Lecture 5

Neuromuscular Physiology
(240-249, 253-267, 270-286, 288-297)

Excluded: muscle length, tension, contraction and velocity, phosphorylation of myosin

Somatic Nervous System

- Consists of axons of motor neurons
  - Originates in spinal cord or brain stem and end on skeletal muscle
- Motor neuron releases neurotransmitter, ACh
  - Stimulates muscle contraction
- Motor neurons = final common pathway
  - Various regions of CNS exert control over skeletal muscle activity
    - Spinal cord, motor regions of cortex, basal nuclei, cerebellum, and brain stem
- Pathologies
  - Polio virus destroys the cell bodies of motor neurons
  - Amyotrophic Lateral Sclerosis (ALS)
    - A.k.a. Lou Gehrig’s Disease
    - Most common motor neuron disease
    - Gradual degeneration of motor neurons
    - Unknown cause

Muscle

- Comprises largest group of tissues in body
  - Skeletal (30-40% BW), smooth and cardiac (10% BW)
- Controlled muscle contraction allows
  - Purposeful movement of the whole body or parts of the body
  - Manipulation of external objects
  - Propulsion of contents through various hollow internal organs
  - Emptying of contents of certain organs to external environment
- Three types of muscle
  - Skeletal muscle
    - Make up muscular system
  - Cardiac muscle
    - Found only in the heart
  - Smooth muscle
    - Appears throughout the body systems as components of hollow organs and tubes
- Classified in two different ways
  - Striated or unstriated
  - Voluntary or involuntary
**Structure of Skeletal Muscle**

- Muscle consists of a number of muscle fibers lying parallel to one another and held together by connective tissue.
- Single skeletal muscle cell is known as a muscle fiber.
  - Multinucleated.
  - Large, elongated, and cylindrically shaped.
  - Fibers usually extend the entire length of muscle.

**Neuromuscular Junction**

- Axon terminal of motor neuron forms neuromuscular junction with a single muscle cell:
  - Terminal button (of neuron)
  - Motor End Plate (of muscle cell)

- Signals are passed between the nerve terminal and muscle fiber by means of neurotransmitter, ACh:
  - AP in motor neuron reaches terminal.
  - Voltage-gated Ca^{2+} channels open.
  - ACh is released by exocytosis.
  - ACh diffuses across the space and binds to receptor sites on motor end plate of muscle cell membrane.
  - Binding triggers opening of cation channels in motor end plate.
  - N\textsubscript{a}^{+} movements (larger than K\textsubscript{+} movements) depolarize motor end plate, producing end-plate potential.
  - Local current flow between depolarized end plate and adjacent muscle cell membrane brings adjacent areas to threshold.
  - Action potential is initiated and propagated throughout muscle fiber.

- Acetylcholinesterase:
  - On the chemically-gated cation channels of the end plate.
  - Inactivates ACh (as ACh molecules attaches and detaches from the receptors).
  - Ends end-plate potential and the action potential.
  - Ensures prompt termination of contraction.
**Neuromuscular Junction**

- Neuromuscular junction is vulnerable to chemical agents and diseases
  - Black widow spider venom
    - Causes explosive release of ACh
    - Prolonged depolarization keeps Na⁺ channels at inactive state
  - Botulism toxin
    - From food infected with Clostridium Botulinum → Botulism
    - Blocks release of ACh
    - Respiratory failure from diaphragm paralysis
  - Curare
    - Poisonous arrowheads
    - Binds at ACh receptor sites but has no activity and is not degraded
  - Organophosphates
    - Pesticide and military nerve gases
    - Prevent inactivation of Ach by inhibiting AChE
    - Effect similar to Black widow spider venom
  - Myasthenia gravis inactivates ACh receptor sites
    - Autoimmune condition (Antibodies against ACh receptors)
    - ACh is degraded before it can act.
    - Antidote is neostigmine (inhibits AChE and prolongs ACh action)

**Structure of Skeletal Muscle**

- **Titin**
  - Giant, highly elastic protein
  - Largest protein in body
  - Extends in both directions from along length of thick filament to Z lines at opposite ends of sarcomere
  - Two important roles:
    - Helps stabilize position of thick filaments in relation to thin filaments
    - Greatly augments muscle’s elasticity by acting like a spring

- **Myofibrils**
  - Contractile elements of muscle fiber
  - Viewed microscopically myofibril displays alternating dark (the A bands) and light bands (the I bands) giving appearance of striations
  - Regular arrangement of thick and thin filaments
    - Thick filaments – myosin (protein)
    - Thin filaments – actin (protein)

- **Sarcomere**
  - Functional unit of skeletal muscle
  - Found between two Z lines
  - Z lines connect thin filaments of two adjoining sarcomeres

- **Myosin**
  - Component of thick filament
    - Several hundred of them
  - Protein molecule consisting of two identical subunits shaped somewhat like a golf club
    - Tail ends are intertwined around each other
    - Globular heads project out at one end
  - Tails oriented toward center of filament and globular heads protrude outward at regular intervals
    - Heads form cross bridges between thick and thin filaments
      - Cross bridge has two important sites critical to contractile process
        - An actin-binding site
        - A myosin ATPase (ATP-splitting) site

**Structure of Skeletal Muscle**

- **Titin**
  - Giant, highly elastic protein
  - Largest protein in body
  - Extends in both directions from along length of thick filament to Z lines at opposite ends of sarcomere
  - Two important roles:
    - Helps stabilize position of thick filaments in relation to thin filaments
    - Greatly augments muscle’s elasticity by acting like a spring

- **Myofibrils**
  - Contractile elements of muscle fiber
  - Viewed microscopically myofibril displays alternating dark (the A bands) and light bands (the I bands) giving appearance of striations
  - Regular arrangement of thick and thin filaments
    - Thick filaments – myosin (protein)
    - Thin filaments – actin (protein)

- **Sarcomere**
  - Functional unit of skeletal muscle
  - Found between two Z lines
  - Z lines connect thin filaments of two adjoining sarcomeres

- **Myosin**
  - Component of thick filament
    - Several hundred of them
  - Protein molecule consisting of two identical subunits shaped somewhat like a golf club
    - Tail ends are intertwined around each other
    - Globular heads project out at one end
  - Tails oriented toward center of filament and globular heads protrude outward at regular intervals
    - Heads form cross bridges between thick and thin filaments
      - Cross bridge has two important sites critical to contractile process
        - An actin-binding site
        - A myosin ATPase (ATP-splitting) site
**Actin**

- Primary structural component of thin filaments
- Spherical in shape
- Thin filament also has two other proteins
  - Tropomyosin and Troponin
- Each actin molecule has special binding site for attachment with myosin cross bridge
  - Binding results in contraction of muscle fiber
- Actin and myosin are often called contractile proteins. Neither actually contracts.
- Actin and myosin are not unique to muscle cells, but are more abundant and more highly organized in muscle cells.

**Tropomyosin and Troponin**

- Often called regulatory proteins
  - **Tropomyosin**
    - Thread-like molecules that lie end to end alongside groove of actin spiral
    - In this position, covers actin sites blocking interaction that leads to muscle contraction
  - **Troponin**
    - Made of three polypeptide units
      - One binds to tropomyosin
      - One binds to actin
      - One can bind with Ca$^{2+}$

**Tropomyosin and Troponin**

- **Troponin**
  - When not bound to Ca$^{2+}$, troponin stabilizes tropomyosin in blocking position over actin’s cross-bridge binding sites
  - When Ca$^{2+}$ binds to troponin, tropomyosin moves away from blocking position
  - With tropomyosin out of way, actin and myosin bind, interact at cross-bridges
  - Cross-bridge interaction between actin and myosin brings about muscle contraction by means of the sliding filament mechanism

**Sliding Filament Mechanism**

- Thin filaments on each side of sarcomere slide inward
  - Over stationary thick filaments
  - Toward center of A band
  - They pull Z lines closer together
- **Sarcomere shortens**
  - All sarcomeres throughout muscle fiber’s length shorten simultaneously
  - Contraction is accomplished by thin filaments from opposite sides of each sarcomere sliding closer together between thick filaments
- **Ca$^{2+}$ plays a key role**
  - Increase in Ca$^{2+}$ starts filament sliding
  - Decrease in Ca$^{2+}$ turns off sliding process
**Power Stroke**

- Activated cross bridge bends toward center of thick filament, "rowing" in thin filament to which it is attached
  - Sarcoplasmic reticulum releases Ca\(^{2+}\) into sarcoplasm
  - Myosin heads bind to actin
  - Myosin heads swivel toward center of sarcomere (power stroke)
  - ATP binds to myosin head and detaches it from actin
  - Hydrolysis of ATP transfers energy to myosin head and reorients it
- Energy expended in the form of ATP

**Sarcoplasmic Reticulum**

- Sarcoplasmic Reticulum (SR)
  - Modified endoplasmic reticulum
  - Consists of fine network of interconnected compartments that surround each myofibril
  - Not continuous but encircles myofibril throughout its length
  - Segments are wrapped around each A band and each I band
    - Ends of segments expand to form sacklike regions – lateral sacs (terminal cisternae)
- T tubules
  - Run perpendicularly from surface of muscle cell membrane into central portions of the muscle fiber
  - Since membrane is continuous with surface membrane – action potential on surface membrane also spreads down into T-tubule
  - Spread of action potential down a T tubule triggers release of Ca\(^{2+}\) from SR into cytosol

**Release of Ca\(^{2+}\)**

- Foot proteins
  - Cover the lateral sacs of the sarcoplasmic reticulum
  - Span the gap between the SR and T tubules as well as SR membrane
  - Half interlock ("zipped") with Dihydropyridine (DHP) receptors on T tubules
- Dihydropyridine (DHP) receptors
  - Voltage sensors
  - Depolarization from AP opens Ca\(^{2+}\) channels of attached foot proteins
  - Ca\(^{2+}\) release opens the remaining foot proteins
Sarcoplasmic Reticulum

- Relaxation - Reuptake of Ca²⁺
  - ACHE degrades ACh at the endplate
  - Electrical activity stops
  - On-going activity of Ca²⁺-ATPase pump returns the Ca²⁺ to the SR
  - Troponin-tropomyosin complex returns to blocking position
  - No interaction between actin and myosin
  - Muscle fiber passively relaxes

Excitation-Contraction Coupling

- Contractile activity
  - AP is very short (1-2 msec)
  - Contraction does not start until enough Ca²⁺ is released
    - Latent period
  - Contraction process requires time to complete
    - Contraction time (~50 msec)
  - Relaxation also requires time to complete
    - Relaxation time (~50 msec)

Skeletal Muscle Mechanics

- Muscle consists of groups of muscle fibers bundled together and attached to bones
  - Connective tissue covering muscle divides muscle internally into bundles
  - Connective tissue extends beyond ends of muscle to form tendons
    - Tendons attach muscle to bone

- Muscle Contraction
  - Contractions of whole muscle can be of varying strength
    - Twitch – Contraction of single muscle fiber from single AP
      - Brief, weak contraction
      - Produced from single action potential
      - Too short and too weak to be useful
      - Normally does not take place in body
      - Two primary factors which can be adjusted to accomplish gradation of whole-muscle tension
        - Number of muscle fibers contracting within a muscle
        - Tension developed by each contracting fiber
Motor Unit Recruitment

- **Motor unit**
  - One motor neuron and the muscle fibers it innervates
- **Number of muscle fibers varies among different motor units**
- **Number of muscle fibers per motor unit and number of motor units per muscle vary widely**
  - Muscles that produce precise, delicate movements contain fewer fibers per motor unit
  - Muscles performing powerful, coarsely controlled movement have larger number of fibers per motor unit
- **Asynchronous recruitment of motor units helps delay or prevent fatigue**
  - Muscle fibers which fatigue easily are recruited later
  - Can engage in endurance activities for a long time but can only deliver full force for brief periods of time

Factors Influencing Tension

- **Factors influencing extent to which tension can be developed**
  - Varying from contraction to contraction
    - Frequency of stimulation
    - Length of fiber at onset of contraction
  - Permanent or long term adaptation
    - Extent of fatigue
    - Thickness of fiber

Frequency of Stimulation

- **Twitch summation**
  - Individual twitches are summed
    - AP much sorter in time than contraction → Multiple APs can be delivered
  - Results from sustained elevation of cytosolic calcium
- **Tetanus**
  - Occurs if muscle fiber is stimulated so rapidly that it does not have a chance to relax between stimuli
  - Contraction is usually three to four times stronger than a single twitch
  - Do not confuse with the disease of the same name!

Lever Systems

- **Bones, muscles, and joints interact to form lever systems**
  - Bones function as levers
  - Joints function as fulcrums
  - Skeletal muscles provide force to move bones
  - Muscles usually exert more force than actual weight of load!
    - Advantages: higher speed, more distance
Skeletal Muscle Metabolism

• Contraction-Relaxation Steps Requiring ATP
  • Splitting of ATP by myosin ATPase provides energy for power stroke of cross bridge
  • Binding of fresh molecule of ATP to myosin lets bridge detach from actin filament at end of power stroke so cycle can be repeated
  • Active transport of Ca²⁺ back into sarcoplasmic reticulum during relaxation depends on energy derived from breakdown of ATP

• Energy Sources for Contraction
  • Transfer of high-energy phosphate from creatine phosphate to ADP
    • First energy storehouse tapped at onset of contractile activity
  • Oxidative phosphorylation (citric acid cycle and electron transport system)
    • Takes place within muscle mitochondria if sufficient O₂ is present
  • Glycolysis
    • Supports anaerobic or high-intensity exercise

• Transfer of high-energy phosphate from creatine phosphate to ADP
  • First energy storehouse tapped at onset of contractile activity
  • Reversible reaction
    • Stores Creatine Phosphate when ATP ↑
    • Contributes ATP when ATP ↓
  • Short duration or bursts of exercise
    • ~160g or 12.5 kcal
    • E.g. 100 m running

• Oxidative phosphorylation (citric acid cycle and electron transport system)
  • Takes place within muscle mitochondria
  • Moderate exercise
  • Sufficient O₂ must be present
    • Aerobic or endurance-type exercise
    • Deeper, faster breathing
    • Heart rate and contraction
    • Dilatation of blood vessels
    • Myoglobin
      • Similar to hemoglobin
      • Increase the transfer and store O₂ in muscle cells
    • Uses glucose or fatty acids
      • Glucose derived from muscle glycogen (chains of glucose) stores
        • Limited (~150g or 600 kcal)
        • Athletes can store more (2000 kcal for marathon runners)
      • Glucose derived from liver glycogen stores
        • Limited (~80-200g or 320-800 kcal)
      • Fatty acids derived from lipolysis
        • Plenty of these (~15kg or 135,000 kcal)

• Anaerobic or high-intensity exercise
  • Limit to the amount of O₂ that can be delivered
  • Respiratory and cardiac maxima
  • Muscle contraction constricts the blood vessels
  • Glycolysis
    • Supports anaerobic or high-intensity exercise
    • Less efficient but much faster than oxidative phosphorylation
    • Quickly depletes glycogen supplies
    • Lactic acid is produced
      • Soreness that occurs during the time (not after) intense exercise
      • Energy depletion and ↓ pH contribute to muscle fatigue
### Skeletal Muscle Metabolism

<table>
<thead>
<tr>
<th>Sport</th>
<th>Oxidative</th>
<th>Glycolysis &amp; Oxidative</th>
<th>Glycolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golf swing</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sprints</td>
<td>90</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Volleyball</td>
<td>80</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Gymnastics</td>
<td>80</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Tennis</td>
<td>70</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Basketball</td>
<td>60</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Soccer</td>
<td>50</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Skiing</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Rowing</td>
<td>20</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Distance running</td>
<td>10</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>Swimming 1.5km</td>
<td>10</td>
<td>20</td>
<td>70</td>
</tr>
</tbody>
</table>

*Table adapted from Fox E. L. et al, The Physiological Basis for Exercise and Sport, 1993*

### Fatigue

- **Contractile activity can not be sustained indefinitely → Fatigue**
- **Muscle Fatigue**
  - Occurs when exercising muscle can no longer respond to stimulation with same degree of contractile activity
  - Defense mechanism that protects muscle from reaching point at which it can no longer produce ATP
  - Underlying causes of muscle fatigue are unclear. Implicated
    - ADP increase (interferes with cross-bridges and Ca²⁺ uptake in the SR)
    - Lactic acid accumulation (may interfere with key enzymes in energy-producing pathways)
    - Accumulation of extracellular K⁺ (decrease in membrane potential)
    - Depletion of glycogen
- **Central Fatigue**
  - Occurs when CNS no longer adequately activates motor neurons supplying working muscles
  - Often psychologically based
  - Discomfort, lassitude or breathlessness
  - Mechanisms involved in central fatigue are poorly understood
- **Recovery**
  - Excess postexercise O₂ consumption (EPOC) helps
    - Restore Creatine Phosphate (five minutes)
    - Repairs ATP
    - Convert Lactic acid to pyruvate for oxidative ATP generation
    - Clear increased general O₂ demand because of higher temperature
    - Nutrient replenishment (1-2 days after a marathon)

### Major Types of Muscle Fibers

- **Classified based on differences in speed of contraction and ATP hydrolysis and synthesis**
- **Three major types**
  - Slow-oxidative (type I) fibers
    - Low intensity contractions for long periods of time (e.g. back)
  - Fast-oxidative (type IIa) fibers
    - High intensity for medium periods (e.g. limbs)
  - Fast-glycolytic (type IIx) fibers
    - Rapid forceful movements (e.g. arms)
- **Fast fibers can contract ~ 10 x faster**
- **Oxidative fibers contain more mitochondria and myoglobin and have a richer blood supply → red meat**
**Muscle Adaptation & Repair**

- Muscle has a high degree of plasticity
  - Improvement of oxidative capacity
    - From regular aerobic exercise
    - Capillaries and mitochondria increase
  - Hypertrophy
    - From anaerobic high intensity exercise
    - Muscle fiber diameter increases (more actin and myosin)
    - Mainly fast-glycolytic fibers
- Testosterone and other steroids increase the synthesis of actin and myosin
  - Steroid abuse
- Fast muscle fibers are interconvertible
  - Oxidative ↔ glycolytic
  - But NOT fast ↔ slow
- Muscle atrophy
  - Disuse atrophy (e.g. space exploration)
  - Denervation atrophy (e.g. paralysis)
- Muscle has limited repair capabilities
  - Satellite cells can create a few myoblasts which fuse and create a few muscle fibers

**Control of Motor Movement**

- Input to motor-neurons
  - Input from afferent neurons
  - Input from primary motor cortex
- Input from afferent neurons
  - Usually through intervening interneurons
  - Responsible for spinal reflexes (e.g. withdrawal)
- Input from the primary motor cortex
  - Corticospinal motor system beginning from the motor cortex
  - Responsible for fine voluntary movement

- Afferent sensory neuron provide continuous feedback
- Three levels of control and coordination
  - The Segmental Level
  - The Projection Level
  - The Precommand Level

- Three levels of control and coordination
  - The Segmental Level
    - Spinal cord circuits including central pattern generators (CPGs)
Control of Motor Movement

- Three levels of control and coordination
  - The Projection Level
    - Premotor and Primary motor cortex
      - Plan and execute voluntary movements
    - Brain stem
      - Multineural reflexes
      - Regulation of involuntary control of body posture
  - The Precommand Level
    - Cerebellum
      - Coordination of movement
      - Maintenance of balance
      - Control of eye movements
    - Basal Nuclei
      - Inhibit muscle tone
      - Select and maintain purposeful motor activity while suppressing unwanted patterns of movement
      - Monitor and coordinate slow and sustained contractions

Muscle Receptors

- Receptors are necessary to plan and control complicated movement and balance
- The brain receives information from all muscles and joints in the body → proprioception
- Two types of muscle receptors
  - Muscle spindles
    - Monitor muscle length and tension
  - Golgi tendon organs
    - Monitor whole muscle tension

Muscle Spindles

- Consist of collections of specialized muscle fibers known as intrafusal fibers
  - Lie within spindle-shaped connective tissue capsules parallel to extrafusal fibers
  - Have contractile ends and a non-contractile central portion
- Each spindle has its own private nerve supply
  - Plays key role in stretch reflex
  - Efferent
    - Gamma motor neurons*
  - Afferent
    - Primary (annulospiral) endings (in the central portion)
    - Secondary (flower-spray) endings (at the end segments)

* Efferent neurons to extrafusal fibers are called alpha motor neurons
Muscle Receptors

- **Stretch Reflex**
  - Primary purpose
    - Resist tendency for passive stretch of extensor muscles by gravitational forces when person is standing upright
  - Classic example is patellar tendon, or knee-jerk reflex

Muscle Receptors

- **Coactivation of alpha and gamma motor neurons**
  - Spindle coactivation during muscle contraction
  - Spindle contracted to reduce length
    - With no coactivation
      - Slackened spindle
      - Not sensitive to stretch
    - Adjustment to keep muscle spindles sensitive to stretch

Muscle Receptors

- **Golgi Tendon Organs**
  - Provide necessary feedback for overall muscle tension
  - Integrates all factors which influence tension
  - Specialized nerve fibers embedded in the tendons
  - Stretch of tendons exerts force on nerve endings
    - Increase firing rate
  - Part of this information reaches conscious awareness
    - We are aware of tension (but not of length) of muscles

Muscle Receptors

- **Smooth Muscle**
  - Found in walls of hollow organs and tubes
  - No striations
    - Filaments do not form myofibrils
    - Not arranged in sarcomere pattern found in skeletal muscle
  - Spindle-shaped cells with single nucleus
  - Cells usually arranged in sheets within muscle
  - Cell has three types of filaments
    - Thick myosin filaments
      - Longer than those in skeletal muscle
    - Thin actin filaments
      - Contain tropomyosin but lack troponin
    - Filaments of intermediate size
      - Do not directly participate in contraction
      - Form part of cytoskeletal framework that supports cell shape
  - No sarcomeres
    - Have dense bodies containing same protein found in Z lines

Smooth Muscle
Smooth Muscle

- Two major types
  - Multiunit smooth muscle
  - Single-unit smooth muscle

Multiunit Smooth Muscle
- Neurogenic (nerve initiated)
- Consists of discrete units that function independently of one another
- Units must be separately stimulated by nerves to contract
- Found
  - In walls of large blood vessels
  - In large airways to lungs
  - In muscle of eye that adjusts lens for near or far vision
  - In iris of eye
  - At base of hair follicles

Single-unit Smooth Muscle
- Most smooth muscle
- Also called visceral smooth muscle
- Self-excitable (does not require nervous stimulation for contraction)
- Fibers become excited and contract as single unit
  - Cells electrically linked by gap junctions
  - Can also be described as a functional syncytium
- Contraction is slow and energy-efficient
  - Slow cross-bridge cycling
  - Cross-bridges “latch-on” the thin filaments → muscle maintains tension
  - Well suited for forming walls of distensible, hollow organs

Smooth Muscle Activity
- Gradation
  - All muscle fibers are contracting
  - Tension can be modified by varying the intracellular Ca²⁺
    - Ca²⁺ from the ECF (no SR)
- Tone
  - Many single-unit smooth muscle cells maintain a low level of tension (tone) even in the absence of APs
- Effect of autonomic nervous system
  - Typically innervated by both branches
  - Does not initiate APs but can modify the activity (rate and strength of contraction)
    - Enhancement or inhibition
  - Smooth muscle cells interact with more than one neurons
**Smooth Muscle**

- Smooth muscle activity
  - Tension-Length relationship
    - Increased tension when stretched
    - Can produce near-maximal tension at lengths 2.5 x the normal length
  - When stretched, smooth muscle has the ability to relax
  - These two properties are very important for hollow organs
    - Can accommodate varying volumes while being able to produce adequate contractile force

**Cardiac Muscle**

- Found only in walls of the heart
- Combines features of skeletal and smooth muscle
  - Striated
  - Cells are interconnected by gap junctions
  - Fibers are joined in branching network
  - Innervated by autonomic nervous system
- You will learn more about cardiac muscle in Cardiac Physiology

**Next Lecture ...**

No more of me!

Email: c pitris@ucy.ac.cy
Tel: 22892297
Fax: 22892260