POINTS TO NOTE ON THE BIOCHEMISTRY OF MUSCLE CONTRACTION

Make sure you understand the following;

1. Excitation-Contraction Coupling

2. The action potential - role of Calcium.

3. The Sliding Filament Theory. Role of all the proteins involved.

4. The Cross-Bridge Cycle ;

   (a) Cross bridge formation - role of calcium, troponin and tropomyosin.

   (b) The Power Stroke

   (c) Cross-Bridge detachment

   (d) Reactivation of myosin head

Functions of ATP;

1. Energising the power stroke.

2. Disconnecting the myosin head from actin after power stroke.

3. Actively pumping calcium back into the SR. Role of Calcium ATPase.

Attempt the following questions;

1. Describe the biochemical events that occur during one cycle of muscle contraction and list the determinants that lead to relaxation of muscle.

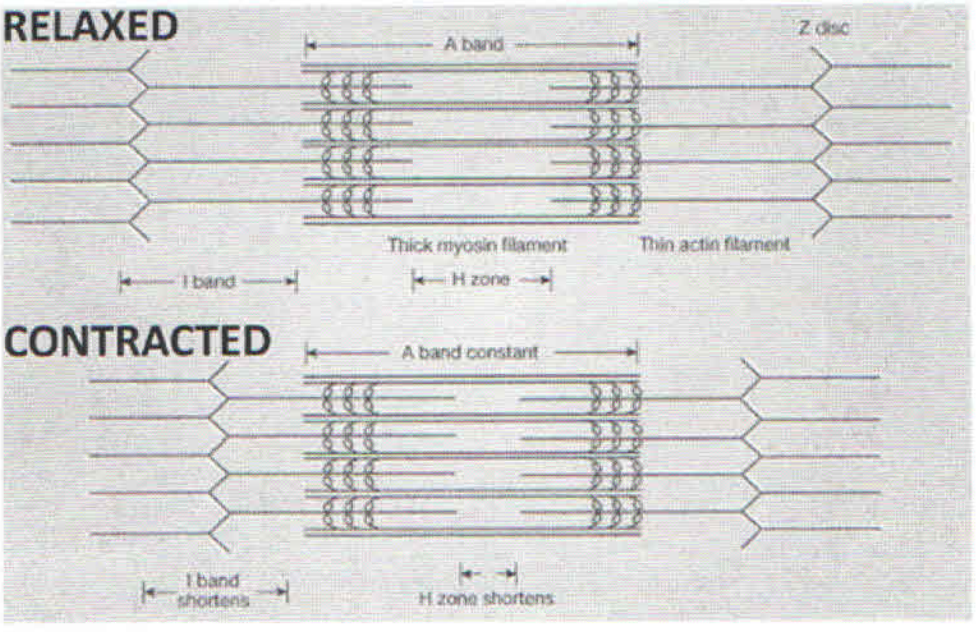
2. Explain the molecular basis of the rigor state.

Read on diseases associated with muscle e.g. Myosthenia gravis and Duchene Muscular Dystrophy. What is their biochemical basis?

Prof. Joseph C. Mukuria

THE SLIDING FILAMENT THEORY - ANALOGY

A



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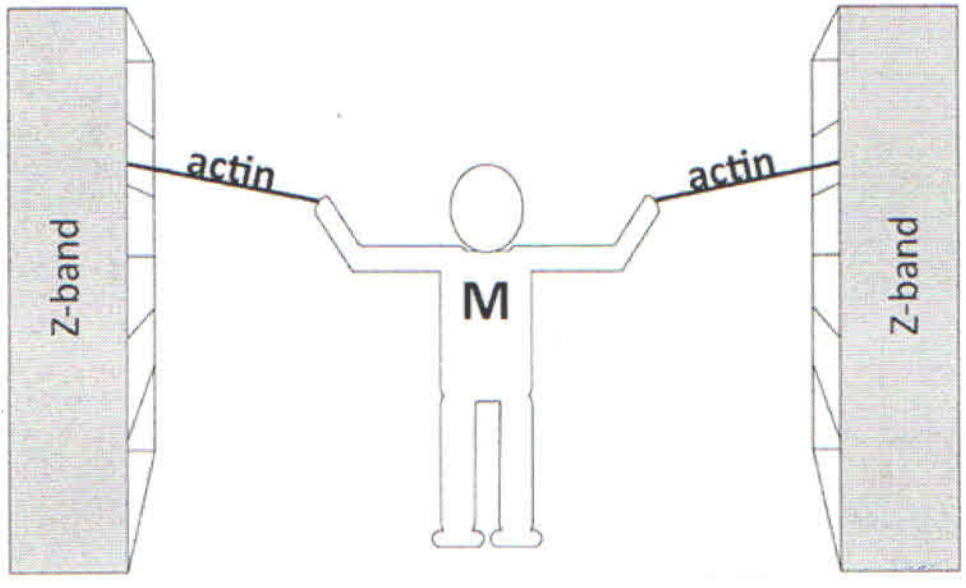
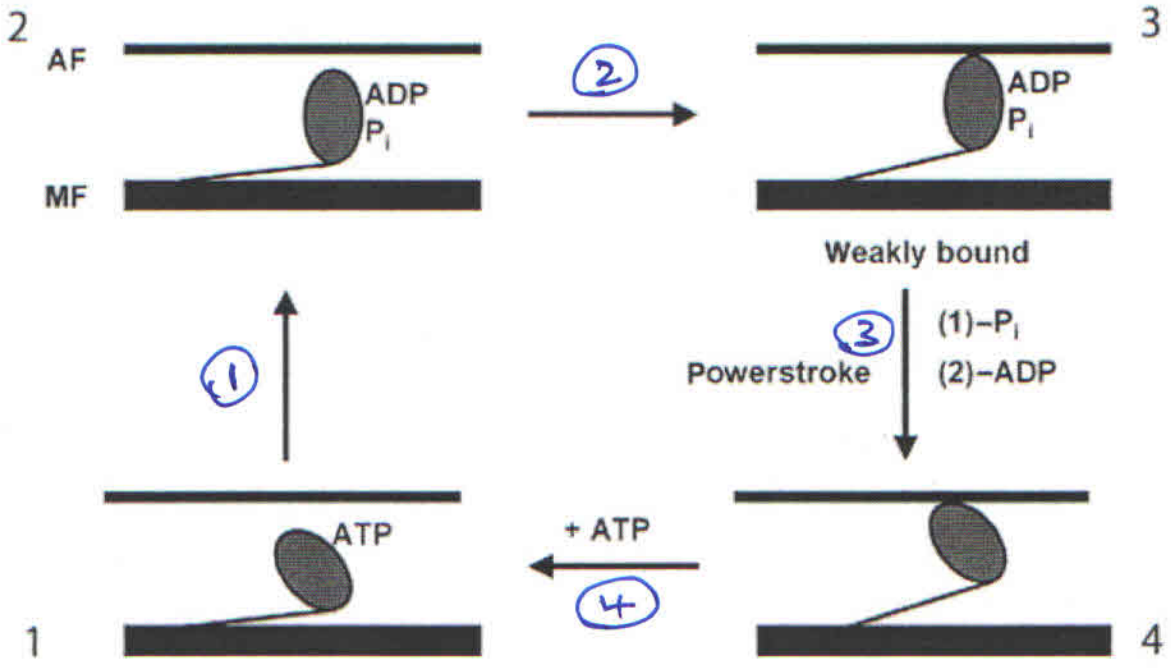
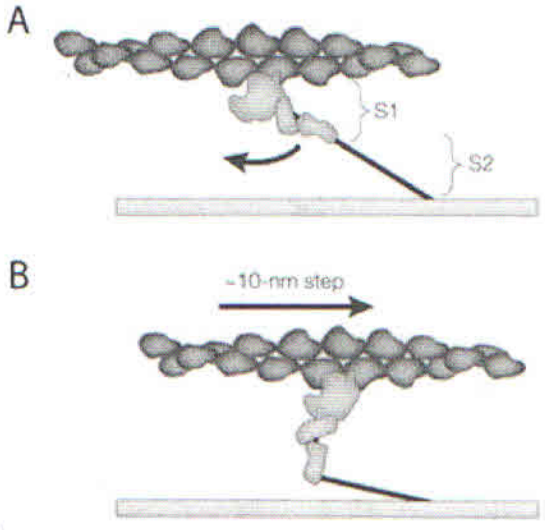


THE CROSS BRIDGE CYCLE - DEPICTING MUSCLE CONTRACTION



1. ACTIVATION
2. CROSS BRIDGE FORMATION
3. THE POWER STROKE
4. CROSS BRIDGE DETACHMENT

THE CROSS BRIDGE



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and muscle fibre is called myoneural junction or NM junction.

(a)

- There are also afferent nerve fibres, mostly non-sensory, from muscles spindles and tendon receptors which convey information about state of stretch of muscle.
- A few nerves convey pain sensation.

MECHANISM OF SKELETAL MUSCLE CONTRACTION

AP arrives along motor neuron to its end foot

↓

Ca^{2+} influx in end foot to mediate Ach release from vesicles (1 impulse = 60 vesicles release Ach)

↓

Ach binds to AchR on the end plate and causes Na^+, K^+ and Ca^{2+} influx that brings about localized non-propagated depolarization known as End Plate Potential (EPP)

↓

EPP reaches threshold level (30-40 mV) to cause propagated AP along muscle fibre

↓

AP spreads on both sides of end plate reaching a magnitude of 120-130 mV

↓

Propagated AP causes muscle contraction (excitation-contraction coupling)

(**Note**: These steps are similar to synaptic nerve transmission where instead of a post synaptic neuron we have a muscle fibre)

Mg^{2+} inhibits Ach release from vesicles. Hydrolysis of Ach at motor end plate prevents continuous response to one stimulus.

Miniature End Plate Potential (MEPP): In the resting state of NM junction, small quantities of Ach are released randomly (1 Ach/sec) which causes a very small **non** propagated depolarization of about 0.5 mV. This gives rise to MEPP.

THEORIES ON MECHANISM OF MUSCLE CONTRACTION

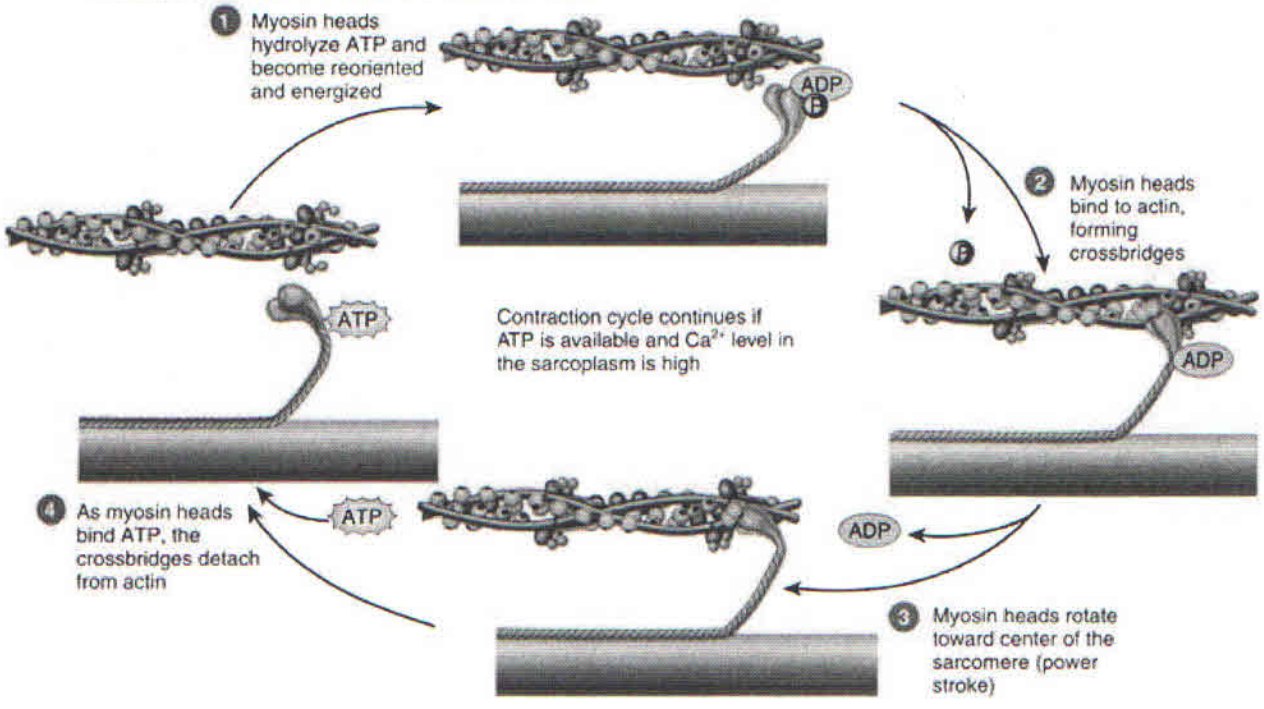
THE SLIDING FILAMENT THEORY (CROSS-BRIDGE THEORY)

According to this theory deduced by **Hugh Huxley** (1954), the actin filament (A) slides towards the myosin (M) filament. The myosin head link with the reactive sites of actin filament, bend and pull it inwards.

A. THE RESTING STATE:

1) Tropomyosin-TN complex prevents interaction of M and A filaments.
2) Reactive sites of A are negatively charged and the M cross-bridges (that are attached to ATP) is also negatively charged (in the absence of Ca^{2+}) and so repel and kept apart.
3) Binding site of actin is also covered by tropomyosin.
4) Only on availability of Ca^{2+} both filaments binds together (- ve charge neutralized by Ca^{2+}).
5) M develops ATPase activity.
6) Ca^{2+} initiates contraction by uncovering the binding site of actin.

B. SEQ. OF EVENTS DURING CONTRACTION



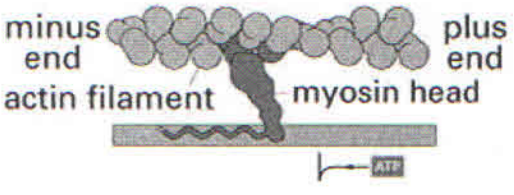
The whole process explained below is known as *Excitation-Contraction Coupling.*

1) AP from nerve fibre reaches NM junction and transmitted to muscle fibre
2) AP in muscle spreads along sarcolemma
3) AP spreads inwards through T-tubules and reaches annulus of triad
4) Ca^{2+} release from terminal cisternae of sarcoplasmic reticulum
5) Ca^{2+} diffuses towards myofilaments and initiates contraction
6) Ca^{2+} binds to TN-C causing TN-I binding with actin weakened
7) Uncovering of binding sites of actin
8) Head of M links to A, and then moves inwards by bending which pulls the A inwards
9) The 2 A of sarcomere move in opposite direction, i.e., towards the centre.
10) The bend in M head exposes ATP binding site and allows ATP to come and attach
11) This causes detachment of M head from A and ATP is split consequently (stimulated by Ca^{2+})
12) Ca^{2+} is then pumped again in to SR and stored in cisternae. This causes muscle relaxation

Energy for transfer of Ca^{2+} in to SR is also provided by ATP. Thus ATP is involved in both contraction and relaxation (plasticizer action) of muscle.

2 TYPES OF CONTRACTION

1. **ISOTONIC**: Involves actual shortening of muscle. It has 3 phases:



a) Latent period (0.01 s) – no apparent change.
b) Contraction phase (0.04 s)
c) Relaxation phase (0.05 s)

2. **ISOMETRIC**: There is not change in length of muscle on changing tension.

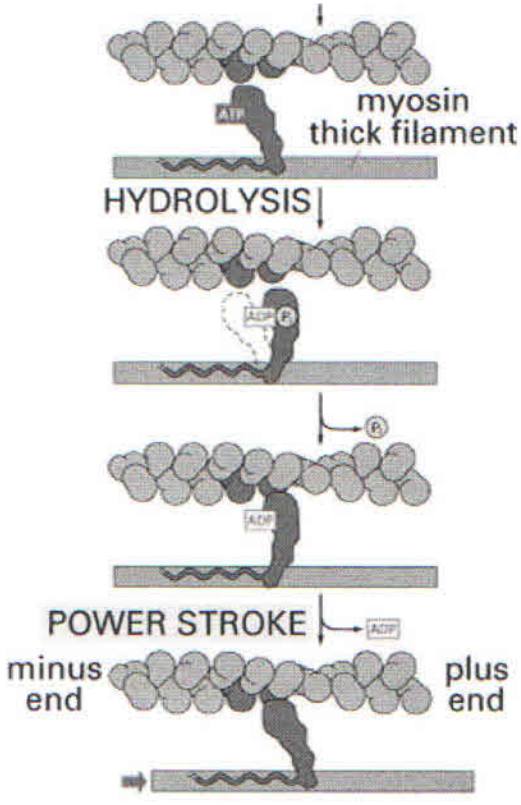


Figure 17-45 Essential Cell Biology, 2/e. (© 2004 Garland Science)

THERMAL CHANGES DURING MUSCLE CONTRACTION

Resting muscle liberates heat at a constant rate, known as *basal heat*. Increased amount of heat is given off during contraction, relaxation and after relaxation by the muscle. It may be divided in to:

a. **INITIAL HEAT**: Heat given off during twitch even under anaerobic conditions. It consists of:

I. *Heat of activation*: Occurs when muscle passes from resting to active state. This is delivered at a rapid rate even before the mechanical process of shortening takes place. A number of such heats get summed up on receiving a number of stimuli to form what is called *maintenance heat*.

II. *Heat of shortening*: Liberated when muscle shortens and thus proportional to it. Present only during isotonic contraction.

III. *Heat of relaxation*: As the muscle lengthens during relaxation, the work done during contraction is liberated as heat. (I and II are the waste heat of chemical reactions).

b. **DELAYED HEAT**: Also known as recovery heat that continues for several minutes after mechanical events are over. This is due to metabolic processes which restore the muscle to its resting state. This value is lesser in anaerobic (*delayed anaerobic heat*) state than in aerobic state (*oxidative delayed heat*).

CHEMICAL CHANGES DURING MUSCLE CONTRACTION

Muscle contains a number of high energy phosphate compounds along with biomolecules that contribute for its energy.

1. ATP ⟶ ADP + Pi (this is an anaerobic exergonic reaction that gives immediate energy for contraction and phosphorylation of glycogen).

2. Creatine phosphate ⟶ Creatine + Pi (anaerobic exergonic reaction providing energy and Pi for resynthesis of ATP).

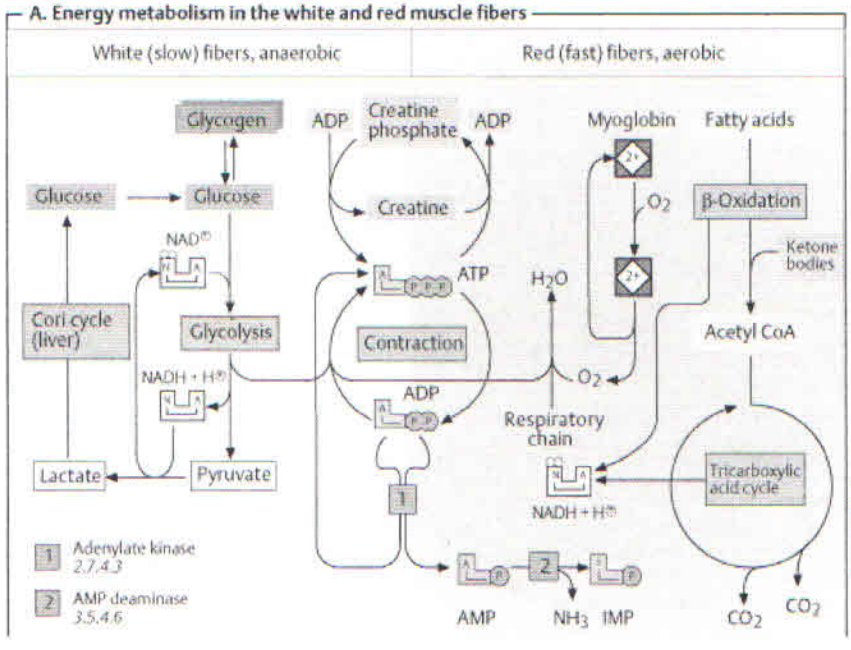
3. ADP + Pi ⟶ ATP
So, Creatine phosphate + ADP ⟶ Creatine + ATP (**Lohmann reaction**)

4. Glycogen ⟶ Lactate (partly aerobic and partly anaerobic that provides energy for resynthesis of CP and ATP).

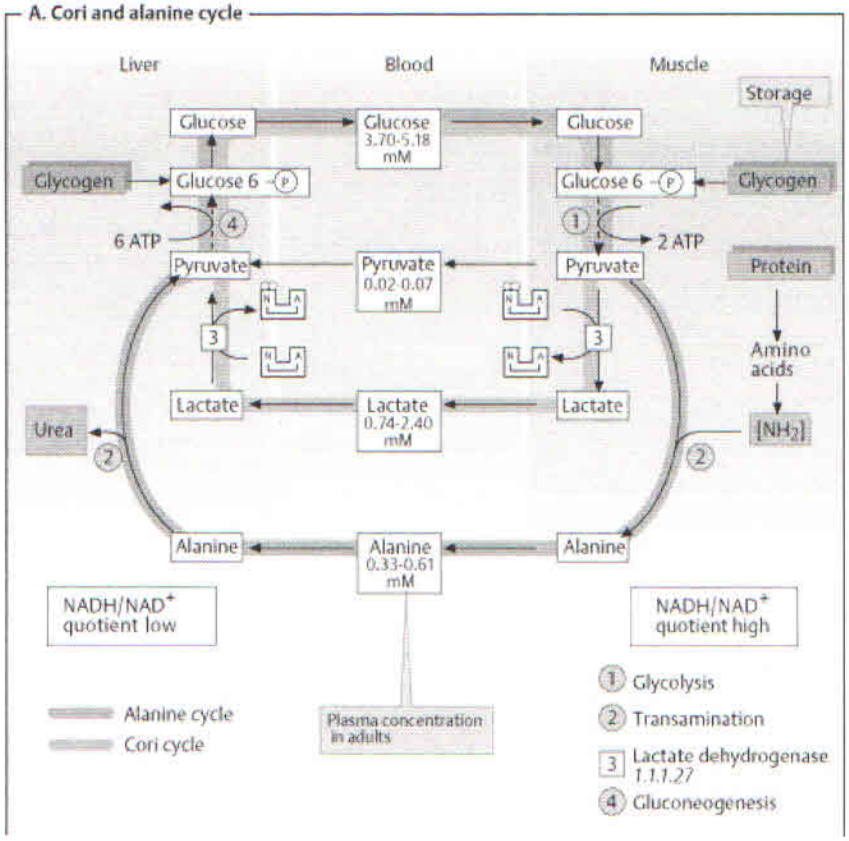
5. Lactate: $1/5^{th}$ oxidized to $CO_2 + H_2O$ and provides energy. $4/5^{th}$ reconverted to glycogen. This doesn't occur in anaerobic condition.

5. FFA: Used as fuel that gives out ATP only during resting and light work conditions.

O_2 DEBT: During severe exercises of short duration, the muscle contracts in the absence of O_2. So, under this anaerobic state, lactate is formed from pyruvate. The extra O_2 required to oxidize lactate is made available after he exercise. This portion of O_2 is the O_2 debt.



CORI CYCLE: When large amount of lactate is produced it diffuses in to blood and gives out the above reaction. 1. Glycogenolysis followed by anaerobic glycolysis, 2. Gluconeogenesis followed by glycogenesis, 3. Aerobic glycolysis, 4. Glycogenesis.



pH CHANGES DURING MUSCLE CONTRACTION

ATP hydrolysis causes fall in pH. Creatine formation raises pH. Later, lactate formation decreases pH when salts, protein and CP act as buffers. Prolonged contraction also liberates NH_3 which serves to maintain reaction.

RIGOR MORTIS (post mortem rigidity)

All muscles after removal from the body or after death undergo changes in the protoplasm associated with permanent loss of irritability. This is rigor mortis. A living muscle fibre has its specific length, it is translucent, elastic, extensible, soft and alkaline (pH 7.3). In rigor mortis, it becomes shorter, opaque, inelastic, inextensible, rigid and acidic (pH 5.8). The proteins get coagulated.

SKELATAL MUSCLE FIBRES – SOME PROPERTIES

1) **ALL-OR-NONE PHENOMENA**: This property is exhibited by an individual muscle fibre. When a muscle fibre is stimulated, it will show maximal contraction irrespective of the intensity of stimulus. So, minimal contraction means a few muscle fibres are involved in a muscle, whereas a maximum contraction means all the muscle fibres are involved.

2) **RHEOBASE**: It is the strength of the weakest galvanic current which will excite a muscle or a nerve when allowed to flow for a sufficient duration of time (*utilization time*).

3) **CHRONAXIE**: The shortest duration of time that a current of twice the rheobasic strength must flow in order to excite a muscle or a nerve. Shorter the chronaxie value greater will be the excitability of muscle.

4) **CONTRACTILITY**: Ability to contract (develop tension).

5) **EXCITABILITY (IRRITABILITY)**: Ability to respond to a stimulus either electrochemical or mechanical (blow to muscle by external force).