle**

#### Purpose

- 1. Describe skeletal muscle structure.
- 2. Describe the passive and active properties of skeletal muscle.
- 3. Relate muscle structure to function.
- 4. Describe how muscles can be injured and how they are repaired.
- 5. Describe how muscles change with aging and adapt to exercise and disuse.



## **Muscle Structure:**

During the past century, extensive investigations have revealed the general structure and function of skeletal muscle. Though much is known about the structural organization of muscle, the constitutive equations describing its behavior have yet to be derived. Descriptions of the contractile characteristics of muscle and structure/function relationships are given in the following section. In this section emphasis is placed on describing the structural organization of skeletal muscle. The description begins at the level of the gross whole muscle and proceeds to the smaller subunits, concluding with the proteins making up the myofilaments. The description given here is quite detailed since muscle behavior is directly related to its structure. An understanding of the material in this section will greatly facilitate understanding the material that follows.

Muscle is composed of many subunits and complex structural arrangements (see Figure 1). Whole muscle is surrounded by a strong sheath called the epimysium. The gross muscle is divided into a variable number of subunits called fasciculi. Each fasciculus is surrounded by a connective tissue sheath called the perimysium. Fascicles may be further divided into bundles of fibers (or muscle cells) which are surrounded by a sheath called the endomysium (Fung, 1981; Anthony and Thibodeau, 1983; Ishikawa, 1983).

The orientation of fibers relative to the orientation of the whole muscle varies among different muscles. Various fiber arrangements observed in the human body are illustrated in Figure 2. Muscle may be classified as fusiform, unipennate, bipennate, triangular, and strap. Fibers attach at both ends to tendon or other connective tissue.

Muscle fibers are multinucleated cells with the nuclei generally located along the cell periphery. The population density of nuclei is estimated to be 50 - 100 per millimeter of fiber length (Ishikawa, 1983).

Muscles have a rich supply of blood vessels. Capillary networks are arranged around each fiber with the capillary density varying around different fiber types (Ishikawa, 1983).

A motor unit consists of a single motoneuron and all the fibers it innervates. The number of fibers per motor unit is variable, ranging from just a few in ocular muscles, requiring fine control, to thousands in large limb muscles (Buethal and Schmalbruch, 1980; Ishikawa, 1983). In intact whole muscle, motor units intermingle throughout the entire muscle cross-sectional area.

The literature is filled with different naming schemes that have been used to identify motor units. The first naming scheme used was based on gross muscle appearance. Fibers were labeled as either red or white. In a second naming scheme, three classifications (red, white, and intermediate) were introduced based on mitochondrial density as viewed under an electron microscope. Based on mechanical properties, a third naming scheme was established classifying fibers as either fast-twitch or slow-twitch (S), with the fast-twitch being further subdivided into fast-twitch fatigue resistant (FR) and fast-twitch fatigable (FF) (Burke and Edgerton, 1975; Bucthal and Schmalbruch, 1980; Chapman, 1985). A fourth naming scheme was established when it was shown that some fibers stain differently when subjected to enzyme sensitive stains. The staining technique has been used to identify three fiber types; slow-twitch oxidative (SO), fast-twitch oxidative-glycolytic (FOG), and fast-twitch glycolytic (FG). To complicate the muscle fiber identification process further, a second enzymatic histochemical naming scheme is commonly used. Fibers are classified as either Type I or Type II, with Type II fibers further divided into Type IIa, Type IIb, and Type IIc (Brook and Kaiser, 1970). Type I fibers are high in oxidative enzymes and low in phosphorylase and ATPase. The reverse is true for the Type II fibers. Efforts have been made to unite the different nomenclatures, but without success (Spurway, 1981). Though the various naming schemes result in similar fiber classifications, they are not the same (Nemeth and Pette, 1981). Regardless of the naming scheme used, fibers within each classification exhibit different chemical and mechanical properties from fibers in other classes.



**Figure 1-** Illustrated is a schematic representation of the organizational structure of muscle. The gross muscle is composed of bundles of fascicles that consist of groups of fibers. Fibers can be further divided into myofibrils that contain the myofilaments making up the sarcomeres.



**Figure 2-** Shown are six possible fiber orientations that may occur in intact whole muscle A) fusiform, B and C) unipennate, D) bipennate, D) triangular, and F) strap.

Fibers have an extensive membrane network (see Figure 3). The muscle fiber is completely enclosed by the plasma membrane which is usually referred to as the sarcolemma (Peachey, 1985; Ishikawa, 1983). The sarcolemma may be resolved into three layers, the plasmalemma, basal lamina, and a thin layer of collagenous fibrils (Peachey, 1985; Ishikawa, 1983). Multinucleated satellite cells can be found between the basal lamina and the plasmalemma. These cells may be involved in forming new fibers following muscle trauma (Peachey, 1985). The muscle fiber contains two distinct membranous systems between the myofibrils; the transverse tubular system (T-system) and the sarcoplasmic reticulum (SR) (Ishikawa, 1983). These membrane systems are distinct membrane networks separate from one another and are responsible for communicating the external stimulus provided by the motor neuron inward to the center of the fiber. The time and process of this communication is termed excitation-contraction coupling (Peachey, 1985; Ishikawa, 1983). The T-system is part of the plasmalemma and makes a network of invaginations into the cell (Ishikawa, 1983). The Tsystem associates in a specific way with the SR. Two terminal cisternae (part of SR) run parallel to the T-system to form a triad (Peachey, 1985). The excitation of the sarcolemma spreads inward through the T-system which communicates this excitation to the SR. The SR then releases calcium ions along the length of the fiber which activates the contractile material within the cell (Peachey, 1985, Ishikawa, 1983). The extent of the T-system varies among different types of muscle fibers. In mammalian muscles, fast twitch fibers have a T-system that is about twice as extensive as that of slow twitch fibers (Ishikawa, 1983). This property gives rise to faster relaxation rates in fast twitch fibers.



**Figure 3-** Illustrated is a schematic representation of the membrane network of muscle fibers. The muscle fiber is enclosed by the sarcolemma. The membranous networks of the sarcoplasmic reticulum and transverse tubules are responsible for communicating the external stimulus provided by the motor neuron inward to the center of the fiber.

Within a muscle fiber can be found bundles of myofibrils, sarcoplasm, and mitochondria. Myofibrils constitute 75 - 85 percent of the fiber volume (Bagshaw, 1982, Ishikawa, 1983). The myofibrils are separated from each other by the sarcoplasm and membranous organelles (Ishikawa, 1983). Mitochondria supply energy for contraction through their oxidative metabolism. The number of mitochondria present within a cell reflects the metabolic pattern of the fiber. Fibers relying on oxidative metabolism have a greater number of mitochondria compared to fibers relying on anaerobic metabolism (a discussion of the different metabolic pathways is presented later in this chapter).

Myofibrils are composed of a serial arrangement of sarcomeres (Loeb and Gans, 1986) (see Figure 1). Sarcomeres are the basic unit of shortening and force generation. A sarcomere is a regular array of parallel overlapping thick and thin filaments (Anthony and Thibodeau, 1983; Loeb and Gans, 1986). Thick and thin filaments are composed primarily of the proteins myosin

and actin respectively. A myofibril volume is 55 percent myosin and 25 percent actin (Bagshaw, 1982).

The terminology used to describe sarcomere anatomy is largely the result of muscle observations using polarizing microscopes (see Figure 1). When viewed with a polarizing microscope, specific zones of a muscle fiber appear darker than other zones. The dark zones have dense protein bands and stain deeply with basic dyes causing the plane of polarization of light to be rotated strongly. These zones have been labeled A-bands (for anisotropic). Other zones are less protein dense, stain weakly and rotate the plane of polarization of light weakly. These zones have been labeled I-bands (for isotropic) (Fung, 1981; Bagshaw, 1982; Loeb and Gans, 1986). In the middle of the I-band is a dense protein zone called the Z-line or Z-disk (for Zwischen-Scheibe meaning interim disk) (Eisenberg, 1985). In the middle of the A-band is a dense protein zone called the H-zone (for Helle-Scheibe) (Bagshaw, 1982; Loeb and Gans, 1986). In the center of the H-zone is a region called the M-line (for middle). The A-band corresponds to the zone of thick filaments. The H-zone is that region of the thick filaments that is not overlapped by the thin filaments. The M-line is composed of a connective tissue network binding the thick filaments and maintaining them in a hexagonal pattern when viewed in a transverse plane. The Z-disk is composed of a connective tissue network binding the thin filaments. Thin filaments are attached at the Z-disk but are free to interdigitate with the thick filaments at their other end. Myosin filaments are separated by 40 - 50 nanometers (nm) (Ishikawa, 1983) while the myosin/actin spacing is 20 - 30 nm (Bagshaw, 1982). A sarcomere is defined as the region between Z-disks in a myofibril. As a muscle shortens the sarcomere I-band and H-zone decrease in length while the A-band length remains constant. These observations lead to development of the sliding filament theory which is discussed in the section on muscle contractile characteristics.

Thick filaments are composed of myosin molecules. Each thick filament contains nearly 180 myosin molecules (assuming two myosin heads per axial repeat location) (Fung, 1981). These molecules are 160 - 170 nm long (Squire, 1981; Bagshaw, 1982) and arranged to give a total thick filament length of 1.55 micrometers ( $\mu$ m) and 12 - 15 nm diameter (Ishikawa, 1983).

The myosin molecule may be divided into two heavy chains and four light chains (Bagshaw, 1982). Each heavy chain forms the bulk of a single head with the remaining portion of the two chains intertwining to form a tail. Two light chains are associated with each myosin head. The myosin molecule structure has been defined in terms of two general regions, the light meromyosin (LMM), and the heavy meromyosin (HMM). The LMM represents part of the tail and accounts for the self association property of myosin. The HMM contains the two heads and the remaining part of the tail not considered part of the LMM. HMM is further divided into subfragment one (S1) and subfragment two (S2). S2 is similar to LMM but allows S1 to project out up to 55 nm (Bagshaw, 1982). S1 contains binding sites for two light chains, ATP, and actin. S1 is where ATP hydrolysis takes place and is needed for acto-myosin binding (Bagshaw, 1982). HMM is often referred to as the cross-bridge because it is the structure that reaches out and binds to actin during contraction.

The thin filament is composed of actin, tropomyosin, and troponin. G-actin molecules polymerize to form F-actin in a right handed double helix chain with an axial repeat length of 35 - 36 nm. G-actin molecules repeat every 5.5 nm (Bagshaw, 1982). One tropomyosin molecule runs in the groove of the F-actin chain a length of seven G-actin molecules. There is one troponin molecule for each tropomyosin molecule. Because of symmetry (a groove on either side of the helix chain) there are two tropomyosin/troponin complexes for a given length of F-

actin. The troponin molecule can be further divided into troponin-C, I, and T (Squire, 1981). Troponin-C regulates calcium ion sensitivity with the other two components (I and T) being less well defined.

Though the general structure (i.e. actin and myosin filament lengths and their lattice arrangement) are similar among vertebrate muscle fibers, there are differences in the regulatory proteins of the myosin - isoforms (Gollnick, 1981; Saltin and Gollnick, 1983; Huxley, 1985). These isoforms exhibit different amino acid sequences, ATPase activity, and affinity for calcium (Perry, 1985). Myosin molecules in fast and slow twitch skeletal fibers have different ATPase activity (Saltin and Gollnick, 1983; Perry, 1985; Reiser, et al., 1985; Greaser, et al., 1988). These differences have been correlated with the different shortening velocities that exist between these fiber types (Gollnick, 1981; Reiser, et al., 1985; Edgerton, et al., 1986; Greaser, et al., 1988; Fitts, et al., 1989). There are also differences in the Troponin-C protein in fast and slow twitch fibers. Only one Ca<sup>+2</sup> site has to be filled to trigger contraction in slow fibers compared to multiple sites in fast fibers (Perry, 1985).

To summarize, the contractile characteristics of a whole muscle depend on both gross muscle architecture and the properties of the fibers comprising the muscle. All vertebrate skeletal muscle fibers are similar in their structural arrangement of actin and myosin (Huxley, 1985), but have variations in their membrane structures, density of mitochondria, specific protein isoforms, and possibly myofibril packing density (Saltin and Gollnick, 1983; Perry, 1985; Reiser, et al., 1985; Greaser, et al., 1988). These differences, at the cellular level, cause differences in fiber contractile characteristics (i.e. fiber force, maximum shortening velocity, and resistance to fatigue). At the level of the whole muscle, differences exist between muscles in their arrangement of fibers and percentages of each fiber type. Variations in fiber properties and gross muscle structure translate into different muscles having different contractile characteristics.

## **Muscle Contractile Characteristics:**

There are many questions yet to be answered regarding the way muscles generate force. To answer these questions we must build from past experience and knowledge. A description of what is currently known about muscle behavior is given in this section. Muscle contractile characteristics are defined in terms of structural and theoretical considerations where possible and empirical relations otherwise.

Determining the fundamental principles underlying muscle contraction is not a simple task. There have been and continue to be discrepancies in experimental results. Discrepancies in early work were shown to be due, in part, to unidentified structural differences existing between various muscles tested (e.g. fusiform vs. penniform, slow-twitch vs. fast-twitch). Many of the structural factors that affect the dynamics of muscle contraction have been identified, but it is likely that there are still others that have not yet been recognized. These unrecognized factors may be the cause of discrepancies reported in experimental data today (e.g. specific tension, maximum shortening velocity, fatigue properties).

Experimental observations indicate that there are many factors that contribute to the overall characteristics of muscle contraction. One of these factors is the force generated per fiber cross-sectional area. All vertebrate muscle filaments are of similar lengths and they are arranged with similar longitudinal cross-bridge spacing (Squire, 1981; Huxley, 1985). This structural similarity might suggest that all vertebrate muscle fibers have similar specific tensions (i.e. maximum force per unit area). However, this is an area of continued debate. Some researchers suggest that fast and slow twitch fibers have different specific tensions (Burke and Tsairis, 1973;

Bodine, et al., 1987), while others suggest that they are similar (Saltin, 1983; Huxley, 1985; Faulkner et al., 1986). The structural similarity among vertebrate myosin filaments suggests that the force generated by the interaction of a single myosin filament and its associated actin filaments must be similar to that which can be generated by other filaments. If differences do exist in specific tension values, then it is likely that these differences are not due to differences in the force generated by individual cross-bridges, but rather due to differences in myofibril packing density in different fiber types and different species.

There is some uncertainty as to the constancy of myofibril packing density among various fiber types. In avian muscles it has been shown that there may be as much as a 50 percent difference in the myofibril packing density between slow and fast twitch fibers with the slow twitch fibers having the lower packing density. This difference is believed to be due to more mitochondria and sarcoplasm taking up space between myofibrils in the slow twitch fibers. Assuming packing density differences exist in mammalian muscles, lower specific tension values would be expected for muscle composed of predominately slow twitch fibers. Such findings have been reported for the cat soleus muscle (Edgerton et al., 1986).

Since the time of the classical experiments of Hill and Huxley in the 1920s, there has been further supportive evidence and general agreement that the amount of force that a muscle can produce depends on its length and shortening velocity (Bucthal and Lindhard, 1939; Bucthal, 1942; Zahalak, et al., 1976; Gans, 1982; Baildon and Chapman, 1983; van Kaam, et al., 1984; Chapman, 1985; Bobbert, et al., 1986). Early light microscope studies revealed that the maximum force developed by a muscle fiber depends on the fiber length. Specifically, the force is proportional to the overlap of thick and thin filaments. This observation led to the development of the sliding filament theory. This theory states that muscle force is created by small cross-bridges acting between thick and thin filaments. Cross-bridges act as individual force generators to pull thin filaments toward the center (M-line) of the thick filament. The fiber length determines the amount of thick and thin filament overlap which determines the number of cross-bridges capable of attaching and developing force. The relation between fiber force and actin and myosin overlap is shown in Figure 4.



**Figure 4-** Shown is a schematic representation of the active force-length relationship of frog muscle and its corresponding relationship to the overlap of thick and thin filaments (from McMahon, 1984). There is an optimal range of muscle fiber length over which the fiber can produce its greatest force. At longer fiber lengths not all cross-bridges may contribute to the force generation and the force declines. At shorter lengths actin filaments from adjacent sarcomeres begin to interfere with each other and the force also declines.

From experimental studies it has been shown that as muscle force increases, the rate of muscle shortening decreases in a hyperbolic fashion as shown in Figure 5. Unlike the force-length relation, the structural basis of the force-velocity relation has not been identified. It

is likely related to the kinetics of the various protein isoforms and their interactions. Nonetheless the force-velocity relation is quite useful for predicting the force generated by a shortening muscle.

Hill observed that the rate of heat produced by a shortening muscle is proportional to the shortening velocity (rate of heat production = aV). He showed experimentally that the rate of heat production (aV) plus the rate of mechanical work performed ( $F \cdot V$ ) depended linearly on the load as given in Equation 1.

(aV + FV) = (Fo - F)b

where: 
$$F = force$$
  
Fo = maximum isometric force  
V = shortening velocity  
a,b = constants  
(f)  
 $F = force$   
 $V = shortening velocitya,b = constants(f) $F = force$   
 $f = force$$ 

**Figure 5-** Illustrated is Hill's force-velocity relationship for muscles shortening (Hill, 1970). As the muscle force increases, the rate of muscle shortening decreases in a hyperbolic relationship.

In recent years as researchers expanded upon earlier work, it became evident that factors other than length and shortening velocity influence the properties of muscle contraction. These factors may be summarized as muscle composition, architecture, activation level, and history.

(1)

Work by Thorstensson et. al. (1976), Viitasalo and Komi (1978), Coyle et al. (1979), and Rall (1985) showed that muscles with a greater percentage of fast twitch fibers generate greater force for a given speed of contraction, are more susceptible to fatigue, and have a shorter delay from the time of activation to the onset of tension. The influence that muscle composition (relative percentage of each fiber type within a muscle) has on the F-V relation is illustrated in Figure 6. As the composition of a muscle changes from having predominately slow-twitch fibers to having mostly fast-twitch fibers, the F-V relation shifts along the force axis resulting in greater force for the same shortening velocity.

As discussed in the previous section, the structural arrangement of the filaments of various vertebrate muscles is the same, however there are differences in the biochemical constituents comprising different fiber types. Different protein isoforms have different rates of actomyosin ATPase activity which results indifferent fiber types having different contraction/relaxation times and maximal shortening velocities (Barany, 1967; Pette, 1985; Reiser et al., 1985; Metzger and Moss, 1987). Fast fibers have maximum shortening velocities three to five times faster than the slow fibers (Rall, 1985; Reiser et al., 1985; Faulkner, 1986; Edgerton, 1986, Fitts et al., 1989). Though there does appear to be agreement that fast fibers can shorten faster than slow fibers, there are differences in the reported values for the absolute shortening velocities. Close (1972) reports maximum shortening velocities of 7-8 resting lengths per second for Wistar rat gracilis anticus fibers at 17.5 degrees Centigrade and 18.7 resting lengths per second for Wistar rat extensor digitorum longus fibers at 35 degrees Centigrade. Faulkner (1986) cites maximum shortening velocities for human slow and fast fibers at 37 degrees Centigrade of 2 and 6 resting lengths per second respectively. For rabbit soleus at 15 degrees Centigrade Reiser et al. (1985) report values of between 0.5 and 1.0 muscle resting lengths per second for slow and 1.33 to 2.99 fiber lengths per second for fast fibers. Fitts et al. (1989) tested fragments of human deltoid fibers at 15 degrees Centigrade and found maximal shortening velocities to be 0.86 and 4.85 fiber lengths/second for slow and fast fibers respectively. More recently it was demonstrated in rat muscle that SO, FOG, and FG have different maximum shortening velocities (1.5, 4.5, and 6.0 fiber lengths/second respectively at 15 degrees Centigrade) (Fitts, 1989, personal communication).

One must be careful when comparing these values. Muscle bioenergetics are temperature dependent and hence the temperature at which a muscle is tested can alter the maximum shortening velocity results. The fibers tested in the study by Reiser et al. (1985) and Fitts et al. (1989) were maintained at 15 degrees Centigrade. The  $Q_{10}$  value (change in intrinsic shortening speed for a ten degree Centigrade change in temperature) is about 2.0 for the range 15 to 25 degrees Centigrade (Close, 1972; Bennett, 1985). Converting Reiser's data to equivalent values at normal body temperature (37 degrees Centigrade) by using temperature conversion graphs (Bucthal, 1942) or a  $Q_{10}$  value of 2.0 results in maximal shortening velocities of 3.5 and 13 resting lengths per second for slow and fast fibers respectively. Slightly higher values are obtained if the data by Fitts et al. are converted (3.5 and 21 fiber lengths/second). The much lower values reported by Faulkner are likely due to differences in the procedure used to obtain the shortening velocity.



**Figure 6** - Illustrated is an example of the effect that muscle composition has on the force producing ability of a muscle (modified from Thorstensson et al., 1976). Muscle composed of a greater percentage of fast fibers compared to a muscle with similar pcsa, can produce greater force for the same contraction velocity.



**Figure 7 -** Shown is an example of the effect that muscle architecture has on the force-length and force-velocity relationships (modified from Woittiez, 1983). Muscles represented in A and B have similar overall lengths. Muscle A has more fibers, shorter fibers, and a greater physiological cross-sectional area (pcsa) than muscle B. Muscles with longer fibers have greater maximum shortening velocities, and a greater total range over which they can produce force compared to muscles with shorter fibers, which tend to have greater pcsa enabling them to generate larger maximal forces.

In muscle reviews by Burke and Edgerton (1975), Bucthal and Schmalbruch (1980), Gollnick (1981), Gans (1982), Woittiez et al, (1983), and Huijing and Woittiez (1984), the architectural arrangement of muscle fibers within a muscle is stated to affect the amount of force exerted along the axis of the muscle, and the speed of contraction. Longer fibers containing more sarcomeres in series tend to have greater contraction velocities. Muscles with more fibers in parallel can generate greater force. Accordingly, pennate muscles are able to produce more tension than fusiform muscles of similar volume. The influence that muscle architecture may have on the force-length and force-velocity relationships of a given muscle as modeled by Woittiez (1984) are illustrated in Figure 7.

Many investigators have demonstrated that the level of muscle activation and hence the number of fibers recruited affect the force generated during muscle contraction (Bouisset, 1973; Zahalak, et al., 1976; Gans, 1982; Baildon and Chapman, 1983; Chapman, 1985; Herzog, 1985; Bobbert, et al., 1986; Zajac, et al., 1986; Hasan, 1987). The level of force generated by voluntary contraction of skeletal muscle is controlled by at least two mechanisms, motor unit recruitment and modulation of the firing rate of active motor units (rate coding). It is generally accepted that motor units are recruited in an orderly manner consistent with the "size principle" put forth by Henneman et al. (1965, 1974). According to Henneman the excitability or threshold level at which a motor unit is recruited is directly related to the diameter of the motoneuron. Thus the participation of a motor unit in graded motor activity is dictated by the size of its neuron. Studies conducted by other researchers lend support to this finding (Hannerz, 1974; Clamann et al., 1974; Freund et al., 1975; Freund, 1983; Broman et al., 1985; Grimby, 1987; Secher, 1987).

The force a muscle generates is not only a function of the number of fibers stimulated, but also both the frequency (i.e. rate coding) and duration of stimulation (Broman et al., 1985; Hennig and Lomo, 1987). There is a frequency of stimulation above which twitch responses become fused and fibers generated their maximal force. Below the fusion frequency, fibers generate submaximal forces.

During gross muscle studies, the effects that rate coding and motor unit recruitment have on electrical signals recorded from the muscle are generally lumped together and expressed as a general activation level. The level of activation tends to alter the F-V relation as shown in Figure 8. As the level of neural activation increases, more fibers are recruited and/or more force is generated per fiber and the force increases for the same shortening velocity.



Velocity

**Figure 8-** Shown is an example of the effect that the level of muscle activation has on the force-velocity relationship (modified from Zahalak et al., 1976). As the activation level increases, the force-velocity curve is shifted upward causing greater force for the same shortening velocity.

It has been known for some time that the past history of a muscle affects the force it can generate (Abbot et al., 1952; Asmussen, 1953; Cavagna et al., 1968; Asmussen, 1979). Both fatigue and enhancement may occur depending on the past history of the muscle.

Fatigue acts to reduce the force that the entire muscle can generate. However, fatigue does not necessarily affect each fiber type the same. To understand some of the mechanisms of fatigue, a brief description of the fuel sources and supply pathways utilized by muscle tissue is needed. Muscle contractile proteins utilize the high-energy phosphate compound adenosine triphosphate (ATP) as their single fuel source. The splitting of ATP into adenosine diphosphate (ADP) and inorganic phosphate (Pi), in the reaction shown below, provides the energy for cross-bridge cycling during force production.

ATP ---> ADP + Pi <-

The amount of ATP present in living muscle can provide enough energy for roughly eight muscle twitches. Obviously the body provides some means of quickly replenishing the ATP available. There are actually three primary energy pathways used by muscle tissue to produce ATP. The pathway most commonly used during the onset of physical activity combines ADP with phosphocreatine (PCr) to produce ATP and creatine (Cr) in the reaction shown below:

$$ADP + PCr \rightarrow ATP + Cr$$
  
 $\leftarrow$ -

This reaction is commonly referred to as the Lohmann reaction and can take place in either direction. However, the equilibrium constant for the reaction favors the production of ATP by a

factor of about 20. The concentration of ATP within a muscle remains constant except under conditions of either extreme fatigue or muscular disorder. For the Lohmann reaction to proceed toward ATP production there must be PCr present in the muscle. Muscle maintains a small reserve of PCr, but not enough to supply the amount of ATP needed for sustained activities. In fact the amount of PCr stored in muscle tissue can provide enough ATP to sustain about 100 twitches. This is much greater than the stores of ATP can supply, but still not sufficient to supply the energy demands placed on the body during daily activities.

Aerobic oxidative phosphorylation, and anaerobic glycolysis are two other primary pathways utilized for ATP production. Actually anaerobic glycolysis can be considered either a process in itself or a precursor to oxidative phosphorylation. Whether or not oxidative phosphorylation occurs depends on oxygen availability to the muscle cell and the content of cytochromes and myoglobin present within the cell. During anaerobic glycolysis, which takes place in the cytoplasm, a series of reactions take place to breakdown glucose to form 2 pyruvic acid, two hydrogen, and 4 ATP molecules. Anaerobic glycolysis utilizes 2 ATP molecules to breakdown glucose, hence the net yield is 2 ATP. Only 1 ATP molecule is needed to breakdown glycogen so the net yield from anaerobic glycolysis of glycogen is 3 ATP. The pyruvic acid and hydrogen molecules generated from anaerobic glycolysis enter the mitochondria where the Kreb's cycle (also referred to as the tricarboxylic acid cycle TCA) takes place. For each pyruvic acid molecule entering the Kreb's cycle 3 CO<sub>2</sub> molecules, 5 hydrogen molecules and 2 or 3 ATP molecules are formed (3 ATP result if carried into the mitochondria by NADH or 2 ATP if carried in by FADH<sub>2</sub>). Fast twitch fibers rely on FADH<sub>2</sub> and therefore are less efficient. The hydrogen atoms released from both the Kreb's cycle and anaerobic glycolysis enter an electron transport system by combining with nicotinamide-adenine dinucleotide (NAD) or flavin-adenine dinucleotide (FAD). Oxidative phosphorylation occurs if sufficient oxygen is available to meet the supply of hydrogen transported to the mitochondria via NAD or FAD. If the oxygen supply is not sufficient, then NADH reacts with the pyruvic acid to form lactic acid. Lactic acid can accumulate in the muscle causing fatigue. At some point, usually during a recovery period, the lactic acid is cleared from the muscle and carried to the liver where it is synthesized into glucose. The nature of the reactions taking place in the electron transport system is not of prime concern, but the results are. From the electron transport system (ETS) 32 ATP molecules are produced along with carbon dioxide (CO<sub>2</sub>) and water (H<sub>2</sub>O). Energy is needed to transport the two hydrogen molecules generated during anaerobic glycolysis from the cytoplasm into the mitochondria. This process utilizes one ATP per hydrogen molecule transferred. Thus the net yield of ATP per glucose molecule from aerobic metabolism is between 36 and 38 (37 to 39 if start with glycogen). The aerobic processes are much more efficient than anaerobic glycolysis acting alone, which yields only 2 ATP per glucose molecule. Also no lactic acid is formed, only CO<sub>2</sub> and H<sub>2</sub>O. Type I fibers are more efficient than type II fibers (42% vs. 38% respectively based on 39 ATP \*7.3 kcal/mol ATP/686 kcal/mol of glycogen OR 36 ATP \*7.3 kcal/mol ATP/686 kcal/mol of glucose).

As discussed previously, different fibers have different myosin proteins and mitochondrial densities. The structural design of SO and FOG fibers allows them to be relatively resistant to fatigue. These fibers are rich in mitochondria and oxidative enzymes. They have the ability to use metabolites from the blood to sustain the metabolic activity needed for continued contraction. This allows them to generate force for long periods of time with or with out depleting their glycogen stores. Fatigue of these fibers occurs when glycogen stores are depleted and insufficient oxygen is supplied to maintain aerobic metabolism. Their rate of fatigue is likely related to the muscle force generated, and the duration of contraction relative to the duration of recovery, commonly expressed as the duty cycle (duty cycle = time of muscle activation/total cycle time).

The other history related factor to consider is enhancement. The term enhancement has been used in the literature to describe basically two different effects, (1) elastic energy storage, and (2) force potentiation (increased force above that of a similar contraction initiated from rest). The first of these effects is related to muscle-tendon elastic properties. The second effect is related to force potentiation of the fiber cross-bridges.

For both forms of enhancement, the magnitude of the effect depends on several factors. Firstly, for any enhancement to occur a stretch/shortening cycle (eccentric contraction followed by a concentric contraction) must take place. Other factors of relevance are the time delay between the two contraction modes (referred to as coupling time), stretch velocity, initial muscle length prior to stretch, and the amplitude of stretch (Edman et al., 1978, 1981, 1982; Bosco et al., 1979, 1981, 1982; Aura and Komi, 1986; Goubel, 1987).

Like fatigue, the exact mechanisms responsible for enhancement have not been isolated. Storage of elastic strain energy in the tendon and SEC of muscle has been suggested as a possible source of the improved mechanical efficiencies reported during certain activities (Abbot et al., 1952; Asmussen, 1953; Cavagna et al., 1968, 1981, 1985; Cavagna, 1970, 1977; Asmussen and Bonde-Petersen, 1974; Thys et al., 1972, 1975; Curtain and Davies, 1975; Alexander and Bennet-Clark, 1977). The amount of strain energy that an active muscle can store has been reported to be 5 J/kg while that of the tendon and other collagenous tissue is 2000-9000 J/kg (Alexander and Clark, 1977). These data suggest that muscle elasticity plays only a small part in storage of elastic energy compared to tendon.

Like elastic strain energy, force potentiation is a complex issue. Cavagna et al. (1985) state that force potentiation created by a stretch/shortening cycle is due in part to greater force developed by each cross-bridge attached. There appears to be an optimal eccentric force or amplitude of stretch, below which the magnitude of the force potentiation increases with increased stretch amplitude, and above which it begins to decrease (Asmussen and Bonde-Petersen, 1974). If cross-bridges are stretched too far, then they break and the increased force is lost. The mechanisms responsible for this force potentiation are not known, but it may be that during an active stretch the myosin heads are rotated to a higher energy state which enables them to generate greater force during the following concentric contraction.

The publications cited above suggest that there are many factors that contribute to the overall contraction characteristics of a given muscle. These factors may be summarized as muscle length, shortening or lengthening velocity, composition, architectural design, activation, and history. Not only do each of these factors affect the contractile force directly, but they also affect each other. For example, golgi tendon organs located between the muscle fiber and the tendon sheath are able to relay information about the force exerted by the muscle to the central nervous system (Burke and Edgerton, 1975; Bucthal and Schmalbruch, 1980). Through central processing, this information may elicit a certain activation response. Another example might be the interaction of muscle length and architectural factors. Fiber orientation affects the amount of force that is transmitted along the axis of the muscle, but the orientation is affected by the length of the muscle. The point to emphasize is that there are many circular relationships. Many factors do not act independently and their interactions are not well understood. It is likely that these factors do not have the same effect under all circumstances of muscle contraction. There may be a complex network of feedback loops from the muscle to the brain and/or spine that

provide a path for sensing and processing neuromuscular conditions. The responses to these conditions create the individual force characteristics exhibited by each muscle during a movement task. It is these many interactions that make muscle modeling a complex yet fascinating area of study.

## **Muscle Development (Maturation and Aging)**

Skeletal muscles develop by differentiation of cells from the mesoderm, the middle layers of the embryo. The developmental process seems to start once mitotic cell division ceases, and is characterized by fusion of cells and synthesis of myofibrillar protein. The earliest form of a muscle cell is called the myoblast (see Figure 9). Myoblasts fuse to form myotubes, these are multinucleated cells with centrally located nuclei. They contain actin and myosin in the form of filaments, but not yet organized. Cells become packed with myofibrils and the nuclei migrate to the periphery.

Beyond the observations stated above, very little is known about the actual process of muscle assembly. There is evidence that there is an inherent ability of actin and myosin to align themselves to form contractile units. Within a myotube the myofibrils form at the outside first and then fill in toward the middle. It is not known which comes first the ordering of the actin and myosin or the cytoskeleton to force them to develop orderly. The sarcoplasmic reticulum seems to develop early on with the T-system developing toward the end of the myotube stage.

It is important to note that all the development discussed so far can occur without any nervous input. Also during these stages muscle size increases due to increased cell number, cell fusion, and increases in cell size. This seems to continue until birth after which the mechanisms of muscle growth seem to change.





Postnatal development is guided by interactions between fibers and nerves (Ridge et al, 1984). At birth some muscle fibers may be innervated by multiple neurons. However, during the first few weeks after birth some neurons withdraw. The mechanism responsible for dictating which neuron remains intact is not known.

Humans are born with about 40 % type I fibers in each muscle. During the first two years after birth the muscle composition changes to 60 % type I in the deltoid and 55 % in the vastus lateralis (Oertel, 1988). Thus, it appears that muscle composition shifts as a function of ageing and muscle utilization.

Muscle growth is achieved primarily by fiber hypertrophy. There is very little increase in cell number. Growth is substantially influenced by the effects of motor nerves. Longitudinal growth tends to occur at the myofibril ends although the exact mechanisms still remain unknown. Lateral growth occurs as myofibrils grow than split. It may also be possible for new myofibrils to develop.

With ageing muscle cross-sectional area tends to decrease. This decrease in area primarily results from a decrease in the cross-sectional area of type II fibers. Lexell (1991) showed a 35 % reduction in the cross-sectional area of type II fibers taken from the quadriceps muscles of 69-84 year old males compared to 19-35 year old males. For the same two groups there was only a 6 % reduction in the cross-sectional area of type I fibers.

Some motor control changes have been noted to occur as a function of age. Moritani, et al (1989) tested ankle plantar flexors in young (9 years) and adult men and evaluated the activation scheme of soleus and medial gastrocnemius (MG) during 4 motor tasks (1 leg stand, 1 leg toe raise, 2 leg hop, 2 leg jump). They found that during postural tasks young subjects used the MG more than older subjects. This suggests that maybe the motor program to use oxidative fibers has not yet been well established in the younger subjects. There were no differences noted in the jumping tasks. Adults did show signs of more MG activation during eccentric contractions which would suggest that they have learned how to the enhancement achieved through a stretch-shortening-cycle.

There tends to be a reduction in the force generated per cross-sectional area in muscles from elderly subjects compared to young adults. It has been suggested that older muscle does not have the ability to recruit all its fibers, or that active fibers do not recruit all their x-bridges, or that x-bridge force decreases with age. Anyone of this effects could cause the observed loss in force. (Bemben et al, 1991)

## Adaptation to Exercise and Disuse:

Muscle responds differently to different exercise modes. Therefore two general modes of exercise are considered - Endurance and Strength. Long duration training at less than 75 % of VO<sub>2</sub> max is considered to be endurance training. During such training there may be some selective hypertrophy of oxidative fibers, but no strong evidence for large bulk gains. There is evidence from rat studies that fiber conversion can occur (Lynch et al, 1991). Several other studies have noted the changes in response to endurance training: 1) increased VO<sub>2</sub> max, 2) increased glycogen stores, 3) increased enzymes for oxidation of carbohydratess and fats, 3) increased oxygen extraction capabilities, 4) increased z-line thickness, 5) increased mitochondrial density, 6) increased capillary density, and 7) decreased rate of Ca<sup>+2</sup> transport and uptake by SR.

Several changes have also been noted to occur in response to strength training. The most notable change is the increase in muscle bulk, which since 85 % of muscle volume is fibers and 15 % extrafiber material, we can assume that bulk gains are due in large part to fiber volume increases which results from increases in contractile proteins. Other changes that have been noted to occur in response to strength training are 1) increased fatigue resistance to this type of exercise, 2) decreased mitochondrial density, 3) fiber conversion to fast twitch fibers, 4)

decreased capillary density, 5) decreased time to peak tension, 6) increased rate of  $Ca^{+2}$  transport and uptake by SR, and 7) increased power potential.

A muscle will respond to disuse by returning to its normal state prior to training. However, there does seem to be some type of a memory effect that results from training. A person that trains, then experiences a period of disuse, and then trains again will be to gain strength at a faster rate during the second training period. The muscle appears to keep the adaptation mechanisms "on-call" for a period of 1 to 30 weeks following the cessation of training Staron et al, 1991).

## **Muscle Trauma and Repair:**

There are basically five types of trauma that may occur to skeletal muscle: 1) cold, 2) puncture, 3) contusion, 4) ischemia, and 5) overload. The types of damage that may occur focal subfiber necrosis (if injury is localized to a part of a fiber), segmental necrosis ( if the injury extends across the whole fiber axially), and regional necrosis (if injury occurs to several fibers). It should be noted that muscles are continually damaged and repaired during our daily physical activities. An noticeable injury occurs when the damage is great enough to cause pain or dysfunction.

Different fibers appear to be susceptible to injury during different types of loading conditions. If a muscle is stretched and immobilized damage will occur in the Type I fibers. If a muscle is loaded eccentrically damage tends to occur in the type II fibers.

There are two common types of healing: continuous and discontinuous. Continuous healing occurs after minor damage and is simply an outgrowth from the partially damaged cells. Discontinuous healing occurs after more sever trauma and consists of complete destruction of an area of the muscle with new fibers arising from myoblasts. Muscle is capable of massive regeneration. Vascularization and neuronal input appear to be very important to the repair process. Severed vessels or nerves will cause a longer healing period. Mechanical stress also seems to be an important factor for healing, but its exact role is not known. If the basal lamina is intact, complete healing occurs can occur in a few days to a week. If however, the basal lamina is broken then some scar tissue may remain and healing may take one to two years. Studies suggest that some remnant of an original fibers is needed to stimulate regeneration as well as some macrophage stimulant to invoke satellite cell response.

## **Summary:**

Muscles are dynamic tissues which generate the active forces which act to stabilize and move our limbs. Skeletal muscle is structurally designed to generate large forces for its relative small volume. Different muscles have different architectural designs presumably to facilitate their different functional roles within the body.

Muscle is a robust tissue. It is capable of generating large forces and it has the potential for massive regeneration should it become damaged. Muscle also has the ability to adapt rather quickly to changes in the demands placed upon it during daily life.