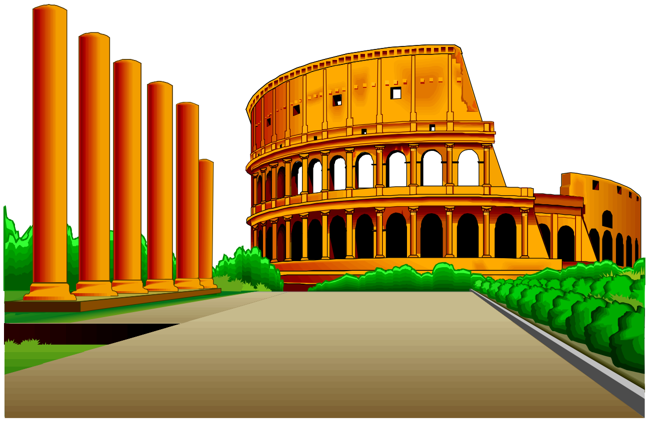
Chapter 1:
A Historical Perspective of Musculoskeletal Research

Purpose

1. Provide a historical overview of musculoskeletal investigations and contributions made from the 3rd century B.C. to the 21st century A.D.



The Greeks, during the third century B.C. in Alexandria, were probably the first to scientifically study medicine and surgery. Prior to this time illness was believed to be an act of the gods and thus priests assumed the role of healer. The Greeks did great anatomical work and constructed detailed paintings and sculptures of the human body. They performed human dissections on criminals. It was during this time that the comprehensive text called "Corpus Hippocrates" was written. This book summarizes much of the human anatomical and functional work performed by Hippocrates (460 - 370 B.C.**)** and others in Athens and Alexandria. It was also during this time that Aristotle (384-322 BC) derived mathematical descriptions of human movement. He was a comparative anatomist that attempted to classify body parts by anatomy.

Despite the extensive anatomical work performed by the Greeks, the Romans were the ones to initiate fundamental studies of muscle mechanics. Scientific progress in medicine shifted to Rome in the 2nd century A.D. following the decline of Greece. It was in Rome where Galen (129 - 200 A.D.), the greatest muscle experimentalist of early times, performed his work. He is often considered the "Father of Experimental Physiology". Galen described the muscle system of the body as a complex but unified organ of locomotion. He was the first to prove the independent contractility of muscle tissue by stimulating isolated muscles from a variety of animals. Galen recognized the connection between muscles and nerves and saw the brain as the center of the neuromuscular system. He was a pioneer in neuromuscular research and his work provided the foundation for many of the studies that followed. He believed that force came from properties of the muscle-tendons themselves not animal spirits sent from brain to muscle-tendon as was the philosophy of the time. However, he thought that force came from connective tissue of the tendon, not the muscle.

There was very little progress made toward describing muscles and their function in the body during the Middle Ages (fifth through fifteenth centuries). This period has also been characterized as the “Age of Faith”. It is not known why people of this day lost confidence in their own observations and took life “on faith”. The decline of Greece and Rome was followed by a rise in power of mystics and Arabian culture. This new culture did not encourage medical research in general and specifically discouraged animal research. As a result, very few medical advances took place during the Middle Ages.

During the Renaissance period (fifteenth and sixteenth centuries) a scientific approach was again accepted in medical research. Whole body dissections were performed and experimental and trial-and-error approaches were commonly used. Jean Fernel (1497-1588) trained in Paris and wrote a book “*A Universal Medicine*” that for the first time divided the study of medicine into physiology, pathology, and therapeutics. Clinical surgery was advanced by the efforts of Ambroise Paré (1517?-1590). Paré was first a barber and then a wound healer. He determined methods for treating gun shot wounds and he developed elaborate artificial hands and arms. Leonardo Da Vinci (1452 - 1519) was a great painter who contributed much to our understanding of muscle. He studied muscles because he wanted to understand how the bodies he portrayed in his paintings actually worked. He is said to be the first person to give a correct picture of practically every muscle in the body. Da Vinci was also the first to study the mechanical leverage system of the musculoskeletal system and to recognize synergistic action of different muscles. He constructed many linkage models to illustrate the interactions between muscles and the bones to which they attach. Andreas Vesalius (1514 - 1564) was another Renaissance-man who contributed to our understanding of muscle. He examined the muscle/nerve innervation and found that if the muscle's nerve is cut, muscle action is abolished, but if the nerve is only injured, muscle function is restored in a short time. He created an entire series of anatomical drawings, or plates, in “*The De Humani Corporis Fabrica*”. Many attribute the beginning of modern medicine to the publication of this work in 1543.

The modern period of medicine began in the seventeenth century. Many of the medical advances that occurred during this time resulted from advances in chemistry, physics, and math. Harvey discovered blood circulation in 1628. Antony van Leeuwenhoek (1632 - 1723) perfected the light microscope and began to examine human tissue. He was the first to observe the sarcolemma and muscle striations. Baglivi (1668 - 1707) was the first to distinguish two different types of muscles which he called "smooth" and "striped". Alfonso Borelli (1608-1779) was a mathematician who also worked on anatomical and physiological problems. He described in great detail the leverage system of the body and showed that the muscles must generate considerably more force then the force created by the objects being lifted. Nicholas Stenson (1638-1686), also known as Steno, was the first person to attempt to develop a theory to describe muscle force. He described the parallel fascicles and fibrils of muscle and proposed that each fascicle had a definite contractile strength (the contractile strength referred to by Stenson is reported as specific tension in modern literature). Stenson believed that the force a muscle generated could be described as the sum total of the forces generated by the fasciculi subunits. He founded the mathematical aspect of muscle biomechanics. John Mayow (1645-1679) questioned the idea of animal spirits, which was a common concept of the time. He noted that the volume of muscle did not change during contraction. This was inconsistent with fluid flowing into muscle. He realized the importance of "nitro-aerial" spirit (oxygen) to muscle contraction. He showed that if the blood supply to the muscle is cut off, then the muscle stops contracting. He also noted difference in arterial vs venous blood color. Francis Glisson (1597-1677) further tested the idea of constant muscle volume (arm in water bath). Jan Swammerdam (1637-1680) discovered red blood cells. He also found muscle volume to remain constant during contraction.

Major advances were made toward understanding the neuromuscular system during the eighteenth century. Albrecht von Haller (1708 - 1777) of Switzerland carried on Stenson's work and showed nerve impulses to be a physiological reaction separate from but controlling muscle contraction. Luigi Galvani (1737-1798) and Volta (1745-1827), in Italy, studied the electrophysiology of nerve muscle preparations. Volta provided the ground work for realizing afferent and efferent nerve pathways. He noted that it was the dissimilarity in metals that caused frog muscles to jump when contacted by the metal. He later developed the battery. John Hunter (1728 - 1793) began to examine the neuromuscular system as a whole. He believed that the brain knew a lot about muscle function but not specific muscles. He also believed that the body could repair muscles if the brain received feedback from the injured muscle indicating the muscle's function or action. Robert Whytt (1714-1766) observed that some muscle activities did not require brain function and hence discovered the spinal reflex.

Improvements in our understanding of muscle synergism, muscle-nerve interactions and chemical processes continued through the nineteenth century. Delpech (1777-1832), in France, examined the role muscles play in joint stability. He believed that muscles act not only to move limbs but also as primary stabilizers of joints. Ligaments, he believed, provide secondary joint support, coming into play only when muscles become injured, diseased, or fatigued. Charles Bell (1774-1848), in London, showed that each muscle is supplied with two nerves, one motor and one sensory. He also showed that the brain is divided into different sections with each section controlling different parts of the body. Guillaume Duchenne (1806 - 1875), in Paris, systematically stimulated nearly every human muscle of the skeleton. He found that purposeful movements are controlled by the nervous system. Berzelius (1779-1848), in Sweden, isolated lactic acid from muscle in 1807. In 1850, Herman von Helmholtz (1821 - 1894) measured the velocity of a nerve impulse. He reported the latent period between muscle stimulation and force development. He also noted that repeated contraction of a muscle causes an acid substance to accumulate in the muscle. He developed a thermocouple to measure muscle heat. He worked on thermodynamics and conservation of energy ideas. Heidenhain (1864) showed muscle heat increased with stimulus intensity, but work output did not increase to the same extent. Muscle became less efficient. Adolf Fick (1829-1901) also studied muscle thermodynamics. He found that heat production decreased with increased frequency of stimulation.

Major advances were made toward understanding the chemical and energetic processes of force production during the first half of the 20th Century. In 1904, T.R. Elliot suggested that the neuromuscular junction transmitter might be a chemical. In 1914, Dale (1875-1968) proposed acetylcholine as this transmitter. In 1907, Fletcher (1873-1933) and Hopkins (1861-1947) showed that the formation of lactic acid took part in a reversible reaction. Eggleton and Eggleton, and Fiske and Subbarow, in 1927, recognized that phosphate is liberated from an organic compound during contraction. Fiske and Subbarow identified this phosphagen as phosphorylcreatine (PC). In 1929, Lohmann discovered adenosinetriphosphate (ATP) in muscle extracts. In 1930, Lundsgaard discovered that contraction is possible without lactic acid formation. This was a major discovery since a commonly held theory at that time, the lactic acid theory, proposed that contraction was caused by folding of long protein chains running along each muscle fiber (Huxley, 2000). These chains were believed to be held extended during rest by repulsive negative charges on the proteins. Excitation was believed to cause lactic acid release that neutralized the negative charges and allowed the chains to fold and thus shorten. Lundsgaard's results provided direct evidence to disprove the lactic acid theory. In 1932, Meyerhof and Lohmann recognized the coupling of biochemical processes through phosphate transfer. It was recognized that liberation of energy during muscle contraction is not an all-or-none consequence of excitation. In 1934, Lohmann found that muscle can only utilize PC through formation of ATP. In 1935, Fenn and Marsh recognized that there was a relationship between speed of shortening, load, and energy liberation. Even today the influence of mechanical conditions on chemical events is not completely understood and often overlooked. In1938, A.V. Hill established the relations between force, speed, and heat production. In 1939, Engelhardt and Lyubimowa discovered that 'myosin' (not the same myosin as known today) is an enzyme that hydrolyzes ATP. In 1941, Engelhardt et al. and Needham et al. discovered that the physical properties of myosin are altered by interaction with ATP. Lipmann proposed the concept of a 'high-energy phosphate bond'. In 1943, Straub resolved 'myosin' into actin plus what is now known as myosin. Szent-Györgi discovered that dissociation of actin from myosin requires ATP.

An increased understanding of muscle structure and metabolic processes took place during the last half of the twentieth century. Muscle-tendon modeling and movement simulations became fundamental tools. Many different theories of force-length relations were proposed. Most people today believe in the sliding filament theory, though there remain supporters of other theories. H.E. Huxley, in 1952, showed, by low-angle X-ray diffraction, the double array of filaments in muscle. In 1953, Hasselbach, & Hanson and H.E. Huxley found that myosin was located in the A-band and accounted for its density. H.E. Huxley showed, using electron microscopy of transverse sections, the overlapping array of thick and thin filaments. A.F. Huxley and Niedergerke, and H.E. Huxley and Hanson suggested in 1954 that the length of the A-band remains constant and that the distance from Z-line to the edge of H-zone also remains constant during muscle contraction. These results provided support for the sliding filament theory, but there were force-length data that did not support the theory. Based on the sliding filament theory a muscle fiber should not be able to generate active force beyond a length equal to the sum of the length of the two filaments. However, some data suggested that force could be produced at longer lengths. This was later found to be due to non-uniform sarcomere lengths within the fiber. Later experiments were able to track single sarcomere lengths and these data supported the sliding filament theory. Despite the general acceptance of sliding filaments the mechanisms responsible for force production remains elusive, but a major focus of considerable research. In 1957, H.E. Huxley showed, with electron micrographs, a double array of filaments in longitudinal cross-sections. Quick release experiments of muscle fibers were performed to study transient responses. Elaborate experiments were designed to quantify the tension developed during single interactions between myosin molecules and actin filaments. At the macroscopic level, ultrasonography and cine-contrast techniques have been used to quantify muscle architecture and function in-vivo.

The field of muscle mechanics has expanded enormously. Yet as our understanding of muscle structure and function has increased, we still do not fully understand either its behavior or how the body coordinates muscles to achieve various movement tasks. There is indeed much work left to be done to unravel the mysteries of muscle structure, force generation and the coordination of muscle force sequencing. Many of the discoveries listed above were important to our current understanding of muscle function. It is worth knowing the controversies and the mistakes that were made along the way so that we might be more efficient in our quest to understand skeletal muscle structure and function.