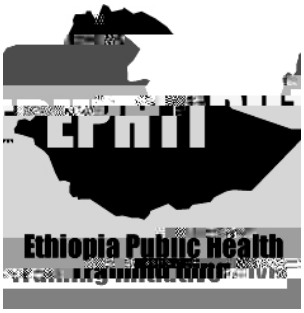
LECTURE NOTES

For Health Science Students

Physiology Part I



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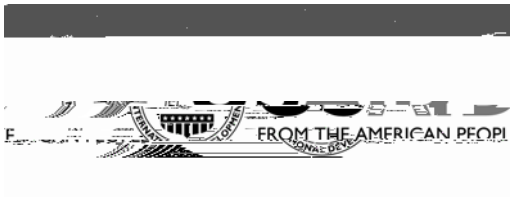

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PREFACE

We have prepared lecture note that fits the academic curriculum designed for the students of Health Sciences in Ethiopia. This lecture note has two parts.

Part one includes the following five chapters: Principles of physiology, Excitable tissues (nerve and muscle), physiology of blood, Cardiovascular physiology and Respiratory physiology;

Part two contains the following seven chapters: physiology of the renal system, physiology of the gastrointestinal system, physiology of the endocrine system, physiology of the reproductive system, Neurophysiology, physiology of the Special senses and the Autonomic nervous system.

ACKNOWLEDGEMENTS

We are grateful to some students and teachers who have commented favorably on the clarity of the writing, and the emphasis on the core aspects of physiology. We express sincere appreciation to the secretaries for meticulous computer type settings of the teaching material.

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After completeing this chapter, the student is expected to know the following.

- Know that cells as the basic units of life.
- Understand that homeostasis is essential for cell survival, disruption in homeostasis can lead to illness and death, homeostatic control systems include closed and open loop systems
- Know the negative and positive feedback mechanisms
-

Physiology tells us how the bodies of living organisms work. Physiology is based on the gross and microstructure. Both structure and function must be studied at all levels from the cellular to the molecular to the intact organism.

All aspects of human physiology evolved in the thousands of inherited units of DNA called genes. This genetic imprint is passed from parents to children. We all inherit a mixture of genes present in parents. There is immense genetic diversity, as a result of small spontaneous change in individual genes, called mutation, occurring from time to time. The natural selection concept of Charles Darwin emphasizes the predominance of the genes in the population that favors survival of the fittest and reproduction in a particular environment.

Early with life on earth cells developed the ability to react with oxygen and carbon compounds and use the energy released by these chemical reactions. With complexity of development cells evolved structure called mitochondria for efficient energy production. The efficiency of oxidative phosphorylation was maximized in natural selection of the best. The mitochondria of cells in mammals are same in appearance and function. Some aspects of human physiology may be rapidly changing on the evolutionary scale of time. Homosapiens have walked on the earth for perhaps 1.5 million years, but human brain has reached its present size only about 35,000 years back. The brain capabilities are probably still rapidly evolving as new pressures are faced. For pain with injury, a warning signal results in sudden withdrawal of the injured part, protecting it from further injury. But step-by-step sequence of events starts with the injury and eventually ends with the contraction of group of muscles that flex the injured limb - stimulus, receptor, electric signals, spinal cord, flexor muscles. There are links between the nerve and the spinal cord, and the muscle. The circuit that creates this response is genetically determined and is formed during early development of the nervous system.

From single cell to organ system cells are the basic units of living organisms. The number of cells is very large. For example, an adult

person contains approximately 100 trillion cells. Humans have several levels of structural organizations that are associated with each other. The chemical level includes all chemicals substances essential for sustaining life. These chemicals are made up of atoms joined together in various ways. The diverse chemicals, in turn, are put together to form the next higher level of organization, the cellular level. Cells are the basic structural and functional units of life and organization. Each cell has a different structure and each performs a different function.

Muscle tissue is specialized for contraction and generation of tension. The different types of muscle tissue are functional adaptation of the basic contractile system of actin and myosin. Skeletal muscles are responsible for movement of the skeleton, cardiac muscle for the contraction of the heart that causes blood circulation; smooth muscle is responsible for propelling contents within soft hollow organs, such as the stomach, intestine, and blood vessels. Smooth muscle is not under voluntary control and has no striations. Cardiac muscle fibers branch but are separated into individual cell by continuity of the plasma membrane, the intercalated discs.

This tissue is specialized for conduction and transmission of electrical impulses and the organization of these nerve cells or neurons is the most complex of any of the tissue.

hormones directly into the blood and the exocrine glands secrete substances via ducts (e.g., salivary glands, pancreas and liver).

It is mesodermal in origin and functions in supporting, connecting and transporting. It covers wide variety of tissues, but having more intercellular materials or matrix, than cells. It also contains extracellular fibers, which may be tough collagenous fibers or the resilient elastic fibers.

: The following are the important life processes of humans:

includes catabolism and anabolism that provides energy and body's structural and functional components

Ability to sense changes in and around us.

: ability to carry the effects of stimulus from part of a cell to another.

: ability to contract in response to stimulus

At an average, 60% of the body weight of young adult male is water. The remaining is composed of minerals, fat and proteins. The human body contains organic compounds such as lipids, proteins, carbohydrates and nucleic acids. The lipids are important forms of storage fuel in addition to providing insulation of the body as a whole or essential component in the structure of plasma membranes, myelin and other membranes. Carbohydrates serve as a lesser form of fuel storage (400-500 gms). Proteins serve as the structural basis for all enzymes, contractile muscle proteins, connective tissue, such as collagen and elastin and in addition as a fuel (about 15%), or precursor for carbohydrate in the process of gluconeogenesis. Ingested glucose is converted to glycogen and stored in the liver, muscle and adipose tissue.

Table 1. Elements in the Human Body

Element	Body weight %
Hydrogen, H	9.5
Carbon, C	18.5
Nitrogen, N	3.3
Oxygen, O	65.0
Sodium, Na	0.2
Magnesium, Mg	0.1
Phosphorus, P	1.0
Sulfur, S	0.3
Chlorine, Cl	0.2
Potassium	0.4
Calcium	1.5

Table 2. Components of Body System

Circulation	Heart, blood vessels, blood
Digestive system	Mouth, pharynx, esophagus, stomach, small & large intestine, salivary glands, pancreas liver, and gallbladder
Respiratory system	Nose, pharynx, larynx, trachea, bronchi, lungs
Urinary system	Kidneys, ureters, urinary bladder, urethra
Skeletal system	Bones, cartilage, joints
Muscle system	Skeletal muscle
Integumentary system	Skin, hair, nails
Immune system	Leukocytes, thymus, bone marrow, tonsils, adenoids, lymph nodes, spleen, appendix, gut-associated lymphoid tissue, skin-associated lymphoid tissue muscosa associated lymphoid tissue
Nervous system	Brain, spinal cord, peripheral nervous system. Special sense organs
Endocrine system	All hormone-secreting tissues including hypothalamus, pituitary, thyroid, parathyroids, adrenals, endocrine pancreas, kidney, intestine, heart, thymus, pineal
Reproductive system	Male: testis, prostate, seminal vesicles, bulbourethral glands, associated ducts Female: ovary, oviduct, uterus, vagina, breast.

Homeostasis is a delicately balanced state. Large part of physiology is concerned with regulation mechanisms that act to maintain the constancy of the internal environment. Many of these regulatory mechanisms operate on the negative feedback. Homeostasis is the dynamic steady state of the internal environment. Departures from the steady state are opposed by negative feedback regulation. The structure and chemical

reactions of living organisms are sensitive to the chemical and physical conditions within and around cells. Cells must be wet and surrounding fluid must be fresh or salty seawater. For multicellular organisms, the surrounding fluid is the interstitial fluid: a component of the extracellular fluid.

The intracellular fluid has a high concentration of potassium and low concentration of Na^+ Cl^-, Mg^{++}, and Ca^+. In addition, cells need a ready supply of nutrients, that serve as structural building molecules, and source of energy as ATP (chemical energy). Body temperature is very crucial for intracellular physiological processes; enzymatic events need a very narrow range of temperature, within the physiological range of temperature compatible with life, cooler temperature favors preservations of cellular structure but slows the rate of chemical reactions carried out by cells. The higher temperature enhances chemical reactions, but may also disrupt the structure of the proteins and other macromolecules within cells. The production of energy for cellular activities requires oxygen and nutrients reaching the cell interior and carbon dioxide and other chemical wastes products be transferred to the environment. Extensive exchange between cells and immediate surroundings, interstitial fluid, occurs by diffusion based on a concentration gradient. Diffusion causes adequate movement of dissolved nutrients, gases and metabolic end products to meet the active needs of the cell, if the distance is short. If the distance increases, the time for diffusion increases too. For the efficiency of diffusion, the diameter of individual cells is usually not more than a few tenths of a millimeter. With the evolution of multicellular organisms, body plans include an internal fluid environment for the cells, called extracellular fluid (ECF). The ECF includes both the interstitial fluid and the plasma. In the circulatory system, blood rapidly moves between the respiratory system, where gases are exchanged; the kidney where wastes and excess of fluid and solutes are excreted; and the digestive system where nutrients are absorbed. These substances are rapidly transported by blood flow overcoming the diffusion limit on large body size.

By maintaining a relatively constant internal environment, multicellular organisms are able to live freely in changing external environment. Cannon called it ‘homeostasis’

(Greek, homeo = same; stasis = staying). Homeostasis of the internal environment

Body systems are made up of cells organized according to specialization to maintain homeostasis.

Information from the external environment relayed through the nervous system.
Nervous system acts through electrical signals to control rapid responses for higher functions e.g., concentration, memory, and creativity

Acts by means of hormones secreted into the blood to control processes that require duration rather than speed, e.g., metabolic activity and water and electrolytes balances

Transports nutrients, oxygen, carbon dioxide, wastes, electrolytes, and hormones throughout the body

Obtains oxygen from and eliminates carbon dioxide to the external environment; helps regulate pH by adjusting the rate of removal of acid-forming carbon dioxide

Important in regulating the volume, electrolyte composition, and pH of the internal environment; removes waste and excess water, salt, acid, and other electrolytes from the plasma and eliminates them into the urine.

Obtains nutrients, water and electrolytes from the external environment and transfers them into the plasma; eliminates undigested food residues to the external environment

:

Supports and protects body parts and allows body movements; heat generated by muscular contraction are important in temperature regulation; calcium is stored in the bones Immune system:
Defense against foreign invaders and cancer cells; paves way for tissue repair

keeps internal fluids in and foreign materials out serves as a protective barrier between the external environment and the remainder of the body; the sweat glands and adjustment in blood flow are important in temperature regulation

Cells are the link between molecules and human. They have many molecules in a very complex organization and have the feature of interaction and represent a living entity. Cells are the living building blocks for the immense multicellular complicated whole body. Cells making the body are too small to be seen by the unaided eyes. About 100 average-sized cells placed side by side would be only about 1mm. Many cells share some common features despite diverse structure and functional specialization. Most cells have 3 subdivisions: the plasma membrane, the nucleus, and the cytoplasm.
Plasma membrane/cell membrane: It is very thin membrane structure that enclose each cell, separating the cell's contents from the surrounding. The fluid contained inside the cell is ICF, and the fluid outside the cell is extracellular fluid (ECF). The plasma membrane holds the cell contents, but has the ability in selectively controlling movement of molecules between the ECF and intracellular fluid (ICF).

This is distinctly oval or spherical shaped central structure surrounded by a double-layered membrane. Within the nucleus is DNA which directs protein synthesis and serves as a genetic blueprint during cell replication. DNA gives codes, or "instruction" for directing synthesis of specific structure and enzymes proteins within the cell. By monitoring these protein synthesis activity, the nucleus indirectly governs most cellular activities and serves as the cell's master. Three types of RNA are involved in protein synthesis. First, DNA's genetic code for a particular protein synthesis. First,

production. During cell replication, DNA ensures that the cell produces additional cells

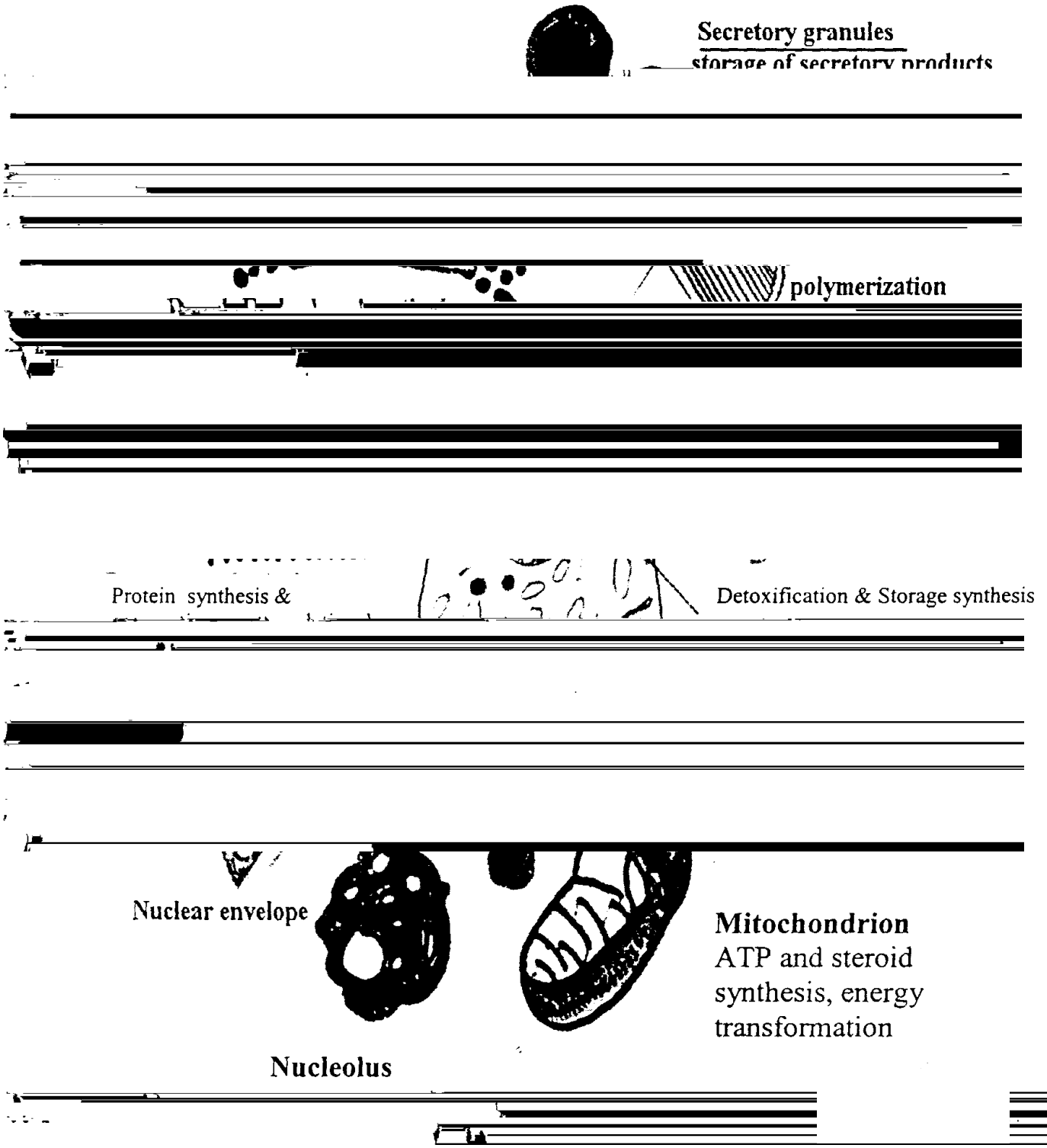

Figure1. The compositions of a typical cell are in the center and the detailed structure of organelles is shown around the outside.


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It does not have ribosomes hence looks ‘smooth’. It serves a variety of other functions that differ in cell types; it does not produce proteins. In most cells, the smooth ER is sparse and serves packaging and discharge site for protein molecules that are to be transported from the ER. All new proteins and fats pass from ER to gather in the smooth ER. Portions of the smooth ER then “bud off/pinch off”, giving rise to ‘transport vesicles’, they contain the new molecule wrapped in a membrane derived from the smooth ER membrane. Transport vesicles move to the Golgi complex for further processing of their cargo. Some specialized cells have an extensive smooth ER, which has additional functions as follows:

- The smooth ER is well developed in cells specialized in lipid metabolism- cells

Number of stacks vary in cells; cells specialized for protein secretion have hundreds of stacks, whereas some have only one

The majority of newly formed molecules budding off from the smooth ER enter a Golgi complex stacks. It performs the following important functions.

1. Processing the raw material into finished products. In the Golgi complex, the "raw" protein from the ER are modified into their final state mainly by adjustment made in the sugar attached to the protein. This is a very elaborate, precisely programmed activity, specific for each final product.
2. Sorting and directing finished product to their final destination. According to their function and destination, different types of products are segregated by the Golgi complex, i.e., molecules that are destined for secretion to the exterior, molecules that will eventually become part of the plasma membrane, and the molecules that will become incorporated into other organelles.
3. The smooth ER of the liver and kidney cells are responsible for the detoxification and inactivation of drugs. Enzymes within the smooth ER can inactivate or destroy a variety of chemicals including alcohol, pesticides, and carcinogens.
4. In skeletal muscle cells, a modified form of smooth ER stores $Ca^{++}$to be released for muscle contraction.


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In the inherited condition known as

lysosomes are not effective because they lack specific enzymes. As a result, harmful waste products accumulate disrupting the normal function of cells, often with fatal results

- Peroxisome has oxidative enzymes that detoxify various wastes.
- Is shorter and smoother than lysosome; several hundreds present in one cell
- Is membrane-enclosed sacs containing enzymes
- Contains several powerful oxidative enzymes and catalase
- Oxidative enzymes need oxygen to remove hydrogen from specific substance/molecule; such reactions are important in detoxifying various waste products within the cell or foreign compounds that have entered in, such as ethanol consumed in alcoholic drinks.
- The major product generated is hydrogen peroxide; hydrogen peroxide itself is a powerful oxidant.
- Also contain catalase, and antioxidant enzyme decomposing hydrogen peroxide into harmless water and oxygen. This reaction is an important safety reaction that destroys deadly hydrogen peroxide, at the site of production, thereby preventing possible devastating escape into the cytosol.
- Peroximal disordersdisrupt the normal processing of lipids and can severely disrupt the normal function of the nervous system by altering the structure of the c.05162(h)1.

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shelves called cristae, which project into an i

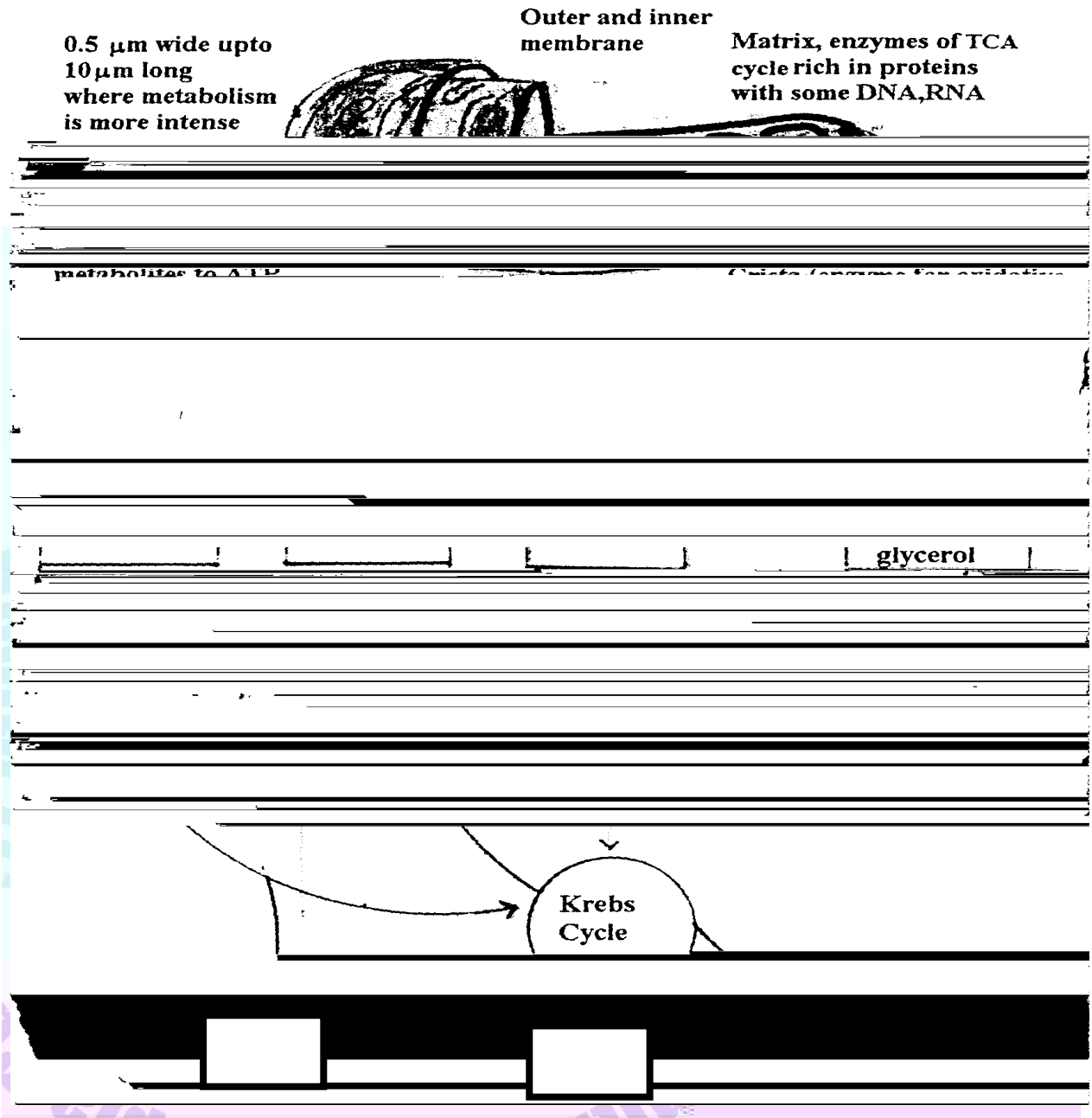

Figure 3. Structure of mitochondrion and the metabolic path ways of a cell.

1. In the matrix they have their own unique DNA called mitochondrial DNA.
2. Mitochondria have the ability to replicate themselves even when the cell to which they belong is not undergoing cell division

The cytosol is semi-solid portion of the cytoplasm, surrounding the organelles and occupies about 5% of the total cell volume. The cytosol is important in intermediary metabolism, ribosomal protein synthesis, and storage of fat and glycogen. Dispersed throughout the cytosol is a cytoskeleton that gives shape to the cell, provides a framework, and is responsible for various cell movements.

Many intracellular chemical reactions involving degradation, synthesis, and transformation of small organic molecules such as simple sugars, amino acids, and fatty acids capturing energy for cellular function and for providing raw materials for the maintenance of the cellular structure and function and for cell growth. Thousands of enzymes involved in glycolysis and other intermediary biochemical reactions are found in the cytosol.

Free ribosmes synthesize proteins for use in the cytosol itself. The rough ER ribosomes synthesize proteins for secretion and for construction of new cellular proteins. Some free ribosomes are clustered as polyribosomes. Excess nutrient not used for ATP production are converted in the cytosol into storage form known as 'inclusions', the largest and the most important storage product is fat. In adipose tissue, the tissue specialized for fat storage, the stored fat molecules occupies almost entire cytosol, as one large fat droplet. The other storage product is glycogen, cells vary in ability to store glycogen, the liver and muscle cell having the largest stores. Stored glycogen and fat provide fuel for the citric acid cycle and electron transport chain, feeding the mitochondrial energy-producing machinery.

The cytoskeleton is a complex protein network that act as the "bone and muscle" of the cell. This necessary intracellular scaffoldings supports and organizes cellular components arrangements and to control their movements; this provides distinct shape, size to the cell. This network has at least four distinct elements:

1. Microtubules
2. Microfilaments
3. Intermediate filaments
4. Microtubular lattice

The different parts of the cytoskeleton are structures linked and functionally coordinated to provide integration of the cell. The microtubule is the largest of the group; slender, long, hollow tubes composed of a globular protein molecule (6 nm diameter) tubulin. to provid20w tubes to1.0001 Tcati

and two non-polar (electrically neutral) fatty acid tails. The polar end is hydrophilic (water loving) because it can interact with water molecule which is also polar, the non-polar end is hydrophobic (water fearing) and will not mix with water.

Such two-sided molecule self assemble into a lipid bilayer, a double layer of lipid molecules when in contact with water. The hydrophobic tails bury themselves in the center away from the water, while the hydrophilic heads line up on both sides in contact with water. The water surface of the layer is exposed to ECF, whereas the inner layer is in contact with the intracellular fluid (ICF). The lipid is fluid in nature, with consistency like liquid cooking oil. Cholesterol provides to the fluidity as well as the stability; cholesterol lies in between the phosphate molecules, preventing the fatty acid chain from packing together and crystallizing that could decrease fluidity of the membrane. Cholesterol also exerts a regulatory role on some of the membrane proteins. On account of fluidity of the membrane it gives flexibility to the cell to change its shape; transport process are also dependent on the fluidity of the lipid bilayer.

The membrane proteins are either attached to or inserted within the lipid bilayer; some extending through the entire membrane thickness; they have polar region at both ends joined by a non-polar central portion.

Other proteins are on either the outside or inner surface, anchored by interactions with proteins that spans the membrane or by attachment to the lipid bilayer. On account of membrane fluidity many proteins float freely, although the mobility of protein that have special function in a particular area of the membrane is restricted - this gives ever changing mosaic pattern of the protein embedded in the lipid layer. Only the outer surface of the plasma membrane contains a small amount of carbohydrate. Short-chain carbohydrates are bound primarily to membrane proteins and to a lesser extent to lipids, forming glycoproteins and glycolipids.

The plasma membrane is actually asymmetrical; the two surfaces are not the same; carbohydrate is only on the outer surface; different amount of different proteins are on the outer and inner surfaces and even the lipid structures of the outer and inner half is

not the same. The plasma membrane is highly complex, dynamic, regional differentiated structure. The lipid layer forms the primary barrier to diffusion, whereas proteins perform most of the specific membrane functions.

Lipid bilayer serves three functions:

Forms the basic structure of the membrane

Its hydrophobic interior/inner side is a barrier to passage of water-soluble substances between the ICF and ECF; water-soluble cannot dissolve in and pass through lipid bilayer.

Responsible for the fluidity of the membrane

Membrane proteins are variety of different proteins within the plasma membrane; serve

plasma membrane of skeletal muscle contains enzyme ACh-esterase that destroys the chemical messenger that triggers contraction.

5. Some proteins are arranged as filaments network/meshwork on the inner side and are secured to certain internal protein elements of the cytoskeleton. They maintain cell shape.
6. Other proteins function as cell adhesion molecules (CAMs). These molecules

Short-chain carbohydrate on the outer membrane surface serves as self-identity marker enabling cells to identify and interact with each other in the following ways:

- Recognition of “self” and cell-to-cell interactions. Cells recognize each other and form tissues; complex carbohydrates act as a “trademark” of a particular cell type, for recognition.
- Carbohydrate-containing surface markers are important in growth. Cells do not overgrow their own territory. Abnormal surface markers present in tumor cells, and abnormality may underline uncontrolled growth.
- Some CAMS have carbohydrate, on the outermost tip where they participate in cell adhesion activity.

Lipid-soluble substances and small ions can passively diffuse through the plasma membrane down their electro-chemical gradients. The plasma membrane is selectively permeable. Highly lipid-soluble particles are able to dissolve in the lipid bilayer and pass through the membrane. Uncharged/non-polar molecules oxygen, carbon dioxide and fatty acids are highly lipid-soluble and readily permeate the membrane. Charged particle sodium/potassium ions and polar molecules such as glucose and proteins have low lipid solubility, but are very soluble in water. For water-soluble ions of less than 0.8 nm diameter, protein channels serve as an alternate route for passage. Ions for which specific channels are available can permeate the plasma membrane. Particles with low lipid-permeability and too large for channels, cannot permeate the membrane on their own.

Some force is needed to produce movement across the plasma membrane.

1. Forces that do not require the cell to expend energy for movement - passive force
2. Forces requiring energy (as ATP) to be expended to transport across the membrane - active force

All molecules in liquid and gases are in continuous random motion as they have more room to move before colliding with another. Each molecule moves separately and randomly in any direction. As a result of this haphazard movement, the molecules frequently collide bouncing off each other in different directions. The greater the concentration, the greater the likelihood of collision. Such a difference in concentration in molecules between two adjacent areas is chemical /concentration gradient. The net movement of the molecule by diffusion will be from the higher area of concentration to the area of lower concentration. Certain factors in addition to the concentration gradient influence the rate of net diffusion across a membrane. These include the:

1. magnitude of the concentration gradient
2. permeability of the membrane to the substance
3. surface area of the membrane to the substance
4. molecular weight of the substance: lighter diffuse rapidly
5. distance through which diffusion must take place

Increasing all the factors increases rate of net diffusion, except distance - thickness, that if increased, decreases the rate of diffusion; and molecular weight if increased, decreases rate of diffusion.

Movement of charged particles is also affected by their electrical gradient. Like charges repel each other, whereas opposite charges attract each other. If a relative difference in charges exist between two adjacent areas, the cations tend to move towards more negatively charged area, whereas the anions tend to move toward the more positively charged areas. The simultaneous existence of an electrical and concentration (chemical) gradient for a particular ion is referred to as an electro-chemical gradient.

Osmosis is the net diffusion of water down its own concentration gradient. Water can readily permeate the plasma membrane. The driving force for diffusion of water is its

concentration gradient from area of higher water concentration (low solute) to the area of lower water (high solute) concentration. This net diffusion of water is known as osmosis. Special mechanisms are used to transport selected molecules unable to cross the plasma membrane on their own.

All carrier proteins span the thickness of the plasma membrane and are able to undergo reversible changes in shape so that specific binding site can alternately be exposed at either side of the membrane. As the molecule to be transported attaches to a binding site on the carrier on one side of the membrane, it triggers a change in the carrier shape that causes the same site to be exposed to the other side of the membrane. Their

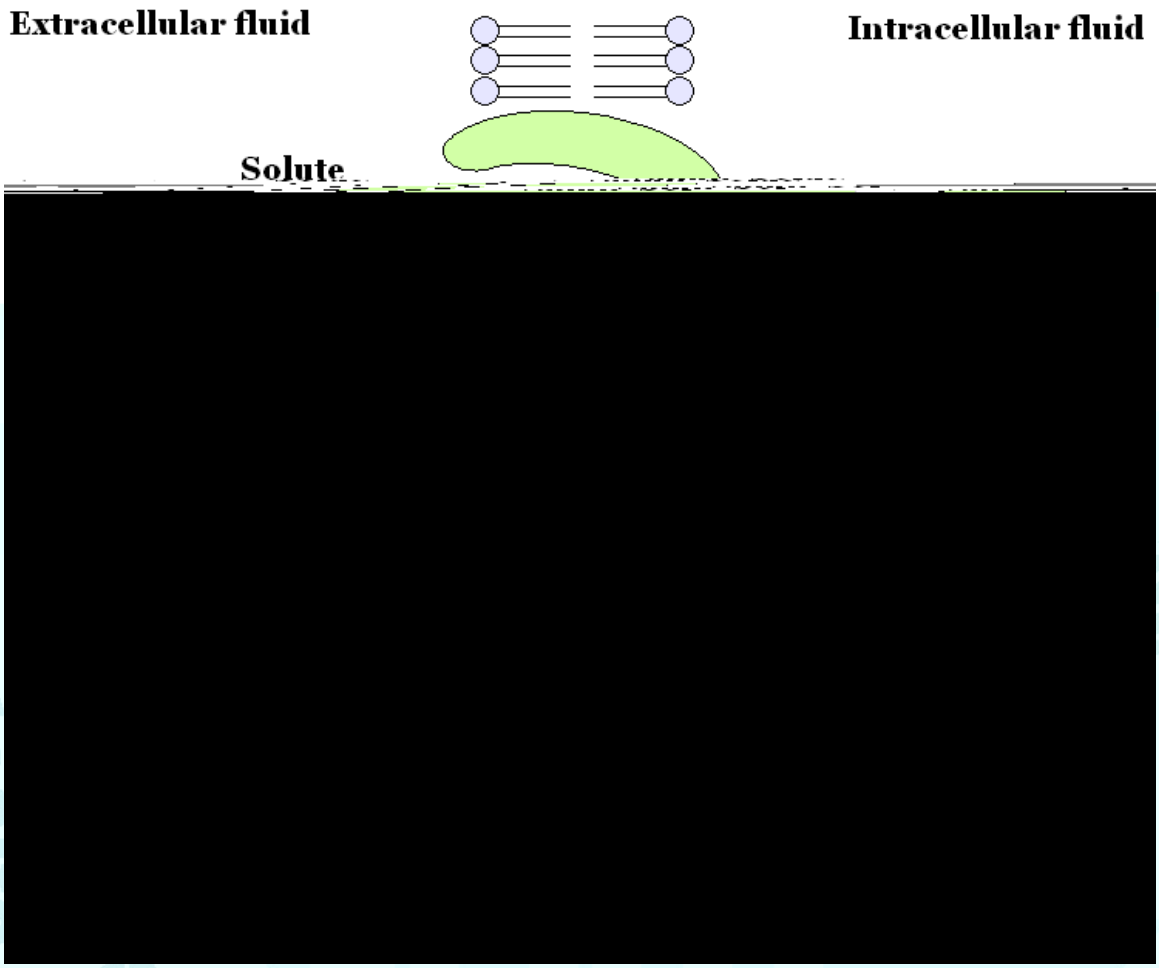

Figure 5. Primary active transport process

Facilitated diffusion uses a carrier protein to facilitate the transfer of a particular substance across the membrane “downhill” from higher to lower concentration. This process is passive and does not require energy because movement occurs naturally

(see fig. 5). Phosphorylation and binding of particle on the low concentration side induces a conformational change in the carrier protein so that passenger is now exposed to the high concentration side of the membrane. This change in carrier shape is accompanied by dephosphorylation. Removal of phosphate reduces the affinity of the binding site for the passenger, so the passenger is released on the high concentration side. The carrier then returns to the original conformation. This active transport mechanisms are often called 'pumps', analogous to lift water by pump that need energy to lift water against the downward pull of gravity; Hydrogen-pump, Na-K-ATPase pump (Na-K-Pump).

1. It establishes sodium and potassium concentration gradients across the plasma membrane of all cells; these gradients are important in the nerve and muscle to generate electrical signals.
2. It helps regulate cell volume by controlling the concentration of solutes inside the cell and thus minimizing osmotic effects that would induce swelling or shrinking of the cell.
3. The energy used to run the pump also indirectly serves as the energy source for the co-transport of glucose and amino acids across the membrane (intestine and kidney cell).

The special cell membrane transport system selectively transports ions and small polar molecules. But large polar molecules and even multimolecular material may leave or enter the cell, such as hormone secretion or ingestion of invading microbe by leukocytes. These materials cannot cross the plasma membrane but are to be transferred between the ICF and ECF not by usual crossing but by wrapped in membrane. This process of transport into or out of the cell in a membrane-enclosed vesicle is - vesicular transport. Transport into the cell is termed endocytosis, whereas transport out of the cell is called exocytosis. In endocytosis, the transported material is wrapped in a piece of the plasma membrane, thus gaining entrance to the interior of the

cell. Endocytosis of fluid is called pinocytosis cell (drinking), whereas endocytosis of large multimolecular particle is known as phagocytosis (cell eating).

1. In most cases, lysosomes fuse with the vesicle to degrade and release its contents into the ICF
2. In some cells, endocytic vesicle bypasses the lysosome and travels to the opposite side of the cell, where it releases its contents by exocytosis. This way intact particle shuttle through the cell. Some materials are transferred through the thin capillary walls cells, between the blood and surrounding tissue fluid.

Exocytosis is the reverse of endocytosis, in which a membrane- enclosed vesicle formed within the cell fuses with the plasma membrane, then opens up and releases its contents to the exterior. Such materials are packaged for export by the endoplasmic reticulum and Golgi complex.

1. It is a mechanism for secreting large polar molecules, such as protein molecules and enzymes that cannot cross the plasma membrane. The Vesicular contents are highly specific and are released only upon receipt of appropriate signals.
2. It enables the cell to add specific components to the plasma membrane, such as carrier, channels, or receptors depending on the cell's need

The rate of endocytosis and exocytosis is maintained in balance to maintain a constant membrane surface area and cell volume.

More than 100% of the plasma membrane may be used in an hour to wrap internalized vesicles in a cell actively involved in endocytosis, needing rapid replacement of surface membrane by exocytosis. Both exocytosis and endocytosis require energy and are active mechanisms. In some cases of endocytosis, receptor sites on the surface membrane recognize and bind with specific molecule in the environment of the cell.

This combination triggers selected trapping of the bound material. Antibodies attach to the bacteria forming a coat that can be recognized by the specific receptor sites in the plasma membrane of the phagocytic leukocyte. Such “marked” or opsonized bacteria are quickly engulfed and destroyed. Exocytosis too is a triggered event. A specific neural or hormonal stimuli initiates opening

Role in membrane transport and signal transduction: the outer surface of the plasma membrane is not smooth; it has tiny, cave-like indentations known as caveolae (tiny caves). These are small flask-shaped pits. In 1990S, it was suggested that they have the following role:

1. Provide a new route for transport into cell, and
2. Serve as “switch board” for relayi

Figure 7. Various ways of cell-to-cell communicaton

Binding on chemical messenger to membrane receptors brings about a wide range of responses in different cells through only a few similar pathways used.

Dispersed within the outer surface on the plasma membrane of cell (muscle/ nerve/ gland) are specialized protein receptors that bind with the selected chemical messenger - neurotransmitter, hormone, or neuro-hormone, that are delivered by the blood or a neurotransmitter released from the neuron.

The chemical messenger binds with receptor triggering a sequence of intracellular events that ultimately influence/control a particular cellular activity important in the maintenance of homeostasis, such as membrane transport, secretion, metabolism, or contraction. There are wide ranging responses, but there are mainly two ways by which binding of the receptor with extracellular chemical messenger bring about the desired effects.

1. By opening or closing of specific channels in the membrane regulating a particular ion to move in or move out of the cell, or
2. By transferring the signal to an intracellular chemical messenger (the second messenger), which is turn triggers a preprogrammed series of biochemical events within the cell. Post-receptor events are fairly common.

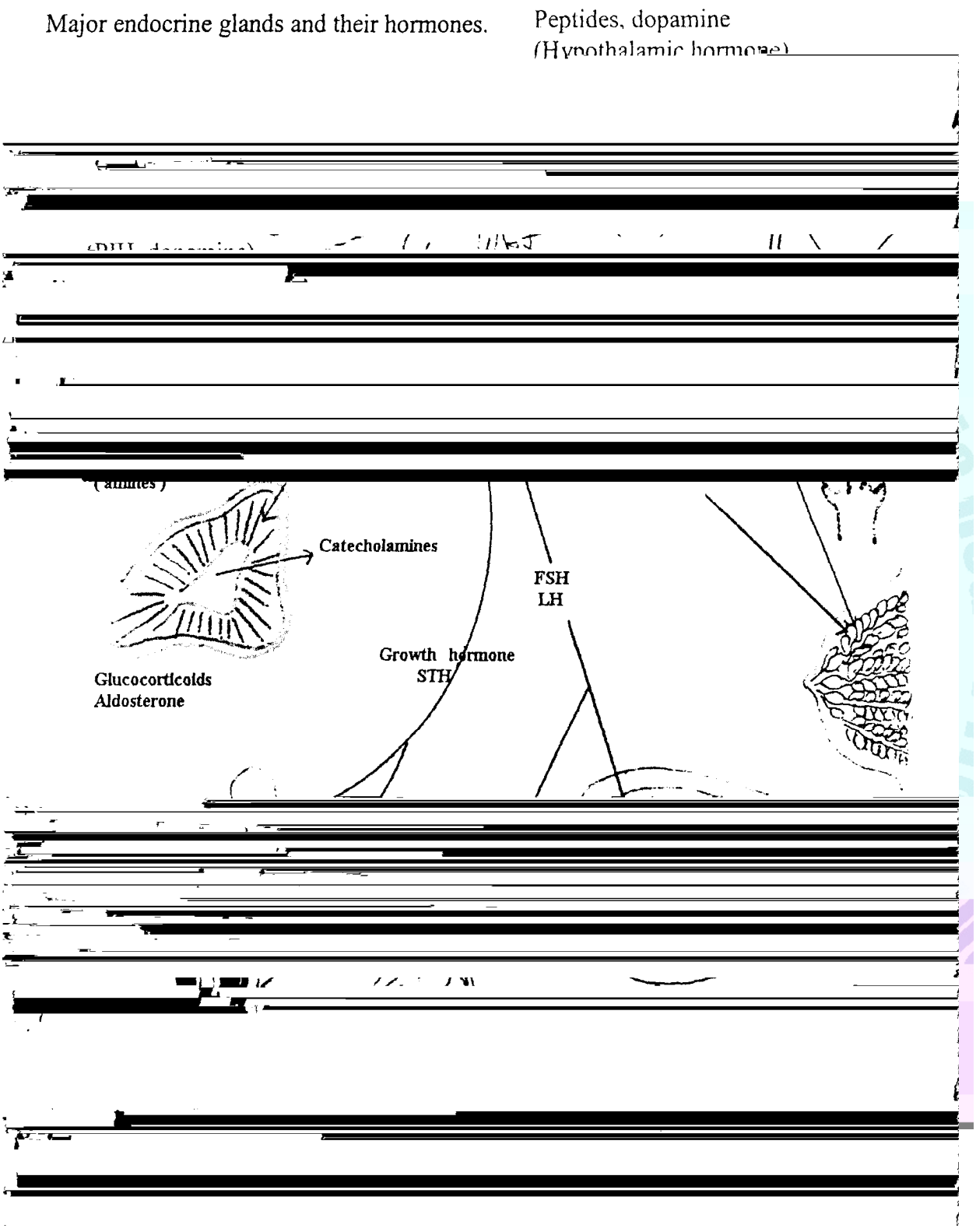

Figure 9. Endocrine communication using hormones as messenger..


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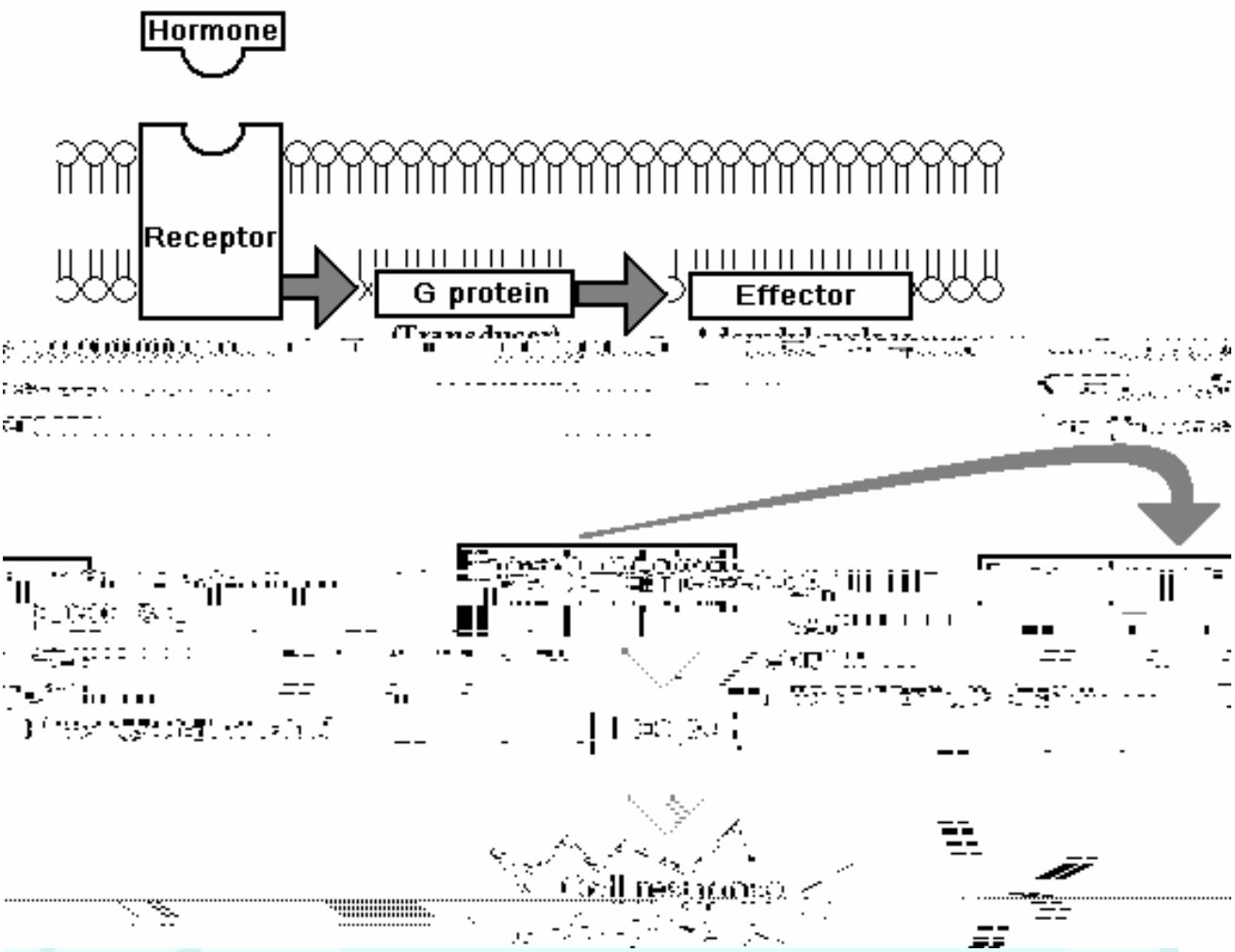

Figure 10. Signal transduction pattern common to second messenger system

PLC = Phospholipase C enzyme
R = receptor
G = GTP - regulatory protein

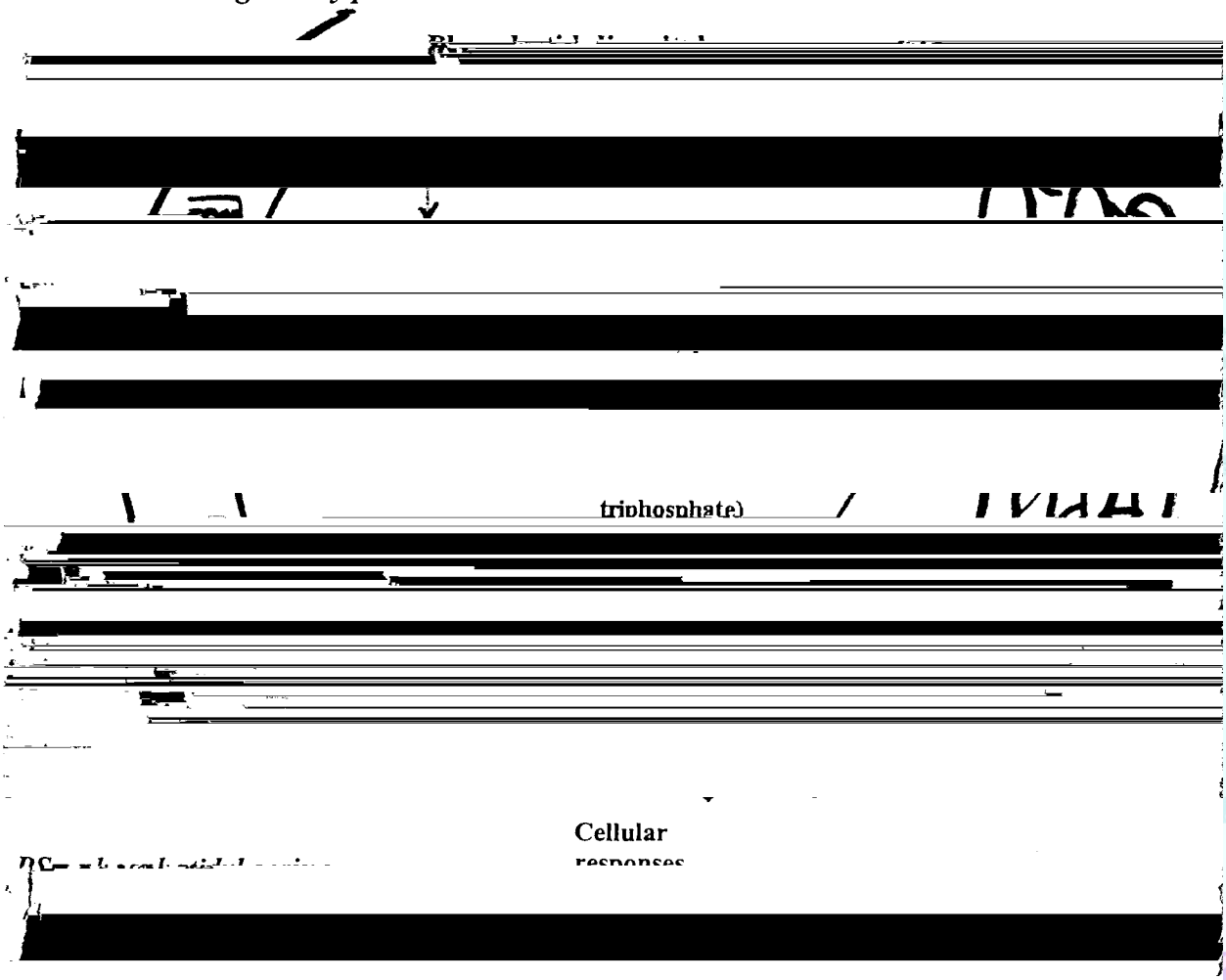

Figure 11. Signals operating through the phosphonoside system

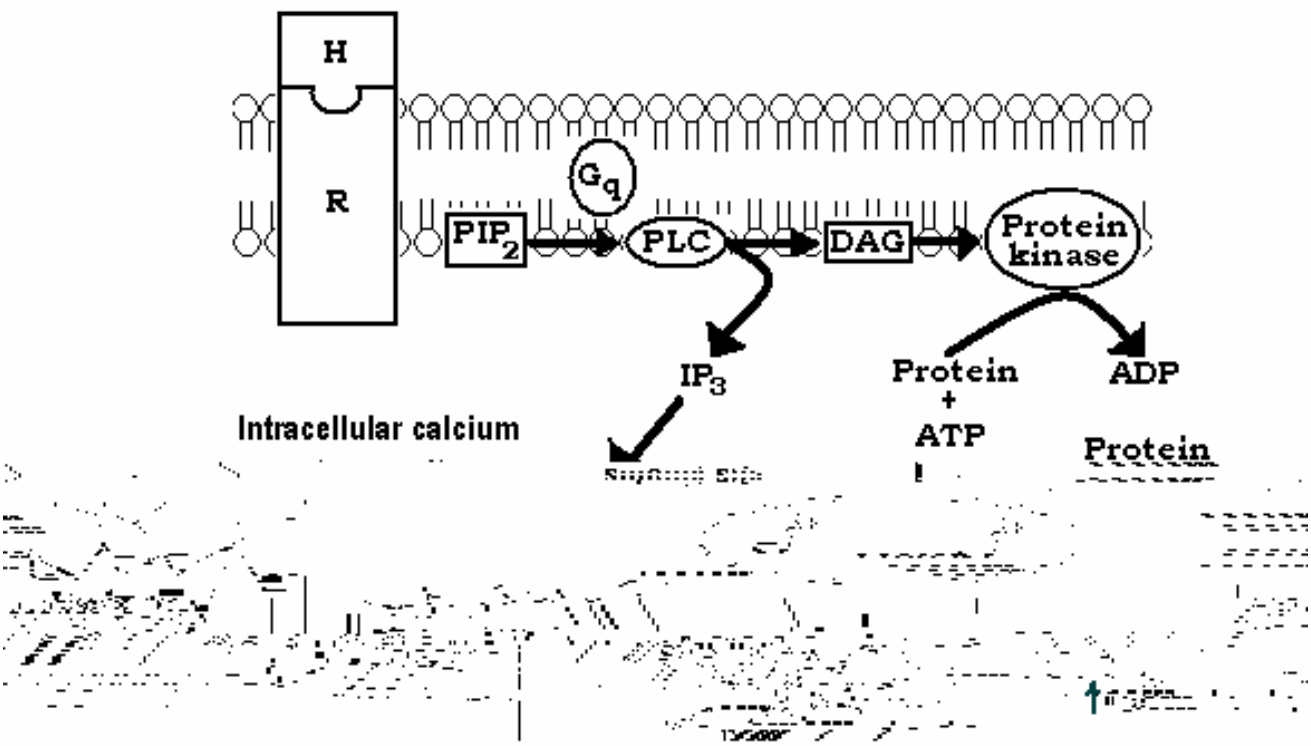

Figure 12. The phosphatidylinositol second messenger system

The human body is a self-controlling unit. Biological control systems have their own complexities and the enormous range and time scale over which they operate. The physiology of the various body systems is inseparable from homeostatic control mechanisms. Many step intracellular chemical events that amplifies a single irritating event is amplified thousands of times. In nervous system, millions of neurons may be involved in as simple act as walking up stairs. Some intracellular regulatory processes operate at the size scale of individual molecules or ions. On the other hand, of the time and size, the development plan of the human body by the endocrine system involves billions of cells, fulfilled on a time scale of decades.

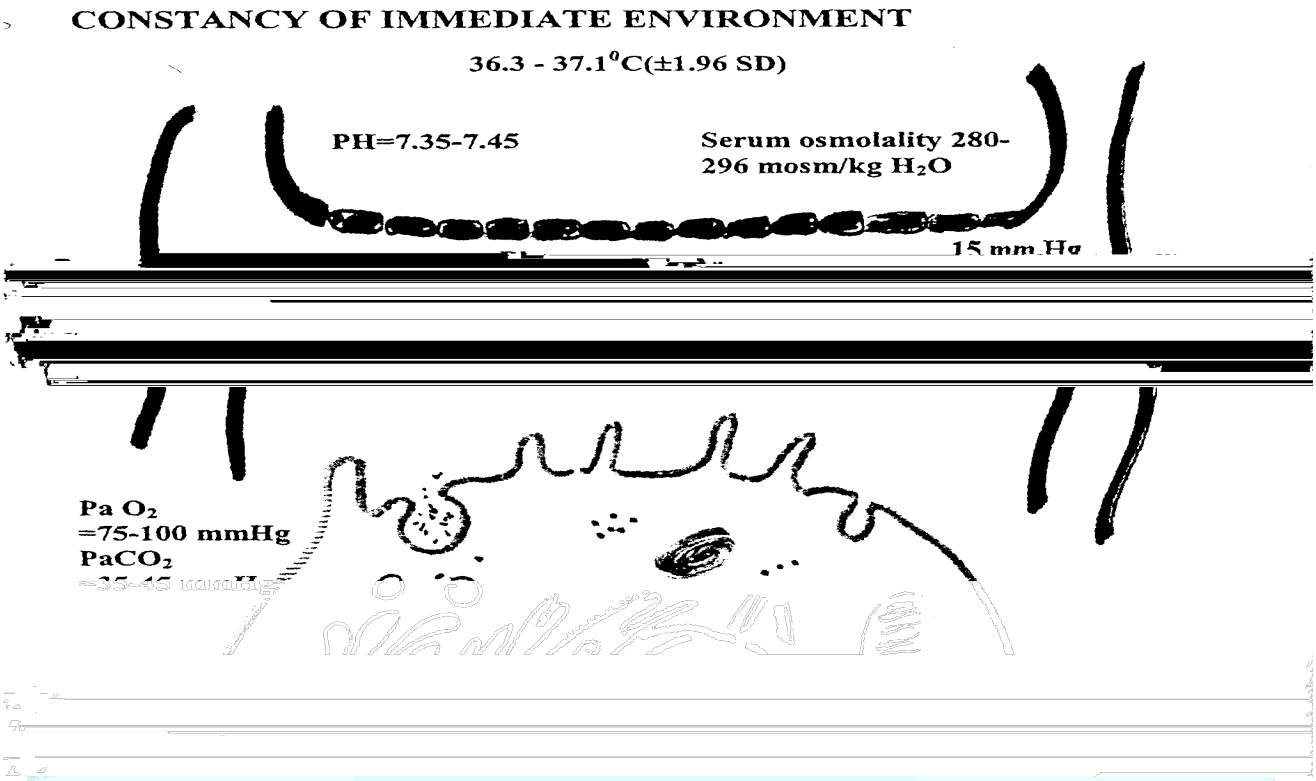

Figure 13. Shows consistency of internal environment of the cell

A “System” is a set of components related in such a way as to work as a unit.

A “control System” is so arranged as to regulate itself or another system

A is a set of components related is such a way as to work as a unit.

A “ is so arranged as to regulate itself or another system

An “ is the stimulus applied to a control system from a source outside the system so a
to produce a specified response from the control system.

An “ is the actual response of a control system.

An “ control system is one in which the control action depends on (is a function of) output.

A ” system is one in which the control action is a function of output in such a way that the output inhibits the control system

A “ ” is a closed loop control system in which the output accelerates the control system.

All negative feedback system has a controlled variable that is the factor (in the case of homeostasis functions) that the system is designed to maintain.

All feedback systems, negative or positive, have a sensor element capable of detecting the concentration of the controlled variable; information gained by the sensor is used to determine the output of the controlling system.

Therefore, in a feedback system, there is a sensor element, which detects the concentration of the controlled variable; there is a reference input, which defines the proper control level; and there is an error signal, which is a function of the error signal, wht4 Tsi1(

Open loop system don't have negative feed back character. Open loop system can result from disease or damage to some part of the feedback loop. For example, damage to parts of the motor control system of the basal ganglia may result in uncontrolled body movements, as in Parkinson's disease. In some physiological systems, open loop systems are part of normal function. Body movements that must occur very rapidly, such as eye movement to follow an object when the head moves, or the boxer's quick punch in fighting, must be carried out according to a learned pattern because they must be completed before feedback could be effective. The skill attained

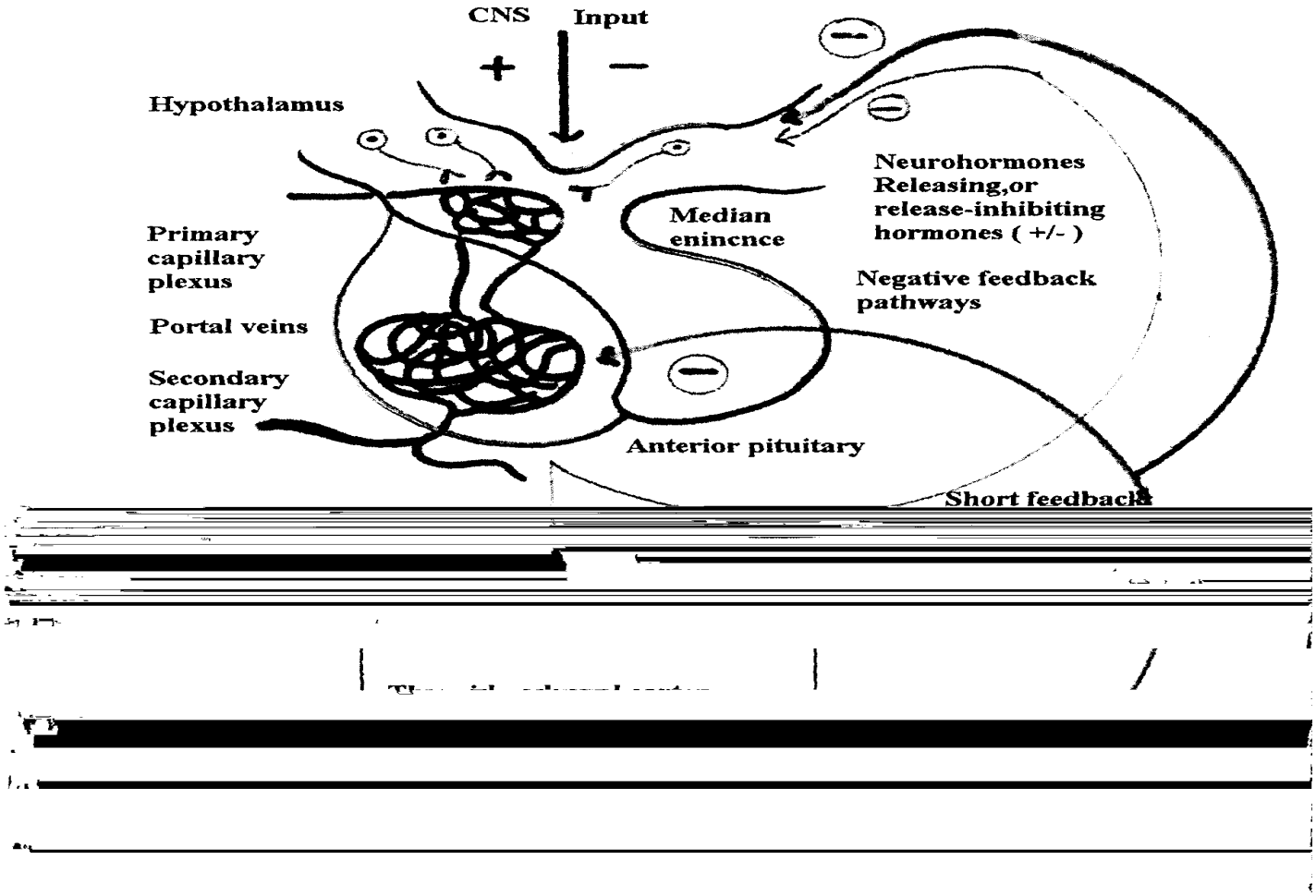

Figure 15. shows negative feedback pathways for pituitary hormones

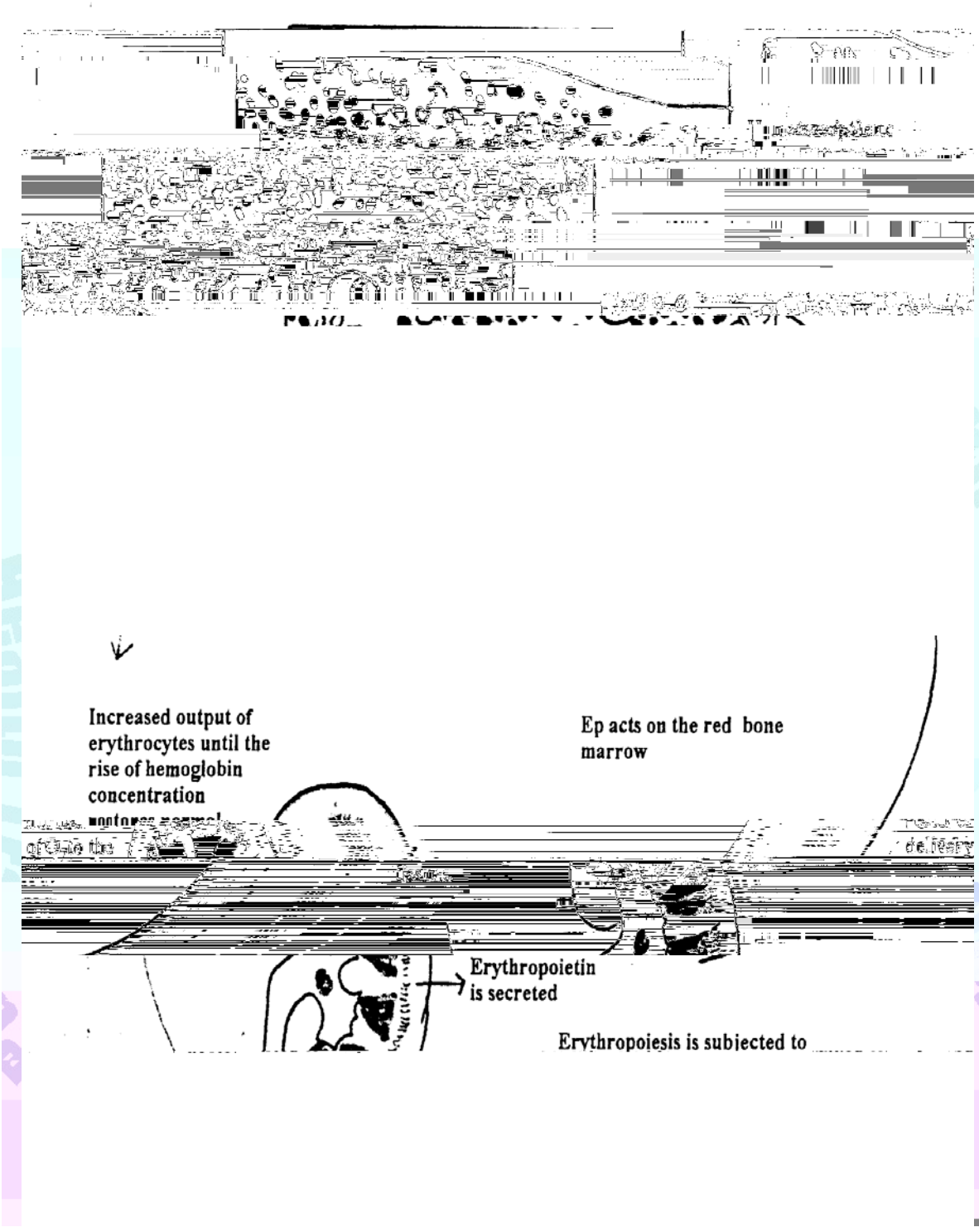

Figure 16. Shows negative feedback control of Red blood cell production.


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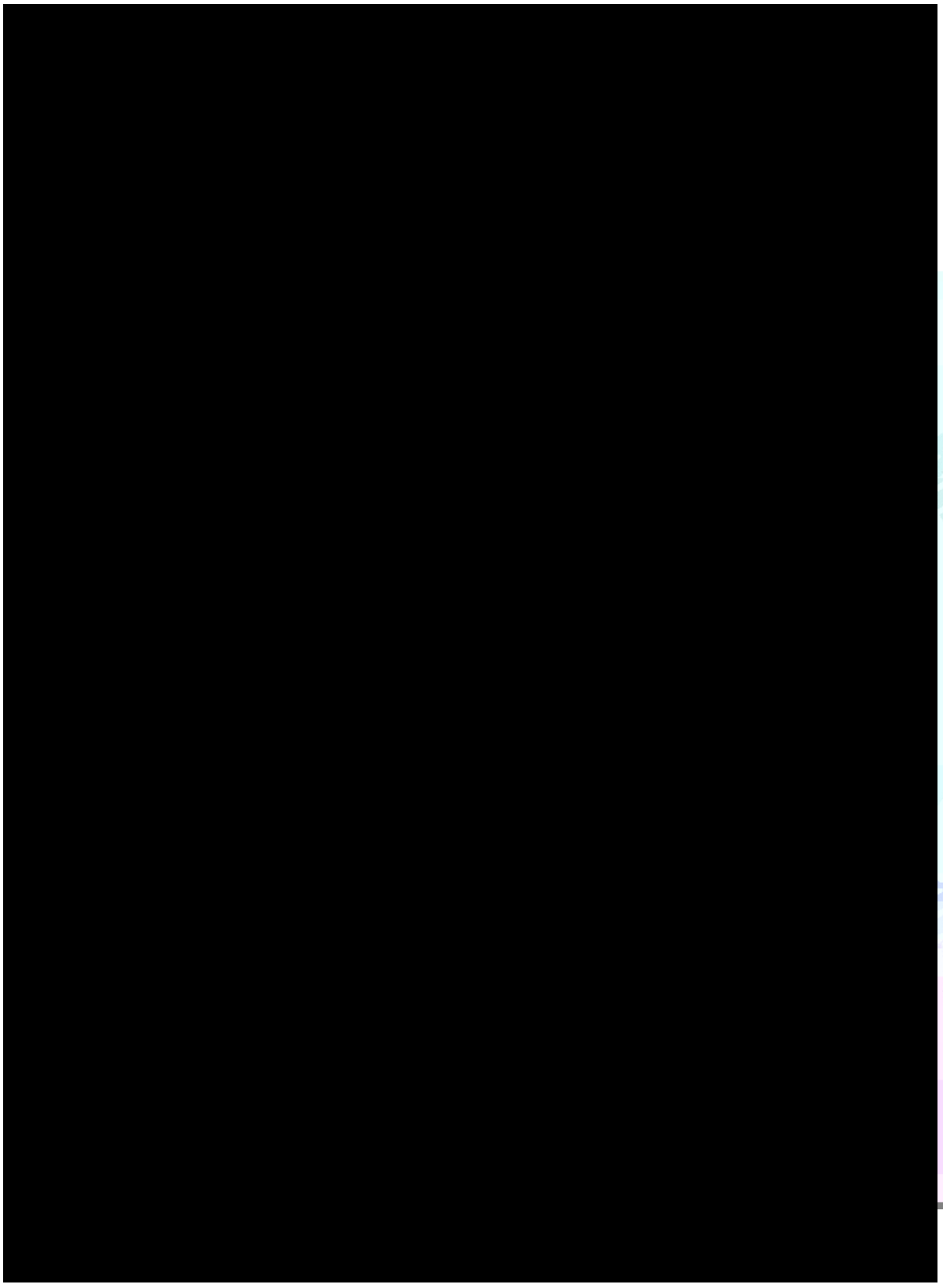

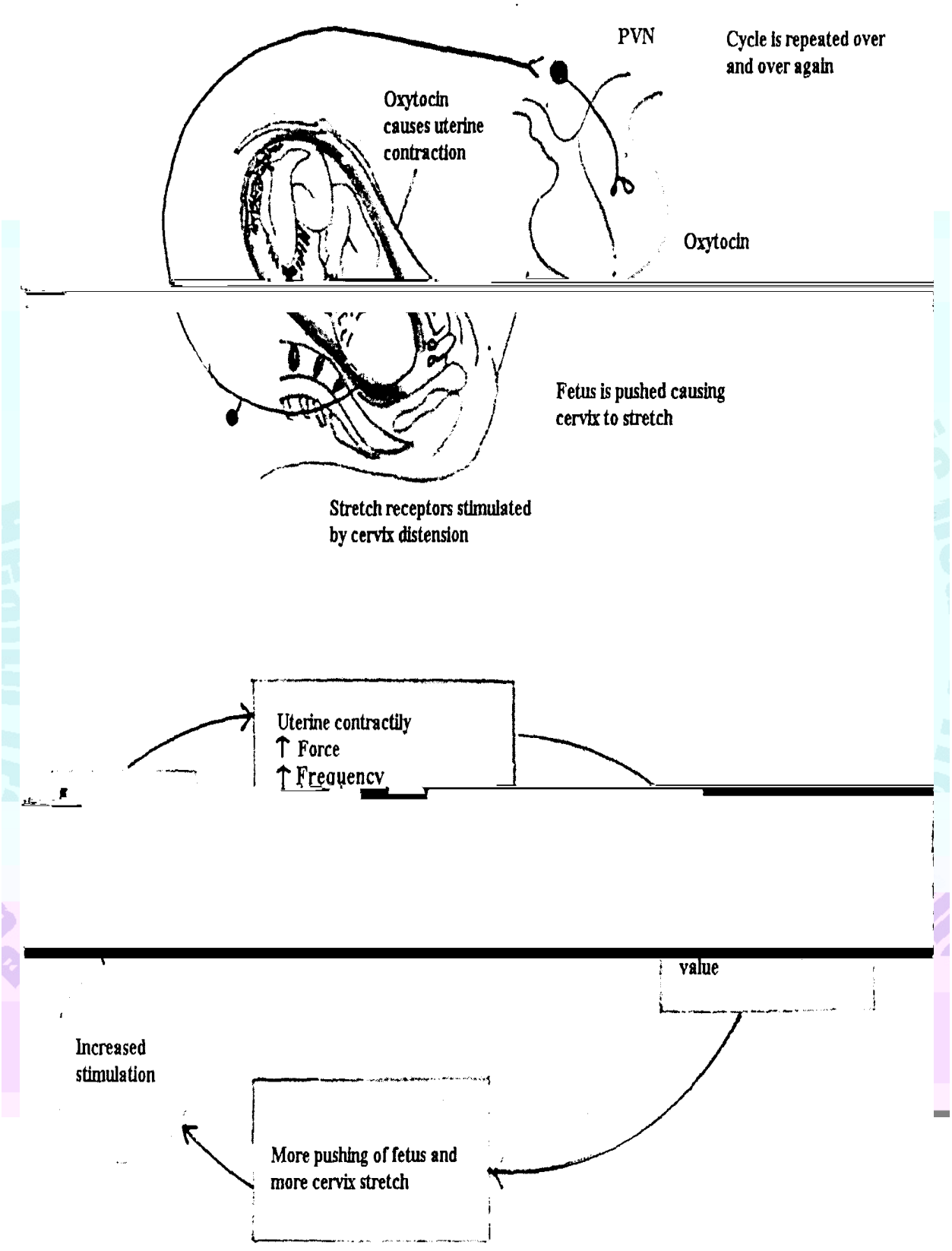

Figure 18. shows positive feedback control of the process of parturition.


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1 Somatic motor reflex, that control skeletal muscle, e.g. withdrawal reflex


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skeletal muscle as in athletes and laborers in which individual muscle fibers increase in thickness and not in number.

Effects of Endurance Training: Aerobic Training

- Increase in the size and number of mitochondria
- Increase in capillary / muscle ratio
- Increase in capacity to oxidize fat
- Increase in level of myoglobin
- The cardiovascular effects are:- increase in cardiac muscle mass and contractility; increased cardiac output at a lower heart rate; increased capillary in the myocardium; decreased peripheral resistance at rest
- In skeletal muscle, hypertrophy by increase in microfilaments, increase in cell enzymes and ATP synthesis; hypertrophy is influenced by blood flow
- There is increase in oxygen delivery and increase in oxidative capacity of skeletal muscle

- Oxygen transporting system: improves endurance for work; large heart volume, increased weight, enhanced vascularization of the heart muscle, increased capillary density, slow resting heart rate, increased centrogenic vagal cholinergic discharge/ drive, stroke volume increase, increased cardiac out put, increased arterio-venous oxygen difference increased at maximal work, increased maximal oxygen uptake
- Locomotion organs: increase in strength of bones and ligaments, thickness of articular cartilage and muscle mass; increased muscle strength, myoglobin, increased capillary density in muscle, and arterial collaterals
- Body density increases, serum cholesterol can decrease

- All adaptive changes are reversible
- As the oxygen content of blood increase, the maximal cardiac output apparently reduces

- Increase in ventilation is by hypoxic drive via peripheral chemoreceptors; greater diffusing capacity; a greater alveolar area and an increased capillary volume would facilitate gas diffusion in the lungs; increase in pulmonary ventilation followed by significant reduction in ventilation; gradual adaptation to chemoreceptor.
- Morphological and functional changes in the tissue: increased capillarization, increased myoglobin content, modifiers enzyme activity, increase in mitochondria, increase in tissue content of cytochrome oxidase,
- Alkalosis is gradually compensated in an acclimatized person
- Other changes include: increased erythropoietin production; increased hemoglobin concentration; increase in the 2,3 - DPG levels enhancing the unloading of oxygen to the tissues; increased hematocrit (in 7 days); increased viscosity 2-7 days; hemoglobin above 19 g/dl

The net effect of acclimatization to high altitude: gradual improvement in the physical performance in endurance events or prolonged work. An increased oxygen availability to the working muscles

Physiologic atrophy is a normal phenomenon of aging in many tissues such as involution of thymus gland after adolescence,0 -1.thymus J-22T6 1 TfMerking mus31.220 Tw( )Tj

- hepatic gluconeogenesis takes place using amino acids (especially muscle protein, there is increased urea excretion)
- as brain and other tissues use ketone bodies, glucose need is reduced. Ketone bodies also reduce glucose use by muscles, gluconeogenesis, protein catabolism and urine concentration decreases
- glutamine is used by the kidney for gluconeogenesis
- Proteins are spared to permit maximal starvation; survival requires of at least ½ of muscle proteins. Total body proteins is 9 -11 Kg; muscle protein is reduced - 20 g/day.

Increased catabolism in prolonged fever or as result of severe trauma may cause skeletal muscle atrophy. Tumors and cysts of an organ may cause pressure atrophy due to interference with blood flow or function of the tissue, e.g., damage to the nasal fibers by pituitary adenoma resulting in bitemporal hemianopia. Irradiation atrophy is due to chromosomal damage, which interferes with mitosis.

Hypoplasia is a state of failure of the tissue to reach normal size during development. It can have various causes: achondroplasia, an i

Hyperplasia without hypertrophy is unusual and one of the few example affects the red blood cells. In hypoxic environment with low oxygen tension, there is compensatory

- open loop and closed loop system
- negative and positive feed back controls

10. Elaborate reflex mechanism
    - autonomic reflex
    - somatic reflex
    - endocrine reflex
11. Discuss adaptation to: Exercise; Hypoxia

1. Adolph EF. Origin of physiologic regulation
2. Jones RW. Principles of biological regulation: An introduction to feedback systems. New ` York: Academic Press, 1973.
3. Yamamoto WS and JB Brobeck. Eds. Physiological controls and regulations.

After completeing this chapter, the student is expected to know the following:

- Understand the mechanisms nerve and muscle excitation
- Know how graded potentials and action potentials are induced
- Define action potentials
- Understand how neurotransmitter carry the signal across a synapse
- Know the composition of striated muscle, smooth and cardiac muscles
- Know the actions of Calcium in excitation contraction of muscle.
- Define the 2 types of muscle contractions: isotonic and isometric.

All cells of the body possess a membrane potential related to the nonuniform distribution and varying permeability to Na^+ and K^+ and large intracellular anions. Nerve


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most of the potential (80%) is caused by passive diffusion of potassium and sodium ions down their gradients.

Concurrent potassium and sodium effects on membrane potential

As potassium is more permeable at rest, it influences the resting membrane potential to a greater extent than does sodium. The resting membrane potential (RMP) of a typical nerve is -70 mV. It is slightly less than potassium equilibrium potential because of the weak influx of sodium. (See Figure 19). Nerve and muscle use the membrane potential for their specialized advantages. They are capable of rapidly and transiently alter the permeability of these ions in response to appropriate stimulation, thereby bringing about fluctuations in membrane potential.

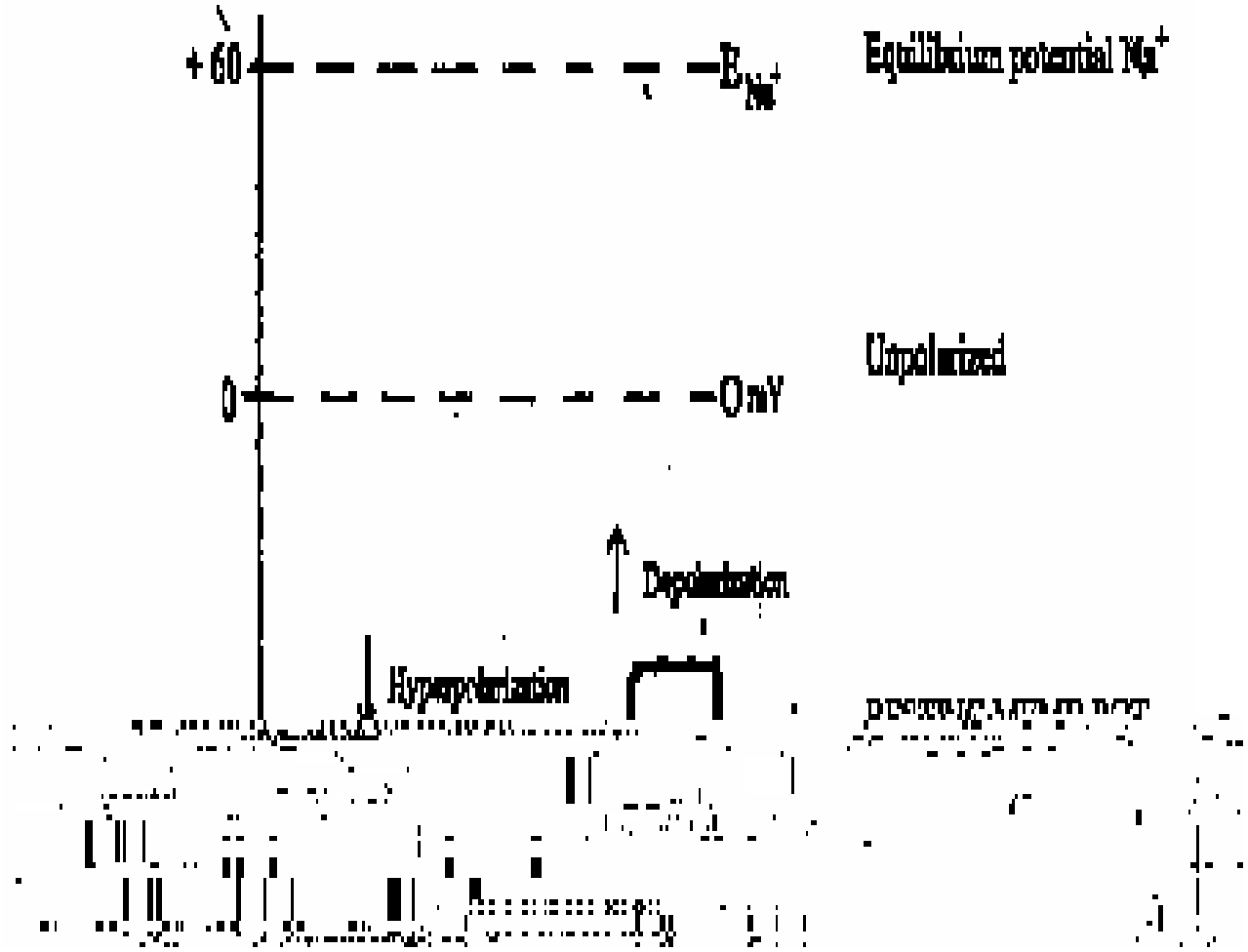

Figure 19. Shows resting membrane potential.

Figure 20. Shows ionic bases of resting membrane potential.

The nervous system consists of cells that are called neurons varying enormously in size, and shape than any other cell. The n

The cells typical of the nervous tissue are the neurons and glial cells.

Neurons: The original neuron is "nerve cell"- cells best equipped to sense and react to the chemical and physical change occurring in their surrounding environment. They are present in the entire human body and communicate with each other regarding their conditions and reactions. Primary neural functions include reception, conduction and transmission. To detect, conduct and transmit stimuli to another cell or cells. Nerve cells grow 2 types of processes from their cell bodies - axons and dendrites.

: are those processes that are concerned with reception of stimuli from environment.

are those processes that are concerned with conduction and transmission of the stimuli-signal to another cell or cells. The axon give


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nonmyelinated. The unnmyelinated fibers in the CNS are covered by astrocytes. A certain relation exists between speed of the impulse and fiber caliber.

Table 5: Fiber diameter and speed of signal conduction.

Fiber type	Diameter (εm)	Cond. velocity (m/s)	Blocking agent	Functions
AŬ (I)	12-20	70-120	Pressure	Proprioception
Aɓ II)	5-12	30-70	Pressure	Touch, pressure
Aɔ	3-6	15-30	Pressure	Motor supply to muscle spindle
Aŭ (III)	2-5	12-30	Pressure	Pain, cold, touch
B	1-3	3-15	Hypoxia	Preganglionic autonomic
C (IV)	0.3-1.3	0.5-2.3	Local anesthetics	Pain, touch, pressure

: A bundle of fibers wrapped in a connective tissue sheath is a peripheral nerve. Within each bundle, between the fibers, collagen fibers and a few fibroblasts are situated. This is called endoneurium.

: nerve cells or neurons make up the nervous system (NS), one of the control systems of the body. The nervous system controls body's muscular and

impulse in 2 forms. 1. Graded potentials- serving as short distance signals, and 2. Action potentials- which serve as a long distance signals without any change.

Graded potentials die out over short distances. These are local membrane potentials. Changes occur in varying grades of magnitude or strength. For example, RMP of -70 mV may become -60 mV or -50 mV. This magnitude is related to the magnitude of the triggering event, i.e. the stronger the triggering event, the larger the graded potential.

The triggering event may be one of the following.

- Stimulus - such as light stimulating photoreceptors on the retina
- Interaction of chemical with a receptor on a nerve or muscle cell membrane (neurotransmitter).
- Spontaneous change of potential caused by imbalance in the leak-pump cycle.

- Graded potential change: magnitude varies with the magnitude of triggering event
- Decremental conduction: magnitude diminishes with distance from initial site
- Passive spread to nearby inactive areas of membrane
- No refractory period
- Can be summed (temporal and spatial)
- Can be depolarized or hyperpolarized
- Triggered by stimulus, by combination of neurotransmitter with receptor or by spontaneous shift in leak-pump cycle.
- Occurs in specialized regions of membrane designed to respond to triggering event: egs: end plate potential, receptor/ generator potential, excitatory postsynaptic potentials, inhibitory postsynaptic potentials

:

- All or none membrane response, magnitude of the triggering event coded in frequency rather than amplitude of action potential
- Propagated through out membrane in undiminished fashion
- Self-generation in nearby inactive areas of membrane
- Refractory period present
- Summation impossible
- Always depolaraization to threshold through spread of graded potential
- Occurs in regions of membrane with abundance of voltage-gated sodium channels

Action potential is generated when an axon is stimulated by sufficient strength electric current so that the membrane is suddenly depolarized from -80 to -60 mV, the critical drop initiating further change in potential. As soon as the critical level of depolarized, the threshold is reached, any further increase in the strength of the applied current do not affect size of the potential. It is all- or- none response. The action potential crosses the zero line it is moving from -80 to +30 mV inside the membrane. The action potential is propagated along the whole length of the fiber membrane with a constant speed and amplitude.

When one electrode is kept inside and the other is outside, potential changes across the membrane can be measured and if properly amplified and electrodes connected to a cathode ray oscilloscope, they can be recorded as the monophasic action potentials. Using 2 surface electrodes on the nerve or muscle, a diphasic action potential can be seen on the screen and recorded (see figure 21)

- Resting membrane potential (RMP): Voltage difference between inside and outside of cell in absence of excitatory or inhibitory stimulation.
- Threshold potential: Membrane potential to which excitable membrane must be depolarized to incite an action potential
- Upstroke or rising phase: This is a very rapid period of change, when the cell is losing its negative resting potential, and becomes depolarized (zero potential) and shows reversal of the membrane potential so that the inside of the membrane is transiently positive.
- Overshoot: The short positive phase is known as overshoot and is usually of about +30 mV- +40 mV in amplitude.
- Repolarization phase: The down stroke of the potential change is the repolarization, a slower process than the initial phase of depolarization.

- Depolarization after potentials: The membrane potential for a brief period becomes more positive than the resting membrane potential and the cell, therefore, is slightly more excitable than normal.
- Hyperpolarization after potentials: some cells reflect a fall in the membrane potential below the RMP for a brief period following the action potential. During this time, the cell is less excitable than normal.

during which time the threshold of the nerve is higher than normal, and so only stimuli of very great strength can evoke a propagated impulse, which is it self smaller and slower. This recovery phase is called relative refractory period. It lasts another 2 milliseconds after the end of the absolute refractory period.

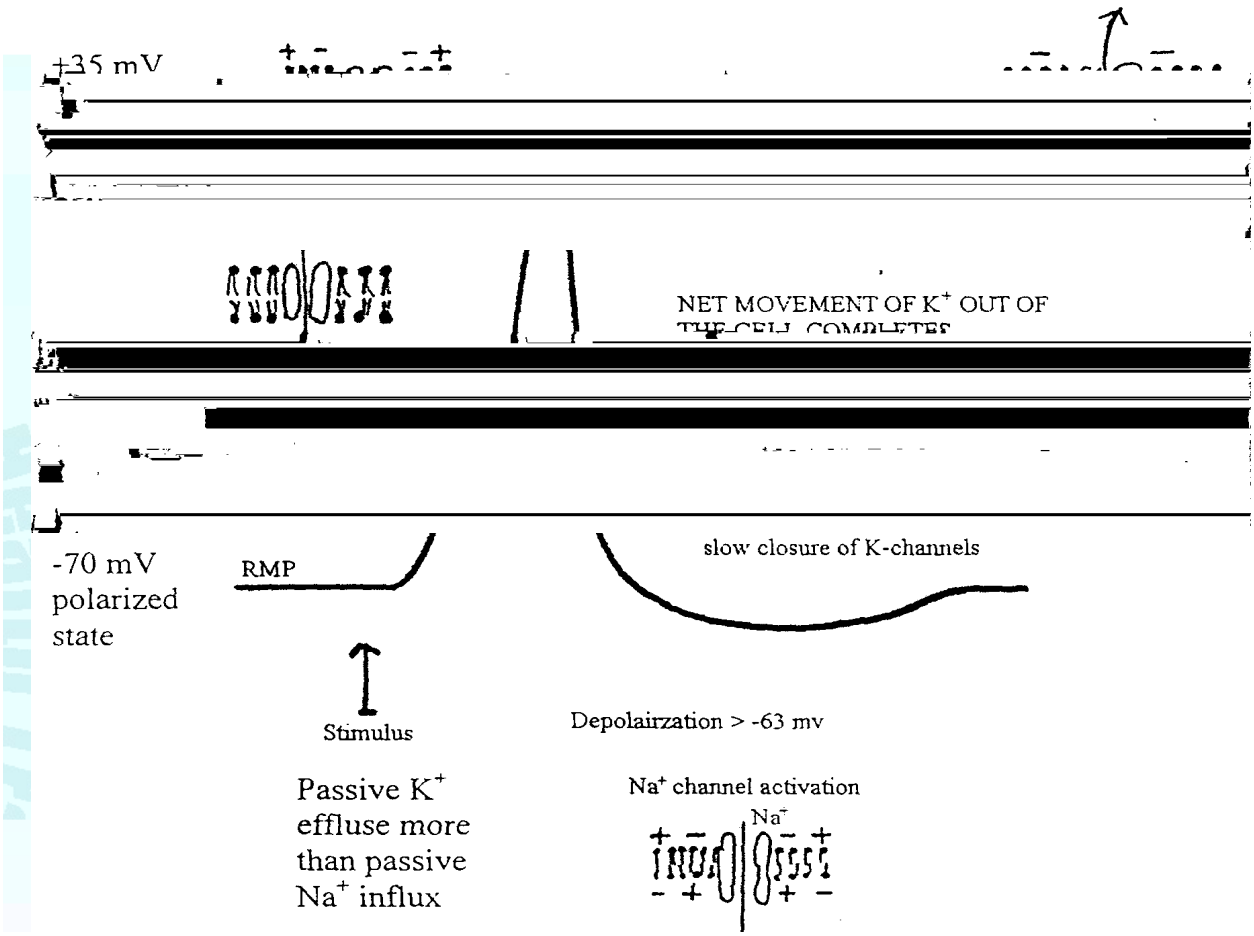

Figure 22. Ionic basis of action potential

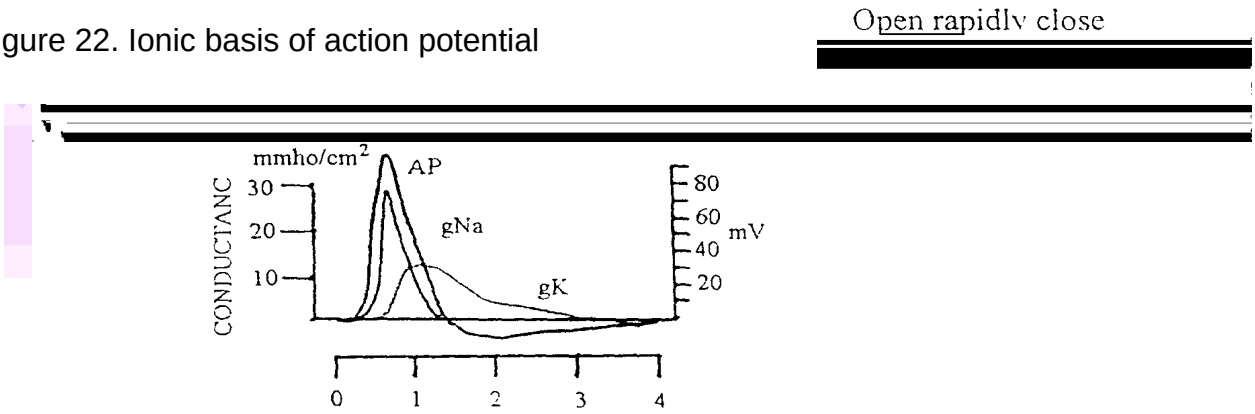

Figure 23. Changes in Na^t and K^+ during action potential.

The action potential is conducted along the nerve fibers by the ionic mechanism of the plasma membrane and also as though the fibers were conducting cables. There exists self regenerative sodium conductance of the stimulated membrane, which changes the initial depolarization to the all or none full-sized action potential that is propagated without loss of amplitude along the entire length of the fiber. Cable conductance is very slow in nerves that lack myelin sheath. Unmyelinated fibers are thin, slow conducting nerves often called "C" fibers on the basis of their diameter of less than 1 micron. Myelinated fibers have the nodes of Ranvier at regular intervals of 1-2 mm. Myelinated fibers are often classified as "A" fibers with diameters of 3-13 μm. The addition of myelin sheath allows an enormous increase in conduction velocity with a relatively small increase in fiber diameter.

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Conduction depends on circular current flow

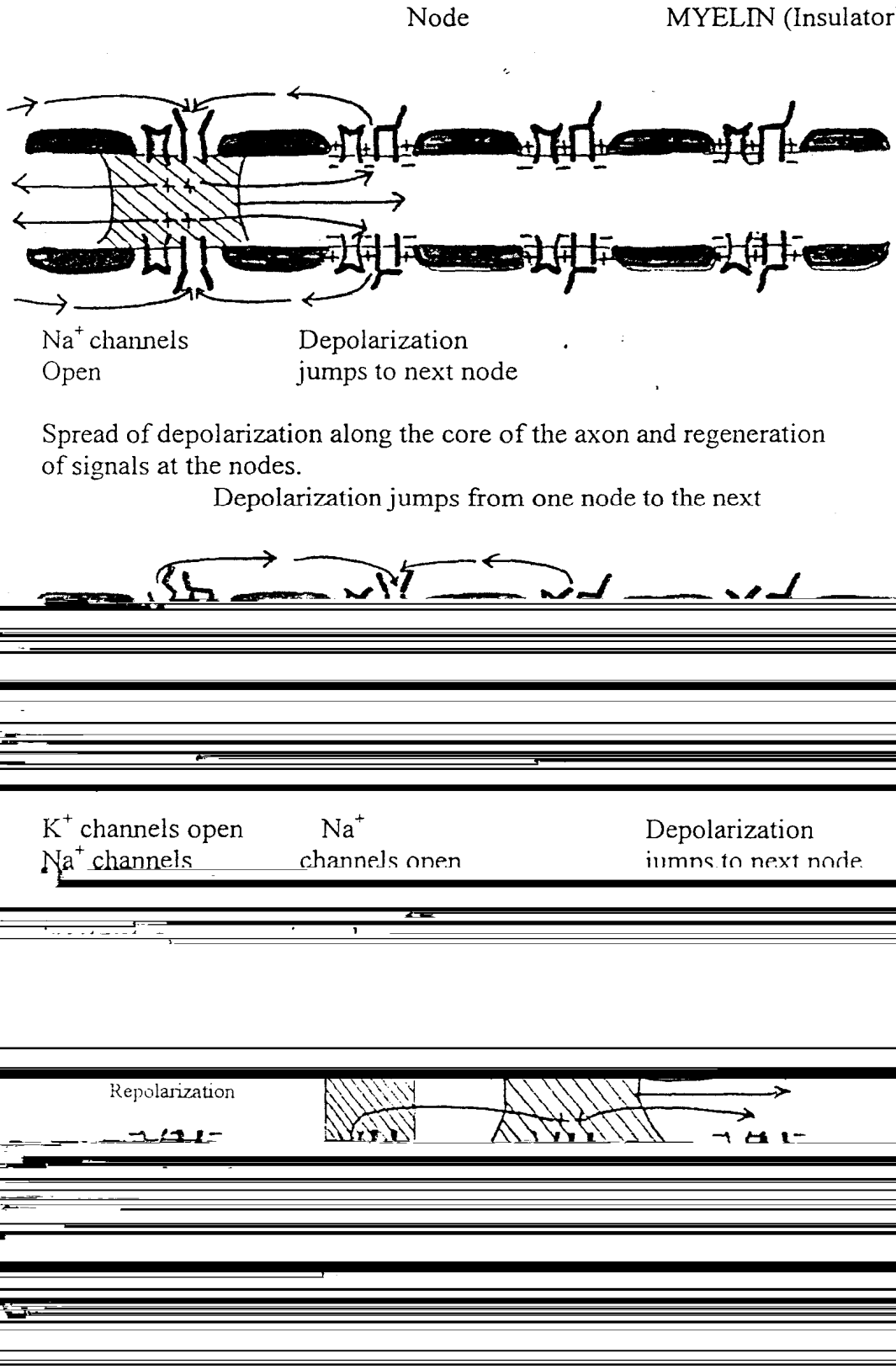

Figure 24. Shows propagation of Nerve impulse in myelinated nerve fibers

A stimulus is any change that can alter the energy state of a tissue sufficiently to depolarize the membrane. A nerve can be stimulated by mechanical, thermal, chemical, osmotic or electrical stimulation. These various stimuli are converted or transduced by the nerve to an electrical response, i.e. an action potential.

Excitability may be defined as the ability of a cell to respond to a stimulus with an action potential.

A stimulus must fulfill to evoke response. It involves the following parameters.

- Strength of the stimulus
- Duration of the stimulus
- Rate of rise of the stimulus intensity.

The neuromuscular junction is the specialized region of contact between nerve and muscle. Each skeletal muscle fiber receives only one of the many terminal branches of the nerve fiber. All movements are composites of contraction of muscle unit, the motor oinervete s Thesrespultng pntraction of m]TJ-20.965 -1.725 TD-.0002 Tc.0182 Tw[(Aech suscle fiber

release occurs. The presynaptic membranes have selective ionic gates, voltage gated Ca^{++} channels

: The cleft is a gap of about 40 mm separating the axon terminal and the muscle membrane.

At the junction area, there is an enlargement of the sarcoplasm of the muscle fiber, known as the end plate. This is the postsynaptic region where depolarization occurs to give rise to the end-plate potential (EPP). The postsynaptic surface area is markedly increased by deep junctional folds.

The postsynaptic membrane is both structurally and physiologically different from the rest of the muscle membrane. The postsynaptic region responds only to chemical stimulation or inhibition. The region of the muscle surface membrane under the nerve terminal is sensitive to acetylcholine.

The EPP is graded in size and at a critical level of depolarization- about 50 mV-it triggers an impulse that travels along the muscle membrane. (See figure 24 & 25).

: The action potential reaching the nerve terminal depolarizes the membrane to about 30 mV to open the calcium channels permitting the influx of ionic calcium down

At the motor end plate, Ach combines with a muscle receptor that results in opening of the ionic gates to cause depolarization, and also it combines with a hydrolytic enzyme - Ach estrase (AchE) which rapidly inactivates it, after its role is over. The Ach receptor is a protein; its conformation changes when Ach binds to it, resulting in the opening of the ionic gates and a change in permeability. Curare also binds to receptor protein but alters it to an inactive form, which does not result in depolarization. Snake venom containing bungarotoxin binds very tightly and specifically to Ach receptor. The receptor density is very high ($3x\ 10^7$) per end plate, which is enough for the 10^4 quanta of Ach released. There are 12,000 -21,000 molecules of Ach per quanta packed in to one vesicle.

The concentration of Ach at the end plate remains high briefly for it is hydrolyzed rapidly by the enzyme AchE into choline and acetate.

A neurotransmitter transmits the signal across a synapse. A neuron terminal ends at a muscle, gland or another neuron. The junction between the 2 neurons is a synapse. Classically, a neuron to neuron synapse is a junction between an axon terminal of one neuron and the dendrites or cell body of a second neuron. Some neurons within the CNS receive as many as 100,000 synaptic inputs.

Some synapses excite the post synaptic neuron whereas others inhibit it, so there are 2 types of synapses depending on the permeability changes in the post synaptic neuron by the binding of neurotransmitter with receptor site. At an excitatory synapse, the neurotransmitter receptor combination opens
subsynaptic membrane, increasing permeability to both ions. Both ions move simultaneously in opposite directions as per their gradients.

A nerve impulse stimulates a muscle cell…all within a few milliseconds

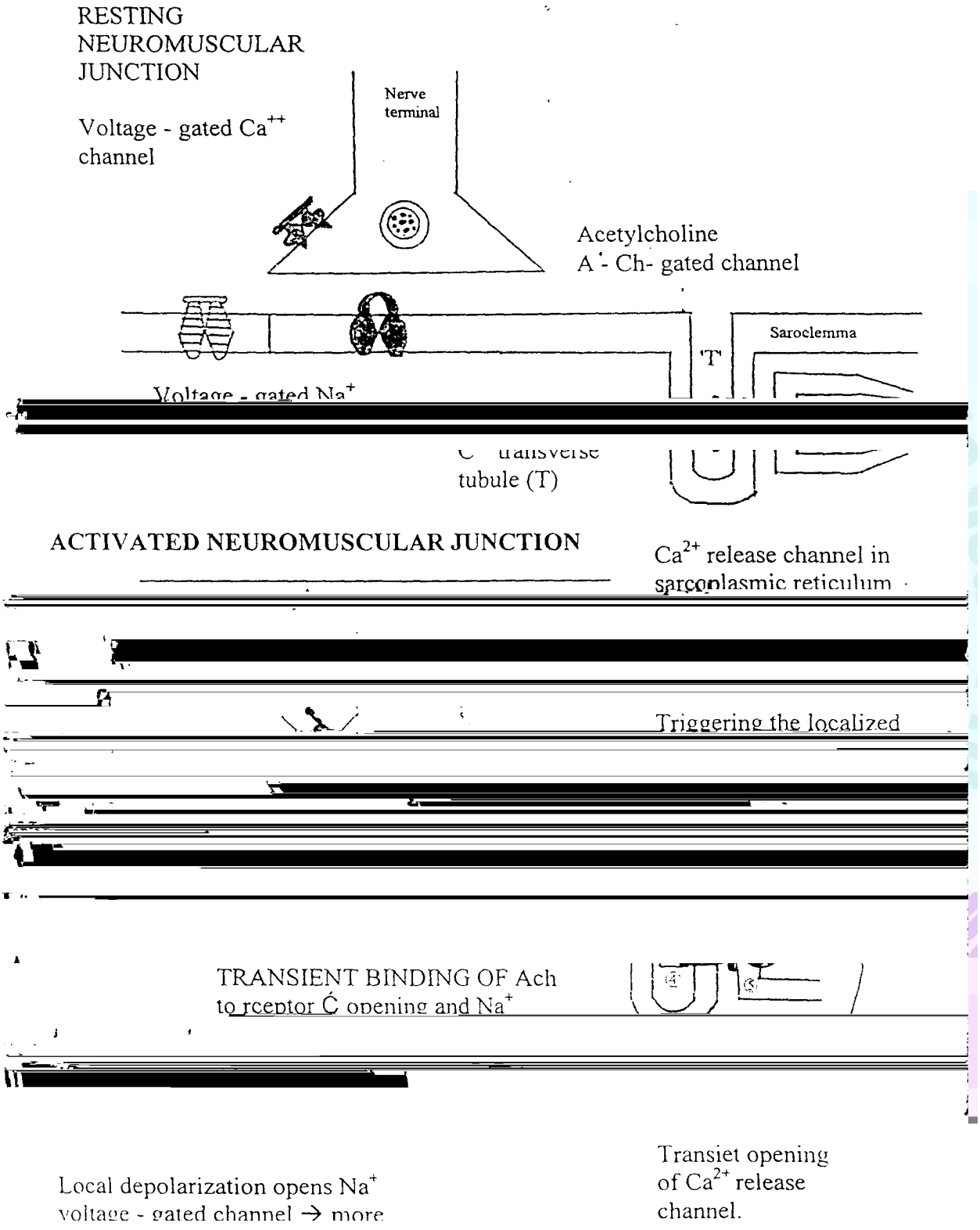

Figure 25.Shows neurotransmission at neuromuscular junction.

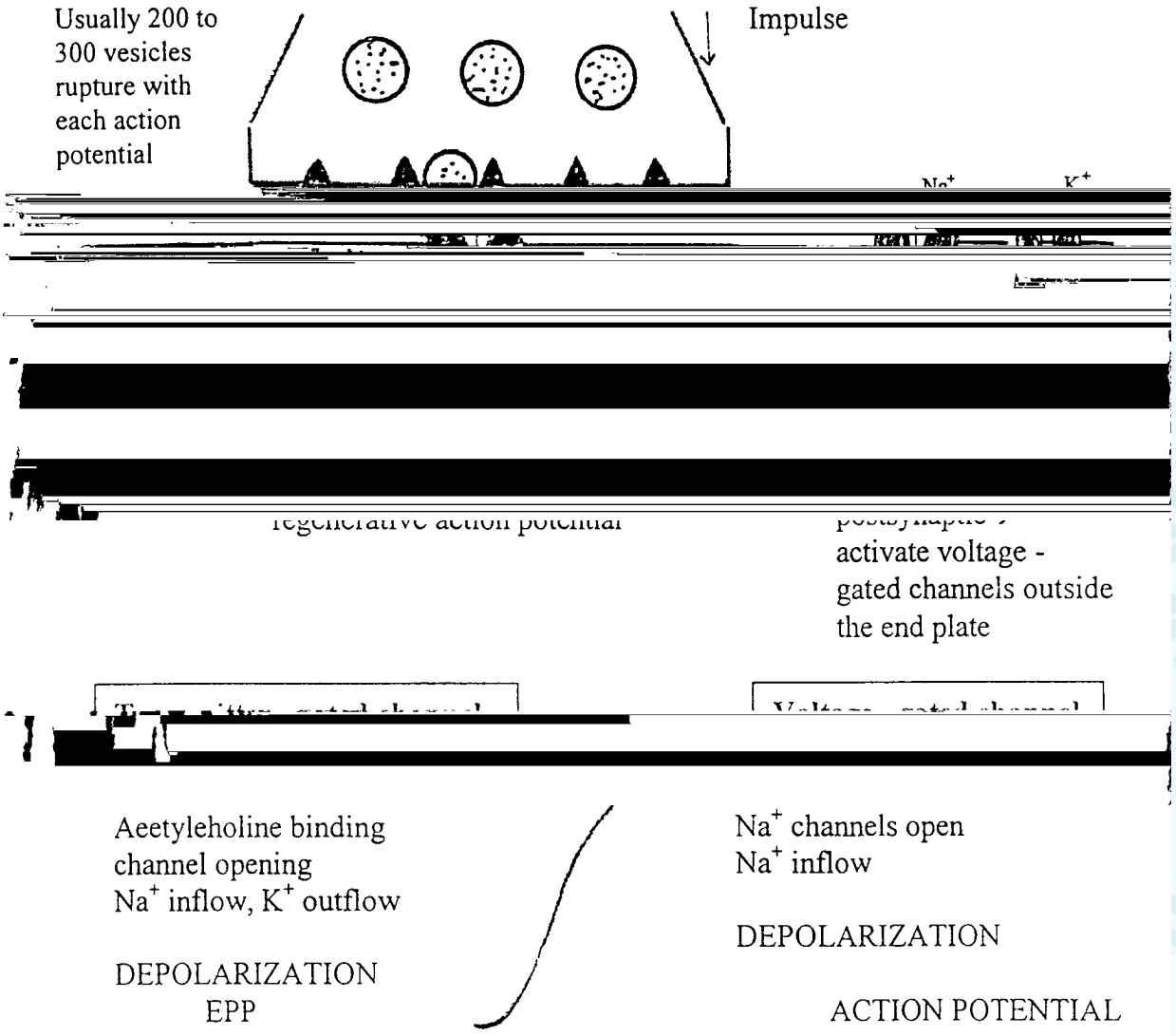

Figure 26. Shows generation of endplate potential

Acetylcholine (Ach), dopamine, epinephrine, norepinephrine, serotonin, histamine, glycine, glutamate, aspartate, gamma-aminobutyric acid:

Beta-endorphin, ACTH, MSH, TRH, GnRH, somatostatin, VIP, CCK, gastrin, substance P, neurotensin, leucine, enkephalin, methionine enkephalin, motilin, insulin, glucagons, angiotensin-II, bradykinin, vasopressin, oxytocin, carnosine, bombesin.

It is important that neurotransmitter be inactivated or removed after it has produced desired response in the postsynaptic neuron, leaving it ready to receive additional message from the same or other neuron inputs. The neurotransmitter may diffuse away from the cleft, be inactivated by specific enzyme within the subsynaptic membrane, or be actively taken back up in to the axon terminal by transport mechanism in the presynaptic neuron for storage and release at another time.

- Chemical transmission is unidirectional
- Chemical transmission is graded, with the amount of transmission chemical released dependent on the frequency of stimulation of the presynaptic neuron.
- The effect of chemical transmitter can be summed so that the final state of the postsynaptic potential will depend on the amount of excitatory transmitter reaching the postsynaptic membrane.(temporal and spatial summation)
- There is delay

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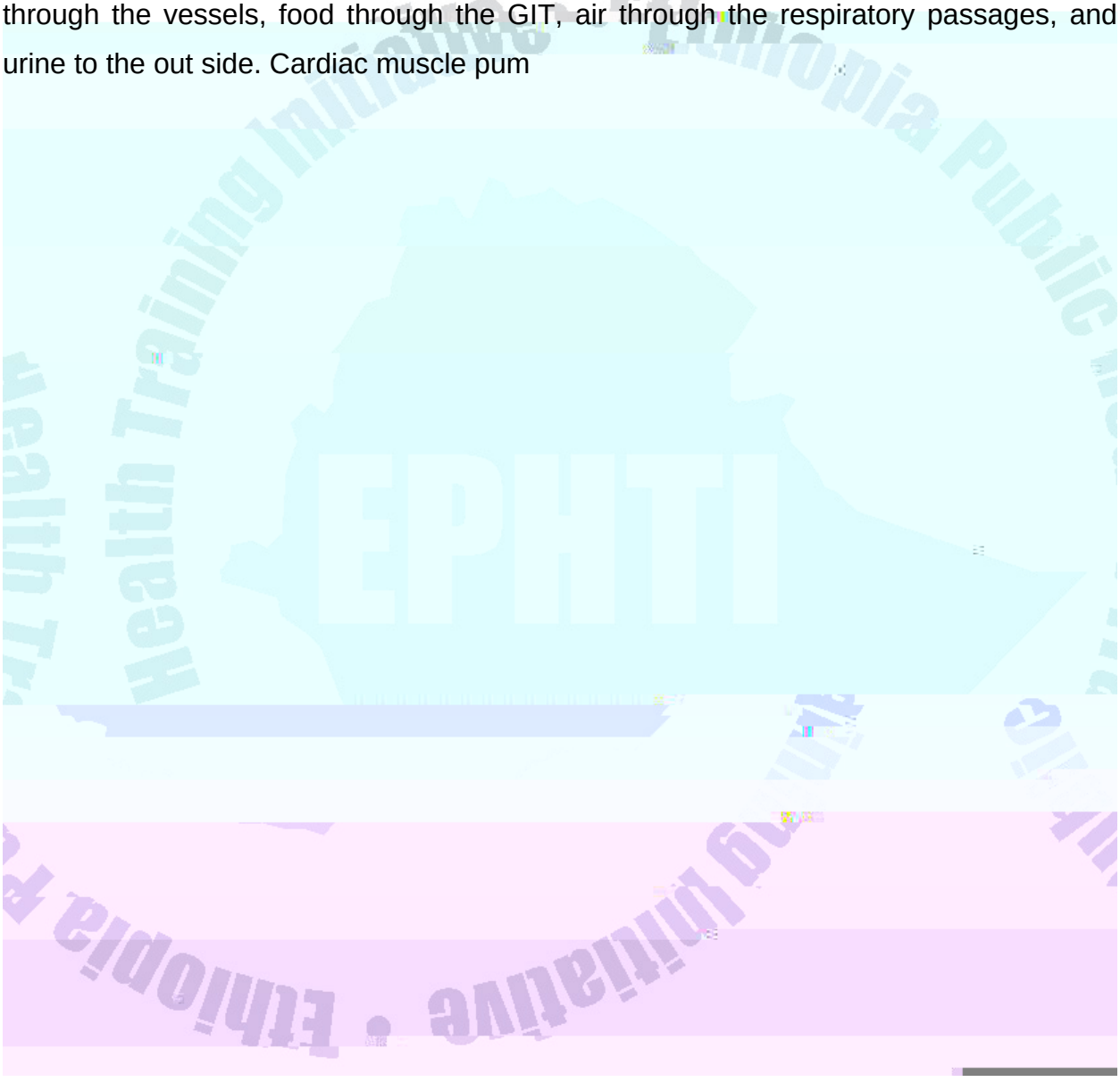
Skeletal muscles attached to the bones contract allowing the body to perform a variety of motor activities; these activities are needed for acquisition, chewing and swallowing of food, and that move the chest for breathing. They also contract in defending the body by protective movements. Smooth muscles are present in all hollow organs and the vascular conduits. Regulated contractions of smooth muscles make the blood flow through the vessels, food through the GIT, air through the respiratory passages, and urine to the out side. Cardiac muscle pum



thick myosin filaments (12-18 nm diameter) and thin actin filaments (1.6 nm in diameter).

A relaxed muscle shows alternating dark bands (A band) and light bands (I band) due to slight overlapping of thick and thin filaments under the microscope. H zone does not have the thin filaments. The "I" band contains only thin actin filaments. In the middle of each I band is a dense vertical Z line, actually a flattened disc like cytoskeletal protein that connects the thin actin filaments of 2 adjoining sarcomers. Relaxed sarcomer is about 2.5 µm in width. (See figure 27).

Figure 27. Structure of myofibrils

Calcium is the link between muscle excitation and contraction. Excitation - Contraction Coupling refers to the sequence of events linking muscle excitation to mechanical contraction. At neuro-muscular junction of skeletal muscle neurotransmitter Ach released from innervating motor neuron results in muscle contraction. The surface membrane dips in to the muscle fiber to form a 'transverse tubule' which runs from the cell membrane surface in to the central portion of the muscle fiber. The T- tubule also has receptors where it contracts the ryanodine receptors. These T- tubule receptors are known as dihydropyridine receptors. When an action potential travels down the T-tubules, the local depolarization activates the voltage-gated dihydropyridine receptors. Activated T- tubules receptors in turn trigger the opening of the Ca^{++} channels (ryanodine receptors) in the adjacent lateral sacs of the sarcoplasmic reticulum. Calcium is released from lateral sacs. Tropomyosin-troponin complex is repositioned; the released Ca^{++} binds with troponin C exposing the binding sites on the actin molecule so that they can attach with the myosin cross bridges at their specific sites. (See figure 28). A myosin cross bridge has an actin binding site and an ATPase site. In skeletal muscle, Mg^{++} must be attached to ATP before myosin ATPase can split the ATP yielding energy in the process. It is to be noted that fresh ATP must attach to myosin to permit the cross bridges link between myosin and actin to be broken down at the end of the cycle. The necessity for ATP for separation of myosin and actin is well evidenced by rigor mortis. This stiffness of death is a generalized locking in place of skeletal muscle beginning 3-4 hours after death and completed in about 12 hours.

A single action potential in skeletal muscle fi

Myasthenia gravis is an autoimmune disease. It occurs in about one of every 20,000 persons, causes the person to become paralyzed because of inability of the NMJ to transmit signals from the nerve fibers to the muscle fibers.

(a) Profound muscular weakness and rapid onset of fatigue.

(b) Weakness of levator palpebrae superioris muscle (muscle of the upper eyelid) leads to drooping eyelids, which is the early prominent sign.
(c) If the disease is intense enough, the patient dies of paralysis, in particular, of paralysis of the respiratory muscles.
(d) In many cases, the thymus is enlarged

It is due to the failure of NMJ transmission which results from binding of antibodies to the ACh receptor on the post-synaptic membrane. This binding stimulates integration and degradation of the receptors. Therefore, there are fewer receptors available for binding with ACh. When an action potential depolarizes the presynaptic membrane, the transmitter cannot activate enough receptors to evoke an action potential in the muscle fiber. The sarcolemal depolarization is insufficient.

Enlarged thymus may also be another cause of myasthenia gravis. Autoimmune thymitis associated with the release of a hormone called thymopoietin (or thymin). Thymopoietin is a polypeptide (MW=5562) which cause neuromuscular block in experimental animal.

As a result of cross bridge activity and the resultant sliding of filaments, a tension is developed internally within the sacromere. This tension generated by the contractile elements is transmitted to the bone via the connective tissue and tendon before the bone can be moved. Intracellular components of the muscle such as the elastic fiber proteins and connective tissue collagen fibers have a certain degree of passive elasticity. These non-contractile elements are the 'series-elastic-components' of the muscle, behaving like a spring placed between the tension generating contractile proteins and the bone that is to be moved against an external lead. Shortening of the sarcomere stretches the 'series- elastic-component' and the muscle tension is passed to the bone by their tightening. This tension application moves the bone against a load.

There are 2 primary types of movement depending on whether the muscle changes length during contraction.

Isotonic contraction: In this type, muscle tension remains constant as the muscle changes length.

tion: In this type, the muscle is prevented from shortening, so tension developed at constant muscle length. The same internal events occur in both types of contractions. Isotonic contractions are used for body movements and for moving external objects. The submaximal isometric contractions are important for maintaining posture and for supporting the object in a fixed position. (See figure 29). During a given movement, a muscle may shift between Isotonic and isometric contractions.

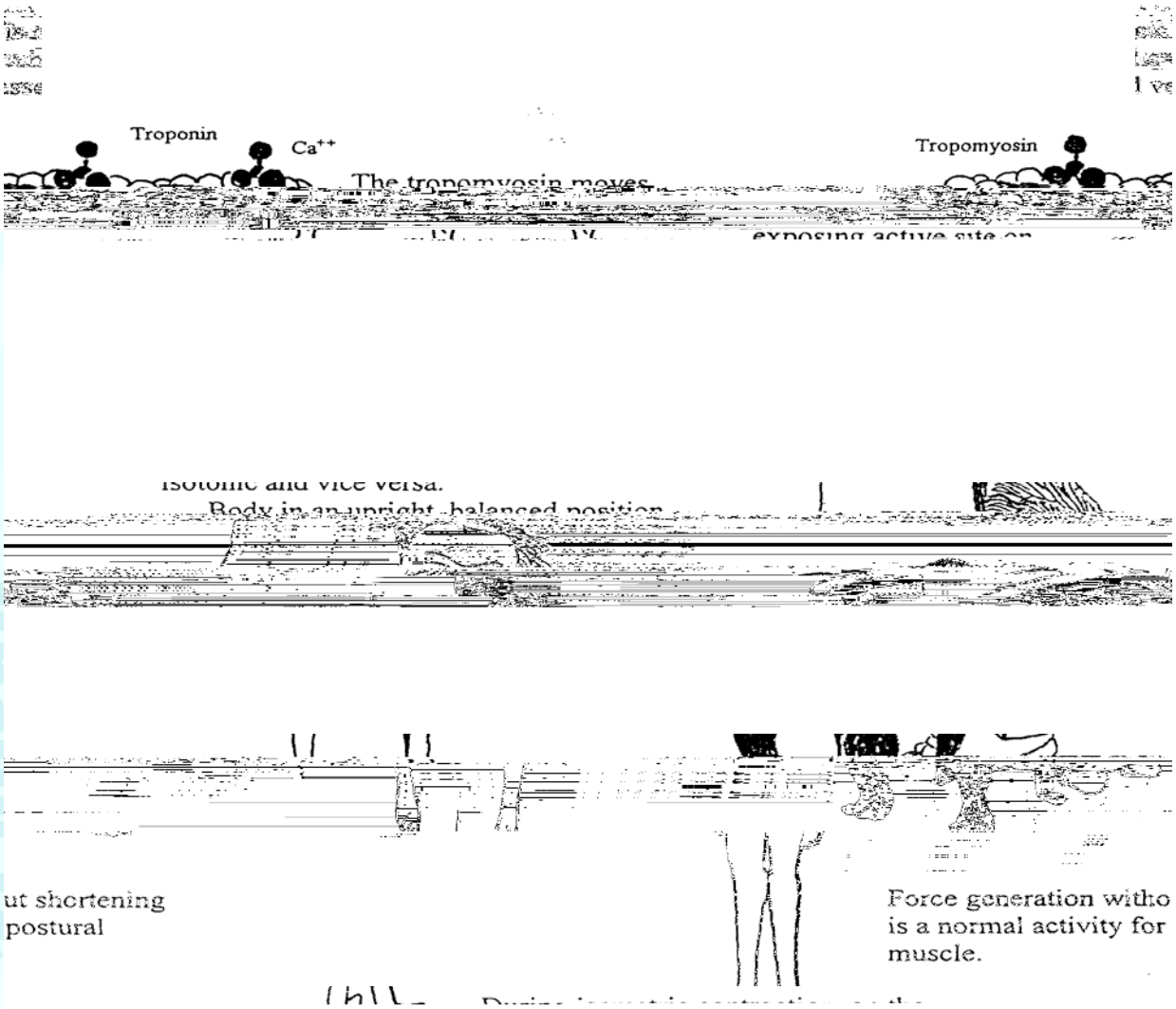
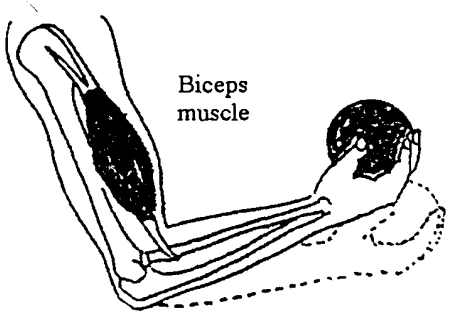


Figure 29. Isometric (constant length) contraction

An isotonic contraction occurs if the loaded muscle contracts and lifts the weight.



Contraction against a constant load, with approximation of the ends of the muscle.

Muscle varies in length when activated isotonic (dynamic) contraction.

It is more correct to use the term 'dynamic, exercise' than isotonic exercise

The length tension relationship is based on the sliding filament theory of muscle contraction.

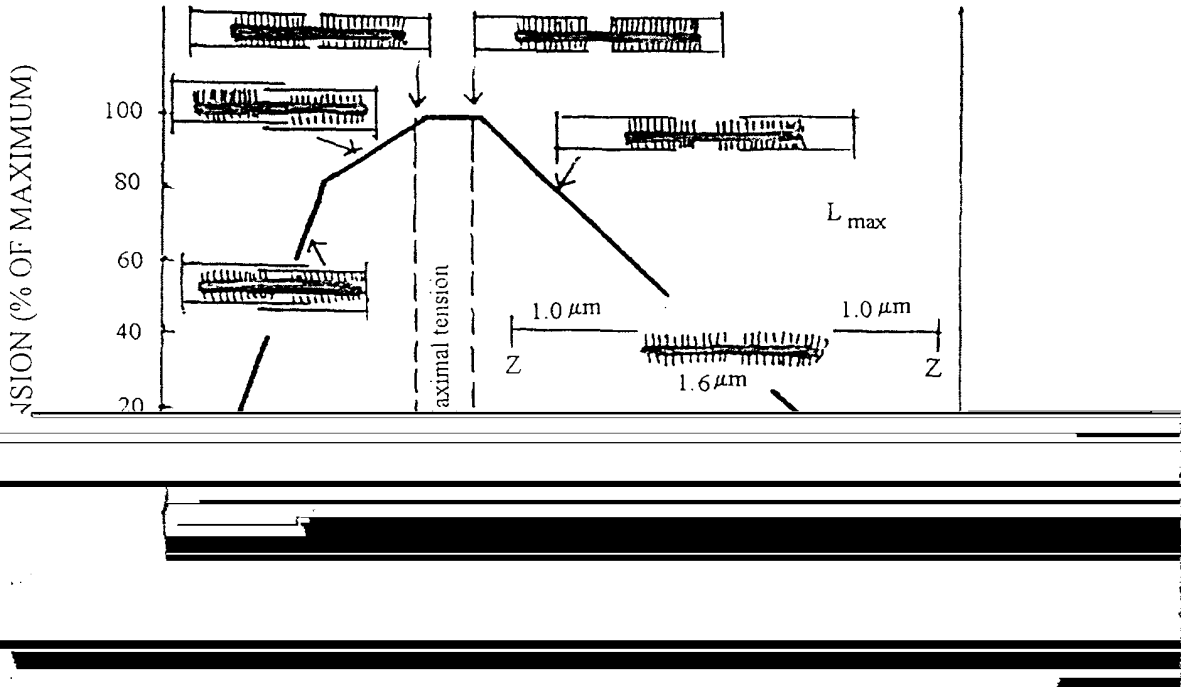


Figure 30. Isotonic contraction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2. Binding of a fresh molecule of ATP to myosin permitting detachment of the cross bridge from actin at the end of the power stroke so that the cycle could be repeated. This ATP provides energy for the next stroke of the cross bridge.
3. The active transport of Ca++ ions back in to the sarcoplasmic reticulum, is energy dependent.

Therefore, ATP must be continuously supplied for contraction activity to continue.

The muscle has small and limited source of ATP for its immediate needs. Three pathways provide additional ATP needed during muscle contraction.

1. Creatinine phosphate transfers high energy phosphate bonds to ADP
2. Oxidative phosphorylation - the citric acid cycle (Kreb's cycle) and electron transport system
3. Glycolysis - aerobic and anaerobic

Smooth muscle shares some basic properties with skeletal muscle and also have some distinctive properties. The same is true for cardiac muscle.

Common features of the 3 muscles:

- All have specialized contractile proteins and made up of actin and myosin that slide past in response to rise in cytosolic calcium to achieve contraction

and 50-100 μm in length). Groups of smooth muscles are typically arranged in sheets. Three types of filaments present in smooth muscles are

- Thin actin filaments, which have tropomyosin but lack troponin
- Thick myosin filaments, longer than those found in skeletal muscles.
- Filaments of intermediate size - serve as part of the cytoskeleton framework that supports the shape of the cell, but does not directly participate in contraction.

Smooth muscles do not form myofibril and are not arranged in sarcomere pattern of skeletal muscle. Smooth muscles don't display striation. (See figure 31).

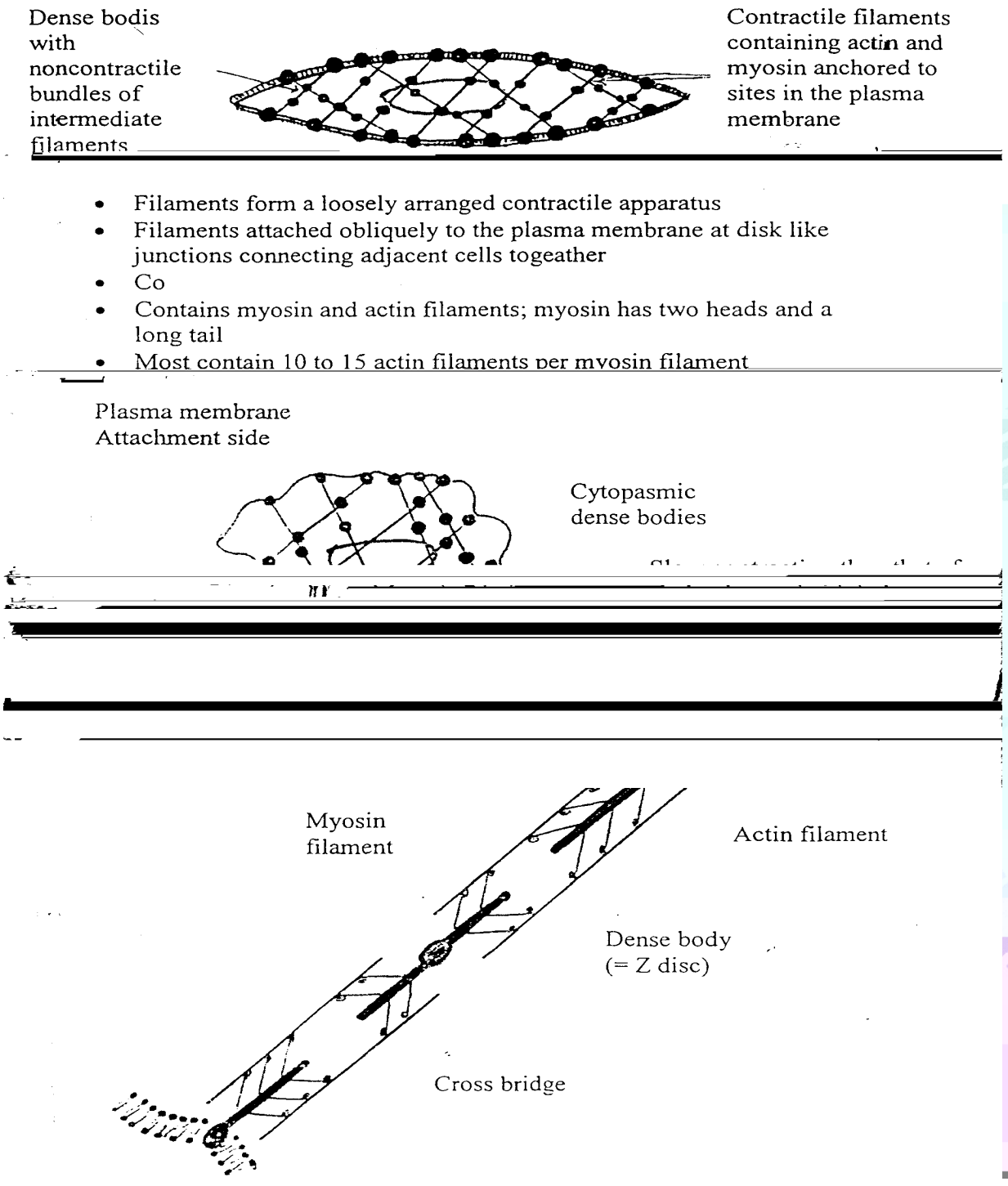

Figure 31. The contraction apparatous in a smooth muscle cell.


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erythrocytes, the hematocrit, or packed cell volume (Hct or PCV), actually represents the total cell volume occupied by red cells. The white cells and platelet after centrifugation are packed in a thin, cream colored layer because they are colorless, the “buffy coat”, on top of the packed red cell column. The hematocrit averages 42% for women, 45% for men, with average volume occupied by plasma being 58% for women and 55% for men.

- the colloidal osmotic pressure is the major force responsible for preventing excessive loss of plasma from the capillaries into the interstitial fluid and thus help maintain plasma volume
- Partially responsible to buffer pH changes
- Contribute to blood viscosity (RBC are more important)
- Plasma proteins are normally not used as metabolic fuels, but in a state of starvation they can be utilized to provide energy for cells

- Binding of substances for transport and contributes to the pressure
- Specific alpha & beta globulin transport thyroid hormone, cholesterol, iron
- Many clotting factors are gloublins
- Inactive factors (precursor protein molecules) such as angiotensinogen is activated to angiotensin.
- Gamma globulin as antibodies, have a crucial role in body defense
- Fibrinogen provides the meshwork in clotting cascade.

Table 6. Blood constituents and their functions.

(a) Water (91.5%) ---------- ĭActs as a solvent of different solutes

ĭCarries heat

(b) Plasma proteins (7%) ---------- ĭMaintain osmotic pressure of blood

Albumins (54%) ĭParticipate in blood clotting

Globulins (38%) ĭDefense against foreign invaders

Fibrinogen (7%) ĭAct as carriers for steroid hormones

Others (1%) ĭAct as enzymes

(c) Other solutes (1.5%)

Waste products ---------- ĭExcretion

Urea, uric acid,

creatine, bilirubin

Nutrients ---------- ĭEnergy source

Amino acids, glucose

fatty acids, glycerol

Regulatory substances

Enzymes

Hormones

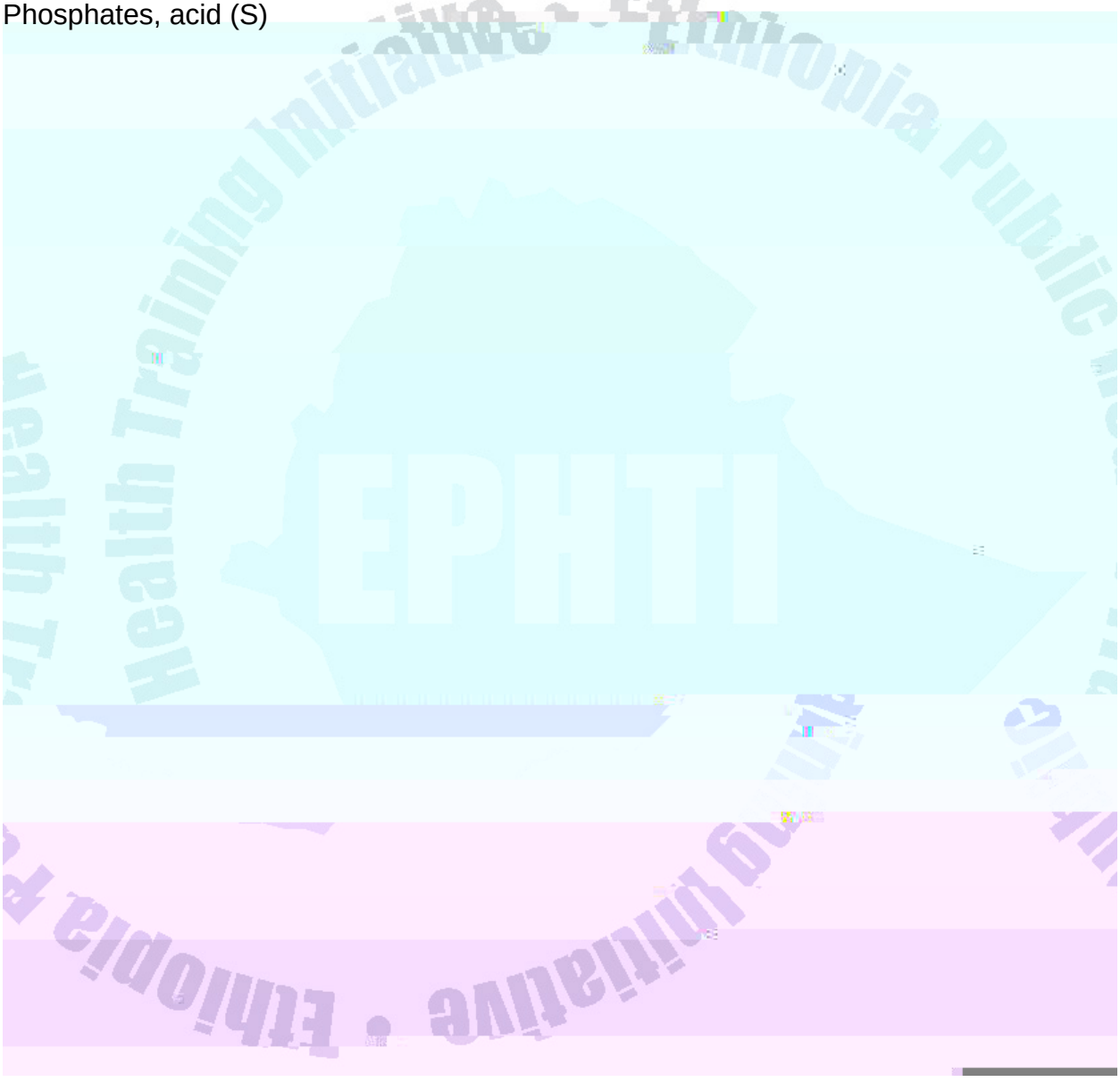
Electrolytes ----------ĭOsmotic distribution of fluid between

Cations: Na^{++}, K^{+}, Ca^{++}, Mg^{++}

Table 7: Elements of the blood

Cell	Normal range (cells/ εl)
Total WBC	Average: 9000
	Range: 4,000-11,000
Neutrophils	Average: 5400
	Range: 3000-6000
	(50-70% of total WBC)
Eosinophils	Average: 275
	Range: 150- 300
	(I – 4% of total WBC)
Basophils	Average: 35
	Range: 0 – 100
Lymphocytes	(20-40% of total WBC)
	Average: 2750
	Range: 1500 – 4000
Monocytes	(5-8% of total WBC)
	Average: 540
	Range: 300 – 600
	(2 – 8% of total WBC)
Erythrocytes	
Females	4.8 million
Males	5.4 “
Platelets	Average: 300,000
(thrombocytes)	Range: 200,000 – 500,000

Potassium	4.0-4.8 mEq/dL
Sodium (S)	135 – 145 mEq/dL
Sulfate (S)	2.9 – 3.5 mg/dL
Some enzymes:	
Amylase (S)	53 – 123 U/L
Phosphates, acid (S)	



flexibility so they can easily pass through small capillaries to deliver oxygen to the tissues.

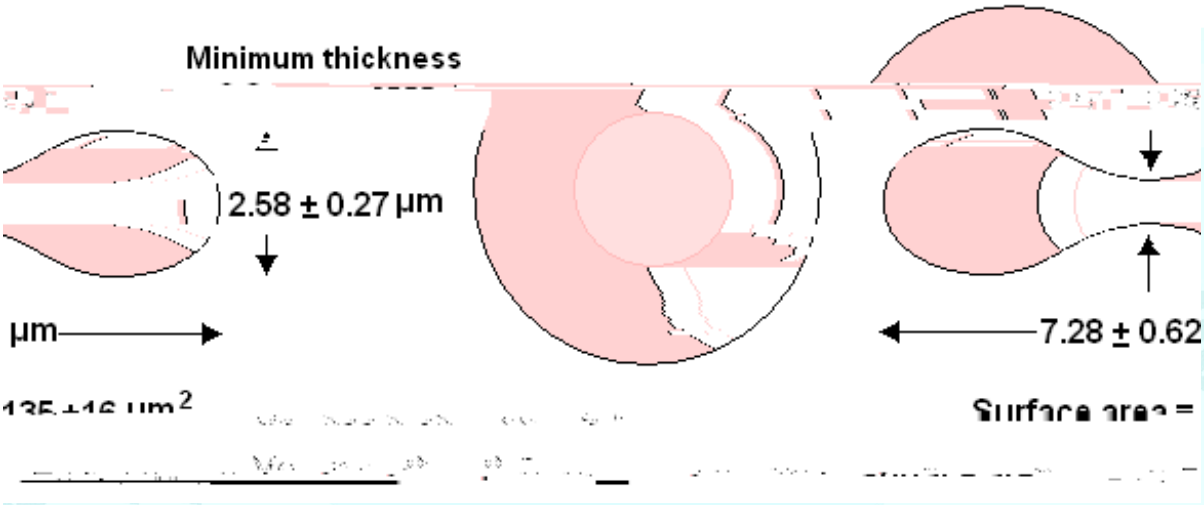


Figure 33. Shape and dimensions of a mature RBC

(see figure 33)

Hemoglobin (gm/dL) Mean= 16.0 (males); 14.0 (females)

Range= 14.0-18.0 (95% range in men; 12.0-16.0 (85% in women)

Packed cell volume (PCV, L/L)

Males = mean 0.46; range 0.41-0.51 (95% range)

Females= mean 4.8; range 4.2-5.5 (85% range)

MCV (mean cell volume) = 82 – 101 femoliters per cell

MCH (mean cell hemoglobin) = 27 – 34 picogram per cell

MCHC (mean cell hemoglobin concentration = 31.5 – 36.0 grams/deciliter

The structure of erythrocytes is well suited to their primary function of oxygen transport in the blood.

It is the major constituent of the red cell cytoplasm, accounting for about 90% of the dry weight of the mature cell. (see fig. 34)

(1) Transports oxygen and carbon dioxide in the blood
(2) Maintains acid-base balance in the blood by its buffering action.
(3) By its inclusion in the RBC, it reduces the viscosity of the blood

Hemoglobin is a conjugated protein with mol wt of approximately 64,500. Heme makes up 3% of the molecule whereas globin makes up remaining 97%. Heme contains a ***porphyrin*** molecule namely ***protoporphyrin*** with iron at its center. ***Protoporphyrin IX*** consists of 4 ***pyrrole rings*** to which 4 methyl, 2 propionyl and 2 vinyl groups are attached. The iron atom is in ***ferrous (Fe^{++}) state*** in the heme of functional hemoglobin. Iron is held at the center of the heme by 4 nitrogen of porphyrin ring. The iron can form 6 coordinated bonds. The other 2 bonds (besides 4 nitrogen) are formed on either side of the planar porphyrin ring. On one side, iron binds with the globin. On the other side, it binds with oxygen. The affinity of hemoglobin for oxygen is affected by *pH*, *temperature*, and *2, 3-diphosphoglycerate* concentration. These factors facilitate oxygen uptake in the lungs and its release in the tissues.

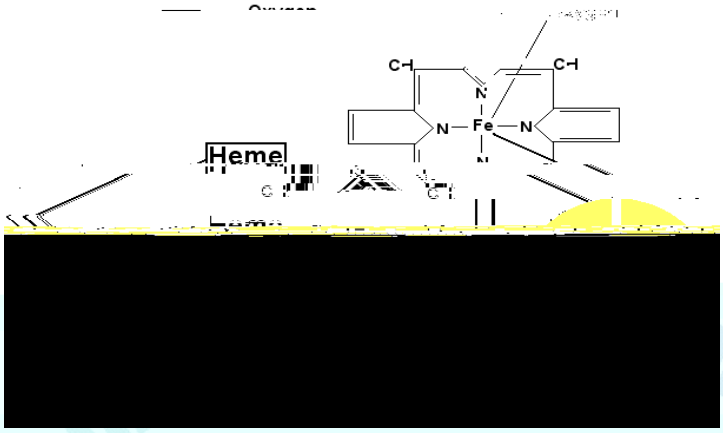


Figure 34. Structure of a hemoglobin molecule

Globin is a tetramer, consisting of two pairs of polypeptide chains. To each of the 4 chains is attached heme. Changes in the polypeptide subunits of globin can also affect the affinity of hemoglobin for oxygen. The major normal variants of hemoglobin, depending on its variation of globin chain is as follows:

Name	Designation	Pol. structure	Adults	Newborns
Adult hemoglobin	HbA	α_2	>95%	20%
Hemoglobin A_2	HbA_2	δ_2	<5%	0.5%
Fetal Hemoglobin	HbF	γ_2	<5%	80%
Glycosylated hemoglobin	HbA_{1C}	$\alpha_{2\text{-glucose}}$	<5%	0
Portland		ζ_2	0	0
Gower I		ζ_2	0	0
Gower II		ζ_2	0	0

The molecular basis of Ŭ-thalassemia is quite distinct from that of ƀ-thalassemia. A majority of the Ŭ-thalassemias are due to *deletion of α-globin gene loci*. Since in most populations there seem to be two Ŭ-globin genes per chromosome, there are 4 possible severities of Ŭ-thalassemia based on loss of 1 to 4 Ŭ globin genes. On one end, a single Ŭ-gene loss is associated with a silent carrier state, whereas, deletion of all four Ŭ-genes is associated with fetal death in utero.

Old red blood cells at the end of their life span are destroyed in the tissue macrophage system of the spleen, the globin portion of the hemoglobin molecule is split off, iron is retrieved and stored for further use, and the heme is converted to biliverdin, most of which is changed to bilirubin. Heme degradation occurs in

The organs, in which blood cells are produced, are called hematopoietic organs. The hematopoietic organs change from time to time in different stags of our life.

Early embryogenesis:

Early fetal life:

Late fetal life-

After birth:

Figure 35 shows the successive divisions of the hematopoietic stem cells from which all the cells in the circulating blood are derived. As these stem cells reproduce, continuing throughout the life, a portion of them remains exactly like the original stem cell (PHSC) and is retained in the bone marrow to maintain a supply of these. The larger portion of the reproduced stem cells, however, differentiates to form other cells .The early offspring still cannot be recognized as different from the PHSC, even though they have already been committed to a particular line of cells. These early offspring of cells are called committed hematopoietic cells. The different committed hematopoietic cells, when grown in culture, will produce colonies of specific types. A committed stem cell that produces erythrocytes is called a colony forming unit-erythrocyte (CFU-E). Likewise, colony-forming units that form granulocytes and monocytes are called CFU-GM.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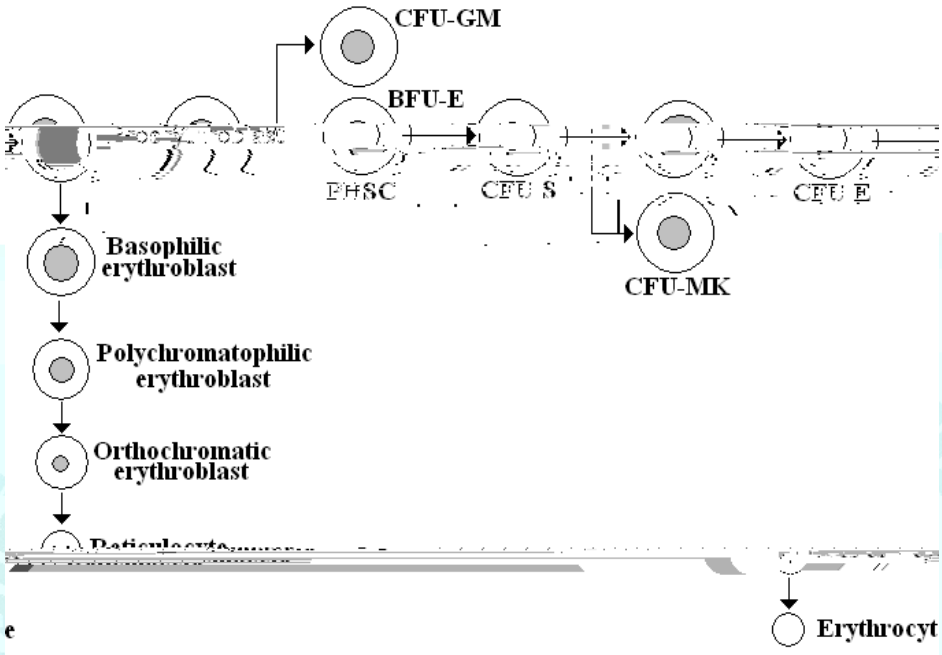

(1) Tissue hypoxia

(2) Erythropoietin (EPO)

(3) Nutritional factors

- ŏ Protein and amino acids
- ŏ Vitamin B_{12} and Folic acid
- ŏ Other vitamins
  - ĭ Vitamin B_6
  - ĭ Vitamin B_2
  - ĭ Nicotinic acid (niacin)
  - ĭ Vitamin C
  - ĭ Vitamin A
  - ĭ Vitamin E
- ŏ Minerals
  - ĭ Iron
  - ĭ Copper


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Antibodies to Rh system antigen occur only after a person has been sensitized to the antigen ‘D’ through blood transfusion or pregnancy. Because D antigen is the strongest antigen (immunogen) of red cell antigen, this may occur in up to 70% of such persons. Sensitization may also occur in an Rh-negative mother carrying an Rh-positive fetus, most commonly at the time of birth, when fetal cells escape into the maternal circulation. All of these immune antibodies are IgG. Fortunately these antibodies do not fix complement and the red cell destruction is mild and extra vascular.

Antigens in these systems may each lead to the development of immune antibodies after an antigen-negative individual is exposed through transfusion or pregnancy. These antibodies at times can cause severe hemolysis. Such patients must be given antigen-negative transfusion.

Because most patients have naturally occurring antibodies, and some develop immune antibodies in other blood group systems that are clinically significant, the choice of red cells for transfusion is to be done carefully to avoid life-threatening hemolytic transfusion reactions.

The patient’s ABO typing is determined from both forward and backward typing. In Rh forward typing is done, because very few have anti-D.

The patient’s serum is tested for “unexpected” (i.e. non-ABO). Antibodies at room temperature (for IgM) as well as at 37 Celsius (for IgG). It is some times called the “indirect Combs test”.

The absence of agglutination is important for a compatible cross match. Potential donor components are chosen to match the patient's red cell type. If any other antibodies have been found, the donor's red cells must be negative for the corresponding antigens. Finally, two drops of the donor's cells must be mixed with the patient's serum at room temperature, at 37^0C, and after the additions of the Coombs reagent.

Table 12: ABO Blood Groups: genotype and phenotype

Phenotype	Genotype	Antibody	Forward type patient Cell with		Back type patient Serum with	
			Anti-A	Anti-B	A cells	B cells
A	AO AA	Anti-B	+	+	+	+
B	BO BB	Anti-A	–	–	–	–
AB	AB	None	+	+	+	+
O	OO	Anti-A & Anti-B	–	–	–	–

+ = positive: - =negative

Table 13: Choosing ABO-compatible red cells for transfusion

	Safe donor types			
Patient blood type	A	B	AB	O
A	Yes	Yes	Yes	Yes
B	No	No	No	No
O	No	No	No	No
AB	yes	yes	yes	Yes

Components preparation allows better storage of individual components. E.g. red cells are stored at 1 to 6 C while platelets require room temperature. Factors from plasma can be concentrated

Platelets and plasma are separated from the red cells shortly after donation, and plasma may be further fractionated. Each unit is 450-50 ml blood mixed with 63 ml anticoagulant and red cell preservative solution such as CPDA -1. Such preservatives include citrate, which binds with calcium, and phosphate, dextrose, and adenine, to improve red cell survival.

Most anemic should be transfused with packed red cells, after removing 80% of the plasma, so that the volume of the component is about 150 ml. One unit of packed red cells raises recipient's hematocrit by 3 percent.

Packed cell still contain WBC, which may cause development of HLA-antibodies in response to previous transfusions or pregnancy may have febrile transfusion reactions because of the presence of donor white cells. WBC can be removed by centrifugation, or with the use of special filters.

Such preparations are needed for individuals who are IgA deficient and have had a life-

long 10 years. Freezing requires the addition of glycerol, a cryoprotectant that enters the cells and limits the formation of intracellular crystals. Glycerol is removed before transfusion.

Platelets are concentrated by centrifugation and stored at 20-24^{0}C since refrigeration destroys their ability to aggregate. Storage is allowed up to 5 days.

Pheresis techniques are used to obtain concentrates of WBC from normal donors for treating severely neutropenic patients. Granulocytes must be transfused as soon as collected, since it is not possible to preserve their function by storage at any temperature. Granulocyte transfusions are frequently accompanied by fever and respiratory symptoms in the recipient; these reactions can often be fatal.

Leukocytes primarily function outside the blood. Leukocytes are the mobile components of the body's defense immune system. Immunity means the body's ability to resist or eliminate harmful foreign materials or abnormal cells.

The leukocytes and their derivatives defend against invasion by disease-causing microorganisms by phagocytizing the invaders or causing their destruction by more complex means; identify and destroy cancer cells that arise within the body phagocytize cellular debris resulting from dead or injured cells; it is essential for wound healing and tissue repair.

The leukocytes go to sites of tissue damage or invasion. They are present in the blood as transit passengers. They can be rapidly transferred from their site of production or storage to where ever they are needed

There are five different types of leukocytes

Leukocytes vary in number, function, and structure. Five different cells - neutrophils, eosinophils, basophiles, monocytes and lymphocytes - each have different characteristic .

Neutrophils, eosionphils, and basophiles are classed as polymorphonuclear granulocytes. (See figure 38). They are classified on the basis of varying affinity of their granules to the red dye eosin and basic dye methylene blue. Monocytes and lymphocytes are mononuclear agranulocytes

Leukocytes are produced at varying rates depending on the changing needs for defense of the body

All leukocytes originate from the same undifferentiated pluripotential stem cells in the red bone marrow that also produce erythrocytes and platelets

The bone marrow produces all circulating blood cells except lymphocytes, which are produced by lymphocyte colonies in lymphoid tissues. Precursor cells for the colonies are from the bone marrow.

Figure 37. Products and functions of blood cells

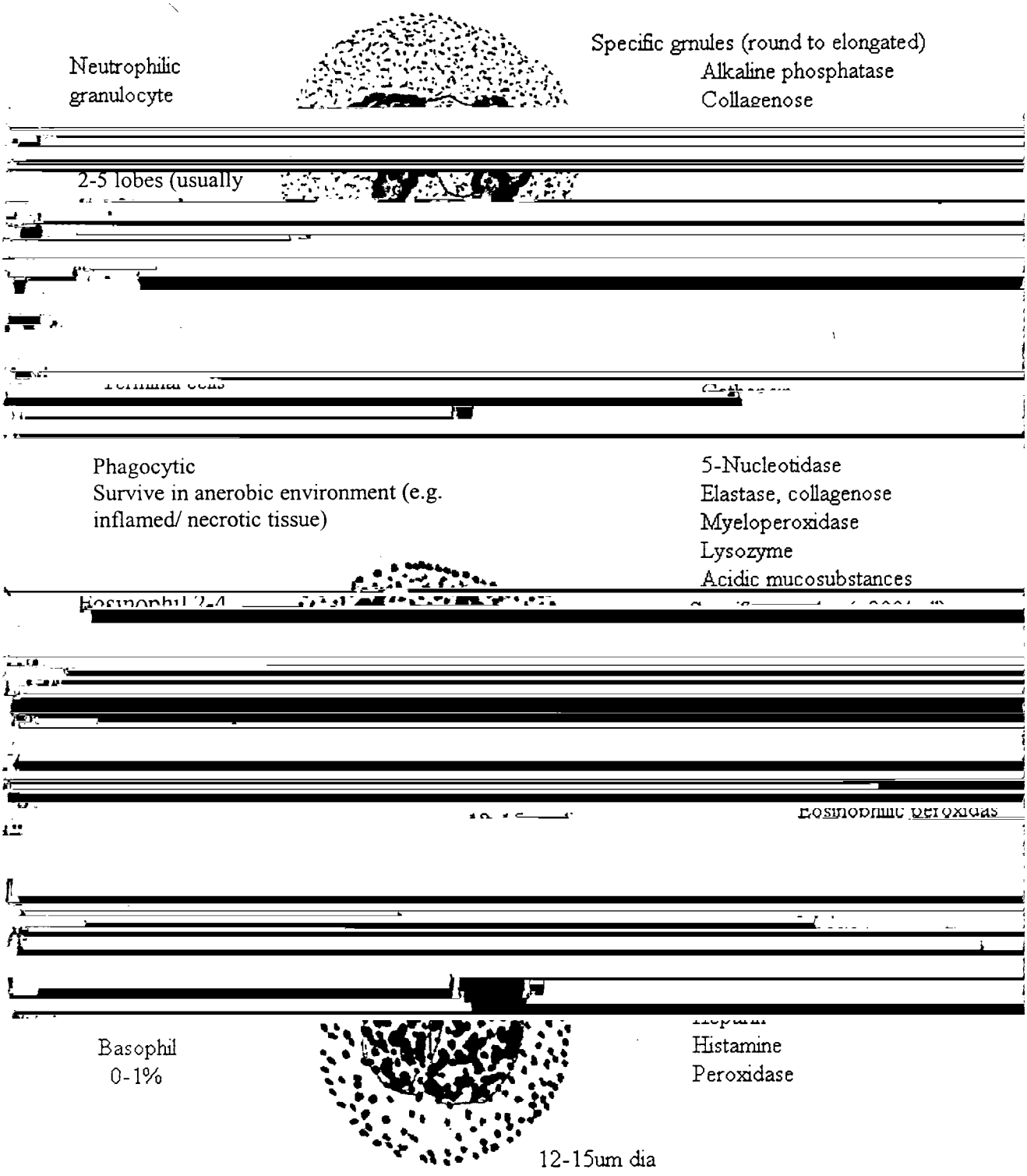

Figure 38A. Granulocytes

Neutrophils and monocyte, which transform into macrophages into the tissues, arise from a common committed progenitor the CFU-GM. The myeloblast is the earliest recognizable precursor in the granulocyte series that is present in the red bone marrow. A series of four to five divisions are associated and the mature neutrophil, cytoplasmic

Hematopoietic growth factors enhance the growth of the corresponding progenitor cells but also increase the rate of mitosis of the precursor cells. They cause differentiation and preparation for their phagocytic function. IL-5 and IL-6 have effect on more than one lineage. There are other growth factors that promote the growth and differentiation of eosinophils and lymphoid cells. The mechanism that regulates the production of GM-CSF, G-CSF, and M-CSF and other growth factors are complex. Activated monocytes and macrophages in areas of infection or inflammation release these factors, such asL-

Figure 38B. Stages of development of granulocytes

Table 15: Normal values for Leukocytes

Cell	Cells/uL	Approximate range	Percent
Total WBC	9000	4000-11000	
Neutrophils	5400	3000-6000	50-70
Eosinophils	275	150-300	1-4
Basophils	35	0-100	0-4
Lymphocytes	2750	1500-4000	20-40
Monocytes	540	300-600	2-8

- neutrophils are phagocytic cells and are the first defenders in combating bacterial invasion and are thus, very important in inflammatory responses
- they scavenge to clean up debris
- to maintain their normal circulating levels, over 100 billions neutrophils are produced daily, they enter tissues by first adhering to the endothelium by binding to adhesion molecules of the integrin family; they then migrate between the endothelial cells by ‘diapedesis’
- chemotactic agents released during inflammation attract neutrophils to the

The eosinophils undergo same stages of development as neutrophils, but content and types of granules are different

Eosinophils are recruiited to sites of allergic reactions by chemotactic factors, the most potent of which is the lipid called platelet-activating factor. In addition, lymphokines and interleukin-5 can cause accumulation of eosinophils in tissues. Eosinophils release several granule derived cationic proteins, including major basic proteins that cause local tissue damage in diseases such as asthma and the hypereosinophilic syndrome. These cationic proteins are beneficial when released as part of eosinophil count is found during most bacterial and viral infections. Stress, endogenous secretion of corticosteroids and exogenous glucocorticoids suppress the number of blood eosinphils

Eosinophils cannot engulf a much larger parasitic worm, but they do attach to the worm and secrete substances that kill it.

Another type of leukocyte with specific granule is the basophil. Basophil granules have a high content of histamine and play a role in acute, allergic reactions. They have high affinity Fc receptors for IgE. Binding of antigen to adjacent cell-bound IgE triggers the release of mediators from basophils. They are quite structurally and functionally similar to mast cells. Both synthesize and store histamine and heparin. Mast cells, however, are not present in the blood, but are found in the bone marrow and in mucosal and connective tissues. Basophilia is most often found with myelocytic leukemia and other meyloproliferative disorders.

The events resulting from the release of contents of basophil or mast cells include:

-increased vascular permeability

-smooth muscle spasm

-mucus secretion

-eosinophil and neutrophil chemotaxis

-pruritis, and
-vasodilatation

Urticaria, rhinitis, asthma, dermatographism, may result from this process

The primitive multipotential stem cell that gives rise to the granulocytes, red cells, and platelets, is also the precursor of the lymphocyte. The lymphoid precursor cells travel to lymphoreticular organs, where they differentiate into cells capable of either expressing cell-mediated immune responses or secreting immunoglobulin. Antibody-producing cells probably processed by the tonsils or bone marrow (bursa of Fabricius) and T cells differentiate in the thymus gland. B cells ultimately differentiate into antibody-producing plasma cells. In normal person both small and large lymphocytes are found in the peripheral blood; the former far exceed the latter cell types. Atypical lymphocytes are seen in viral illnesses such as infectious mononucleosis.

The monocyte is produced from a committed progenitor cell, the CFU-M, which is derived from the CFU-GM, the common progenitor cell for both the granulocytic and monocytic series. Mature monocyte are released into the circulation, enter the tissues, and there transform into the macrophages of the mononuclear phagocytic system also called reticuloendothelial system. Monocyte and macrophages are more efficient at phagocytizing mycobacterium, fungi, macromolecules, and sensitized erythrocytes and less effective in ingesting pyogenic bacteria. They have a long life span and can synthesize digestive enzymes. Complement components, transferrin, interferon, endogenous pyrogen, lysozyme, colony-stimulating factors, and many other substances can be produced and secreted by the monocyte-macrophage system. The cells in the monocyte-macrophage system assist in the removal of aged or damaged cells, such as red cells and tumor cells, and also interact with lymphocytes in cellular immunity and antibody production.

Monocytosis is often found with chronic infections, such as tuberculosis and sub acute bacterial endocarditis, and in inflammatory diseases, including collagen vascular conditions and inflammatory bowel disease. Other causes are preleukemia, myelocytic leukemias, lymphomas, and the myeloproliferative diseases. 'Histiocytosis X' is indolent form of neoplasia of the monouclear-phagocytic system. The bone marrow, skin, and lungs are the organs most commonly affected.

Table 16: Some humoral mediators (lymphokines) produced by T- lymphocytes

Lymphokine	Regulatory functions
Interleukin-1	Activates resting T cell
	Hematopoietic growth factor
	Mediates inflammatory reactions
	Endogenous pyrogen
Interleukin-2	Growth factor for activated T cells
Interleukin-3	Growth factor for stem cells
Granulocyte-macrophage stimulating factor (GM-CSF)	Promotes growth of hem
Granulocyte CSF (G-CSF)	
Monocyte CSF (M-CSF)	
Interleukin-4	
Interleukin –6	
Interferon (alpha, beta, gamma)	
Tumor necrosis factor	

Activates macrophages, Mediates

The immune system protects against microbes and cancer cells and contributes to tissue repair. The man is exposed to external environment that abounds in external agents that could harm the body if they enter the body. Many such agents are disease causing microbes. The body responds through complex, multiple defense strategy - the 'immune system' - which provides effective protection against attack by foreign agents. The immune defense system either destroys such agents on recognition or neutralizes foreign material that are different to the 'normal self'

Defense against pathogens

removal of worn out cells such as aged erythrocytes and tissue debris i.e. tissue damaged by trauma or disease

recognition and destruction of abnormal or mutant cells that have originated in the body - the immune surveillance is the very crucial internal defense against cancer

Inappropriate immune response may lead to allergy or to 'autoimmune diseases' in which antibodies are produced against 'itself' leading to destruction of a particular type of the body's own cells

Immune system is also responsible for rejection of tissue cells of foreign origin

Pathogenic bacteria and viruses are the major targets of the immune defense system. Bacteria are well equipped with its own machinery necessary for their own growth,


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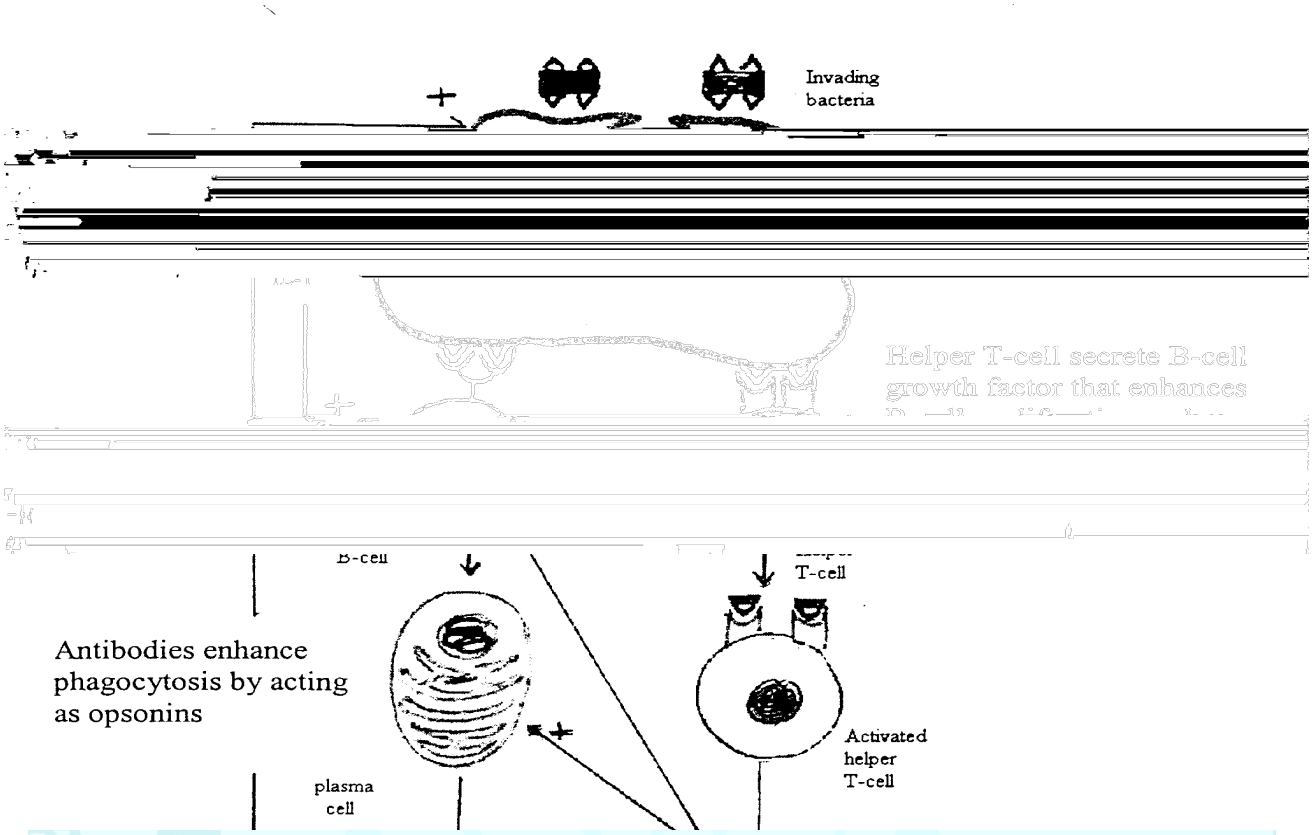

Figure 40. Response of lymphocytes.

Hemostasis is a collective term for mechanisms, which prevent or minimize blood loss when a blood vessel is opened. Hemostasis is vital because unchecked hemorrhage eventually leads to cardiovascular collapse and death. Hemostasis can be viewed as four separate but interrelated events:

1. Local vasoconstriction
2. Formation of a platelet aggregate (platelet aggregation)
3. Formation of a blood clot

4. Retraction of clot
5. Dissolution of clot

When a blood vessel is injured, its immediate response is to constrict and thereby reduce blood flow. This initial vasoconstriction is due to the local spasm of the smooth muscle in the wall of the blood vessel and to sympathetic reflexes.

Platelet aggregation, at the site of injury, serves as a poor but prompt stopper, which tends to stop the bleeding efficiently.

The third mechanism for hemostasis is formation of the blood clot. Coagulation is the process by which some of the blood loses its fluid consistency and become a semisolid mass (clot).

Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot within 20 to 60 minutes.

After hemorrhage has been checked and tissue repair has proceeded, a clot is gradually dissolved by breaking down fibrin into soluble fragments. The enzyme that degrades fibrin is called plasmin.

More than 50 important substances that affect blood coagulation have been found in the blood and in the tissues. Some of these substances promote coagulation, called

Ka	Kallikrein	
PL	Platelet phospholipid	

The complex sequence of chemical events that produce clot (fibrin) is divided into three stages

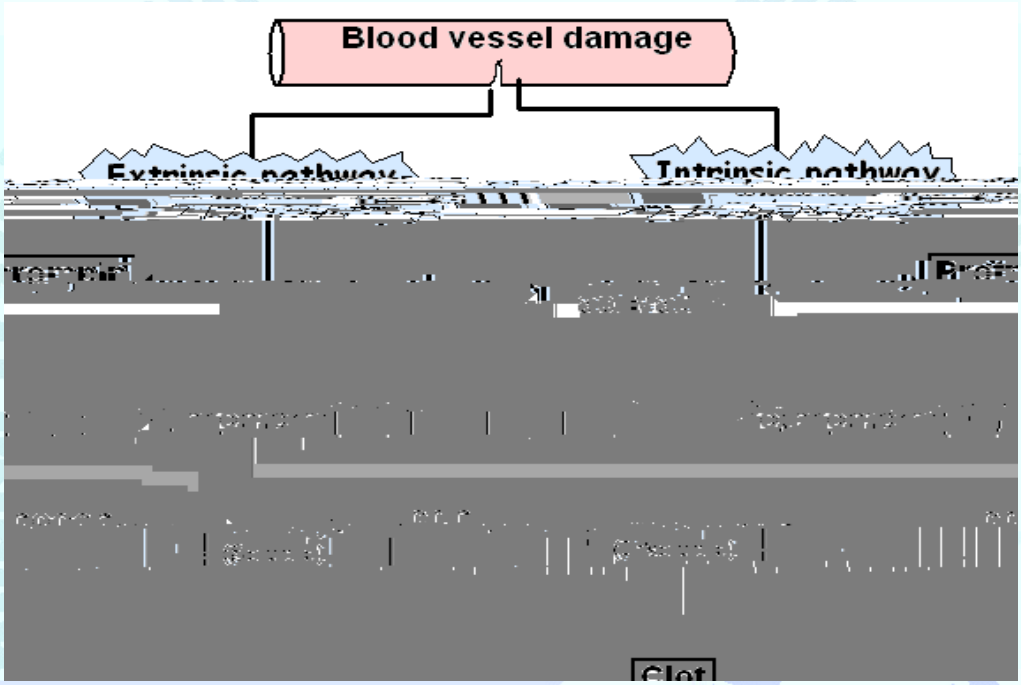

Figure 41: An overview of blood coagulation

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It begins with trauma to the vascular wall and surrounding tissues.

Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin or factor III. This is composed of mainly phospholipids from the membranes of the tissue plus a lipoprotein complex.

The tissue factor (III) further complexes with factor VII, and in the presence of Ca^{++}, acts enzymatically on factor X to form activated factor X.

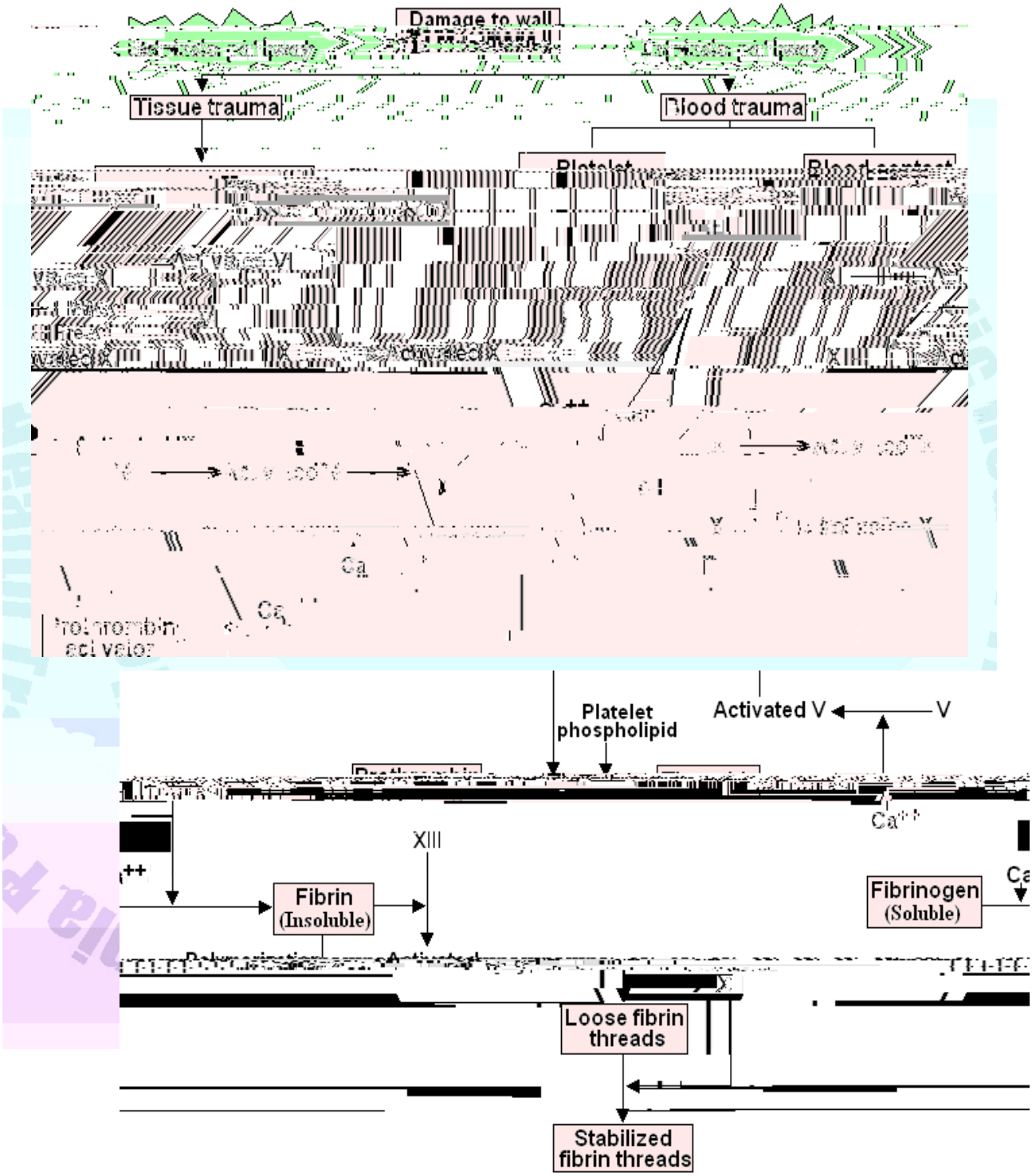

Figure 42: Stages of blood coagulation

The factor Xa combines immediately with tissue phospholipids that are part of tissue factor or combine with factor V to form the complex called prothrombin activator.

It begins in the blood itself, i.e., trauma to the blood or contact with damaged endothelial cells or with collagen. The intrinsic pathway is more complex than the extrinsic pathway.

Trauma to the blood or exposure of blood to collagen or to wetable surface such as glass alters the molecular configuration of factor XII. Simultaneously, the blood trauma also damages the platelets and releases phospholipids that contain the lipoprotein called platelet phospholipids

fragments: one inert and the other possessing the properties of thrombin. Initially the conversion of prothrombin proceeds too slowly to produce significant amounts of thrombin needed for coagulation. Thrombin itself, however, increases its own rate of formation by converting proaccelerin (factor V) into accelerin which then accelerates the formation of thrombin.

(a) Thrombin acts on fibrinogen to remove four low mol wt peptides from each molecule of fibrinogen, forming a molecule of fibrin monomer. Fibrin is insoluble in plasma.

(b) Fibrin monomer has the automatic capability to polymerize with other fibrin monomers, thus forming fibrin thread within seconds

(c) Many fibrin fibers constitute the reticulum of the clot. The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets and plasma proteins.

Excessive bleeding can result from deficiency of any of the many blood-clotting factors. With few exceptions, almost all the blood clotting factors are formed by the liver. Therefore, diseases of the liver such as hepatitis, and cirrhosis can sometimes depress the clotting system.

Vitamin K is necessary for the liver formation of five important clotting factors namely prothrombin, factor VII, factor X, and protein C. In absence of vitamin-K, subsequent insufficiency of these coagulation factors in the blood can lead to serious bleeding tendencies.

Hemophilia is an inability of the blood to properly coagulate due to a genetic lack of a coagulation factor. It occurs almost exclusively in males. Females are carrier of this disorder.

: involves deficiency of factor VIII. It is genetically transmitted. About 85% of hemophilia is type A.

(Christmas disease): It involves the deficiency in factor IX. Clinically it is indistinguishable from hemophilia A

: It is not sex linked and results from a deficiency in factor XI.

Hemophilia is characterized by spontaneous or traumatic subcutaneous hemorrhage, blood in urine, and bleeding in the mouth, lips, tongue, and within the joints.

Thrombocytopenia is characterized by a prolonged bleeding time, with a normal coagulation time. A platelet count of 100,000/cu mm or less is generally considered to

myocardial infarction, v***ulvulitis***). It is important to note that endothelium does not need to be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of prothrombotic and antithrombotic effects can influence local clotting events. Thus, significant endothelial dysfunction may occur from the hemodynamic stresses of ***hypertension***, or ***bacterial endotoxins***.

Turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis. Normal blood flow is laminar such that the platelets elements flow centrally in the vessel lumen separated from the endothelium by a slower-moving clear zone of plasma. Stasis and turbulence therefore:

(a) Disrupt laminar flow and bring platelets into contact with the endothelium

(b) Prevent dilution of activated clotting factors by fresh-flowing blood

(c) Retard the inflow of clotting inhibitors and permit the build-up of thrombi

(d) Promote endothelial cell activation.

Hypercoagulability generally contributes less frequently to thrombotic states but is nevertheless component in the equation. It is loosely defined as any alteration of the coagulation pathways that predisposes thrombosis, and it can be divided into primary (genetic) and secondary (acquired) disorders.

(a) Inherited: Of the inherited causes of hypercoagulability, *mutations in the factor V gene* and prothrombin gene are the most common. The characteristic alteration is a mutant factor Va that cannot be inactivated by protein C; as a result, an important antithrombotic counter-regulatory pathway is lost.

(b) Inherited: Among acquired causes, hypercoagulability may be related to increased hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III. *Use of oral contraceptives* and the hyperestrogenic state of *pregnancy* are some common examples of this category.

It is characterized by activation of the coagulation sequence, leading to formation of thrombi throughout the microcirculation. As a consequence of the widespread thromboses, there is consumption of platelets and coagulation factors and, secondarily, activation of fibrinolysis

Blood carrying nutrients and oxygen reaches the tissues through a system of vessels of different diameters, elasticity, capacity, and permeability. The systemic circulation, which supplies all the tissues, is a high-resistance system with a large pressure difference between the arteries and veins. The arteries are highly elastic and muscular; they distribute blood to the smaller arterioles and ultimately to the network of capillaries, where exchange of fluid, small molecules and nutrients occurs acro575 06ts and coagu.amay ela

alveoli. And highly specialized pulmonary capill

valve. Both valves are fastened to small conical ‘papillary muscles, on the ventricular walls through several tendinous, the ‘chordae tendinae’. The papillary muscle and the ventricles contract at the same time to prevent valve’s excursion into the atrium.

Both large arteries are guarded by the semilunar valves at the exit of the two ventricles. Each valve is made up of three half-moon cusps; the cusps are thin but very strong, fitting very closely, enabling them to withstand very high pressures that cause the valves to open and to snap shut during ventricular contraction and at the end of systole. The semilunar valves close during t

The heart beat is initiated by the pacemaker (SA Node) lying between the superior vena cava and the right atrium. The rhythmic depolarizations generated by the SA node are conducted through the atria to less rapidly firing AV node lying in the right atrium, close

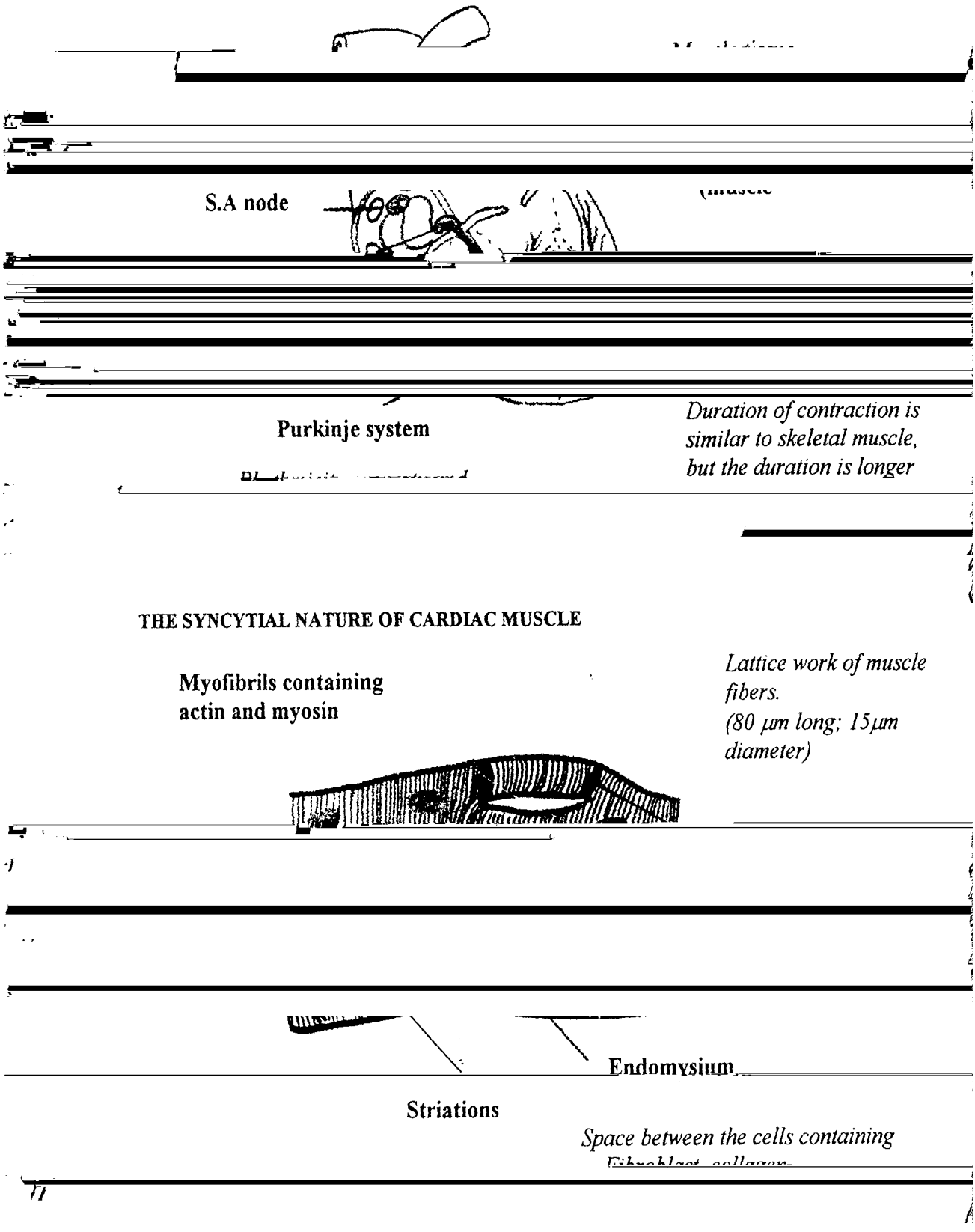

Figure.44 shows cardiac muscle cells

Cardiac muscle has more mitochondria and rich myoglobin than most skeletal muscles. Myoglobin stores oxygen and facilitate its transport from the sarcolemma to the mitochondria

The transverse tubular system (T system) penetrates into the substance of the muscle fiber and also runs longitudinally within the fiber. The T system is in contact with the ECF space, and permits passage of large molecules. The sarcoplasmic reticulum is adjacent to the T-system. The T-system is associated with the conduction of the action potential; it depolarizes the SR causing the release of ionic calcium that initiates the muscle contraction.

The sliding of the contractile elements is brought about through the formation and breaking of 'cross-bridges' between the actin molecules and the heads of the myosin molecules. This process is dependent on rapid changes in intracellular ionic calcium levels. An action potential along the sarcoplasmic reticulum results in the influx of extracellular ionic calcium through the T-system, and the release of calcium from the SR. Calcium binds with troponin, which results in the displacement of the long tropomyosin that has been blocking the binding sites for myosin on actin.

Tropomysosin and troponin are known as regulatory proteins. Actin and myosin are the contractile proteins. ATP provides the energy required for these mechanical actions. Relaxation needs the rapid removal of Ca^{++} from the myofilament environment. The SR uses ATP for actively transporting calcium back into its cisternae and channels. The fall in cytosolic Ca^{++} affects the troponin-tropomyosin complex, pulling tropomyosin molecules back into their blocking position, opening the cross-bridges, and permitting the thin actin filaments to slide apart as the muscle relaxes.

The heart gets nerve supply from both the sympathetic & the parasympathetic system that exerts a continuous but changing tonic influence on it. They affect the performance

of the heart by change in heart rate, contractility, refractory period, & excitability and conductivity of the specialized conduction tissue through the heart. The parasympathetic vagi innervate the SA & AV nodes & the atria, & innervations to the ventricles. Sympathetic from the stellate & caudal sympathetic ganglia, innervate the same structures like vagi, with a particularly rich innervations of the ventricles.

The force contraction refers to inotropic state and changes in the heart rate refer to the chronotropic characteristic. Autonomic actions of the nerves are affected by changes in blood temperature, pH, & the amount of blood returning to the heart. Both characteristics are sensitive to many drugs, which can alter the effects of nerves activity.

- Acetylcholine has a marked negative inotropic effect on myocardium decreasing contractility.
- ACh also reduces heart rate and makes heart more refractory, and slows conduction through the heart

-

The heart cells can be divided into “leader-cells” and “follower-cells”. The SA node has the highest rhythmicity (110-120); AV node (60); myocardium (20-40).

The strength of contraction is not dependent on the strength of the stimulus. Cardiac muscle responds to an adequate stimulus with a maximum strength. This is

principle. Although the heart responds with maximum contraction, the maximum varies with the physiological conditions. The degree of the heart’s filling with blood, hormones, changes in the ionic concentrations, temperature changes - all modify both the rate and the strength of contraction.

The cardiac muscle has much longer refractory period than that of

The most important cations are calcium, potassium, and sodium.

- In Hypokalemia, the PR interval is lengthened, the ST segment is depressed, the T wave is inverted, and a prominent 'U' wave is recorded in the ECG/EKG
- Hyperkalemia presents as very tall, slender peaked T wave
- Further elevation of plasma potassium result in ventricular tachycardia and ventricular fibrillation.
- Hyperkalemia decreases resting membrane potential, the intensity of the action potential also decreases, which makes the contraction of the heart weaker.
- Hypokalemia prolongs the relative refractory period; there is increased incidence of bradycardia, and high risk of arrhythmias
- Hypercalcemia results in increased myocardial contractility.

Myocardial contractility is affected by the following three factors:

1. Contractile state
2. Stretch or preload
3. after load

The SA node has most rapidly discharging cells. (See figure 45 & 46). The rhythmic excitation (Depolarization) begins in the SA Node; it is responsible for the subsequent excitation, and consequently contraction, of the atria and ventricles, in that order. The SA node discharges at a heart rate 72 per minute, resulting in heart rate of 72 beats / min. AV node discharges 60 times /min; Atria= 40 times/min: ventricles 10 - 20 times/ min.

Action potentials generated in the SA node rapidly travels through the atria, at about 0.3 meters /sec & conducted very rapidly to the AV node 0.5 meter /sec. Atrial fibers form the atrial bundles; bundle connecting the two nodes is the internodal pathway.

Its fibers conduct very slowly, about 0.2 & 0.5 meters/second. This delay in conduction creates efficiency of the heart, since the delay allows time for the atria to empty before ventricular depolarization and contraction begins. (See figure 46 & 47).

This is made up of specialized cardiac fibers, the purkinje fibers that originate in the node and form a bundle in the septum separating the two ventricles.

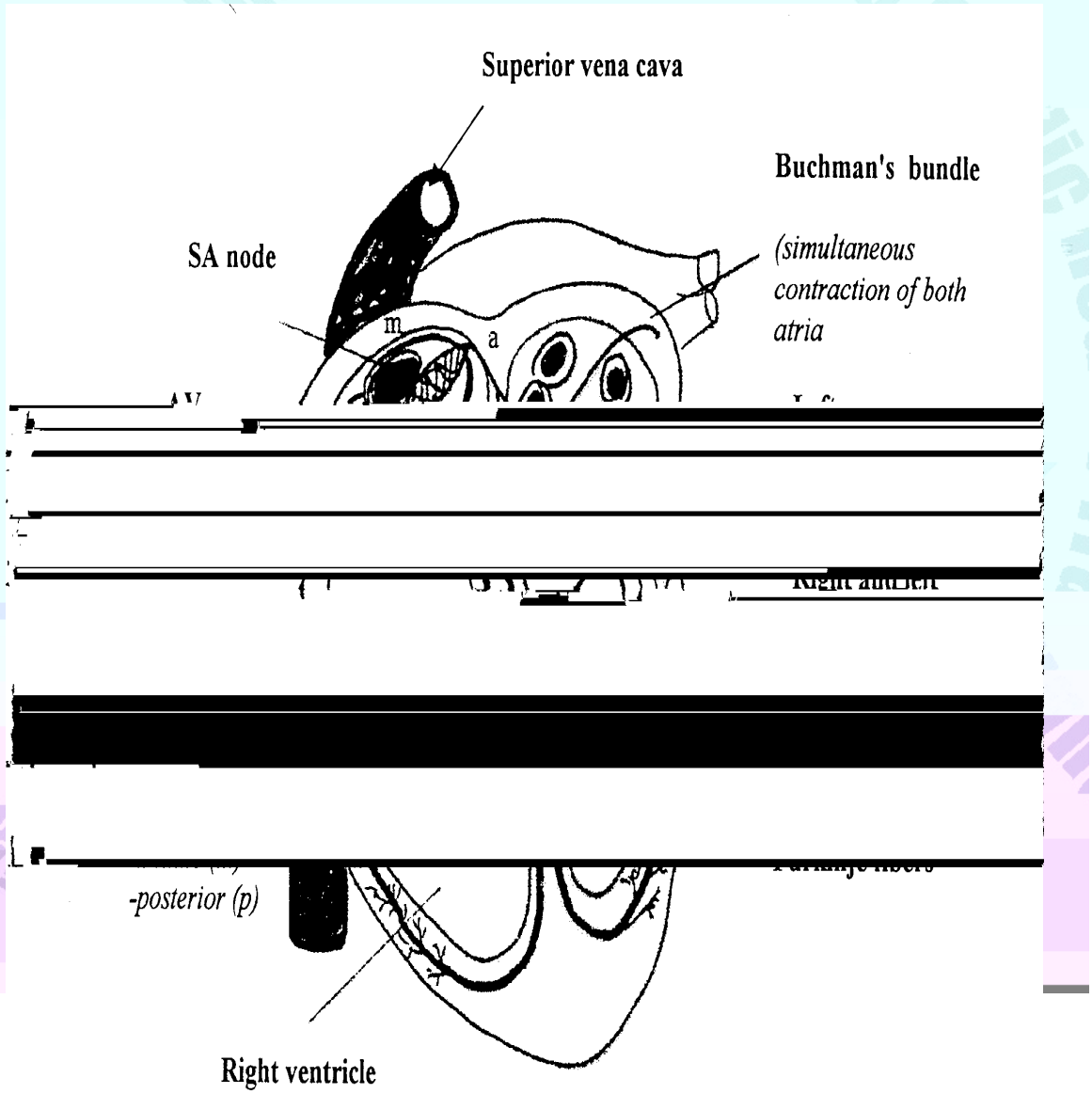

Figure 45. The nodal tissues of the heart.

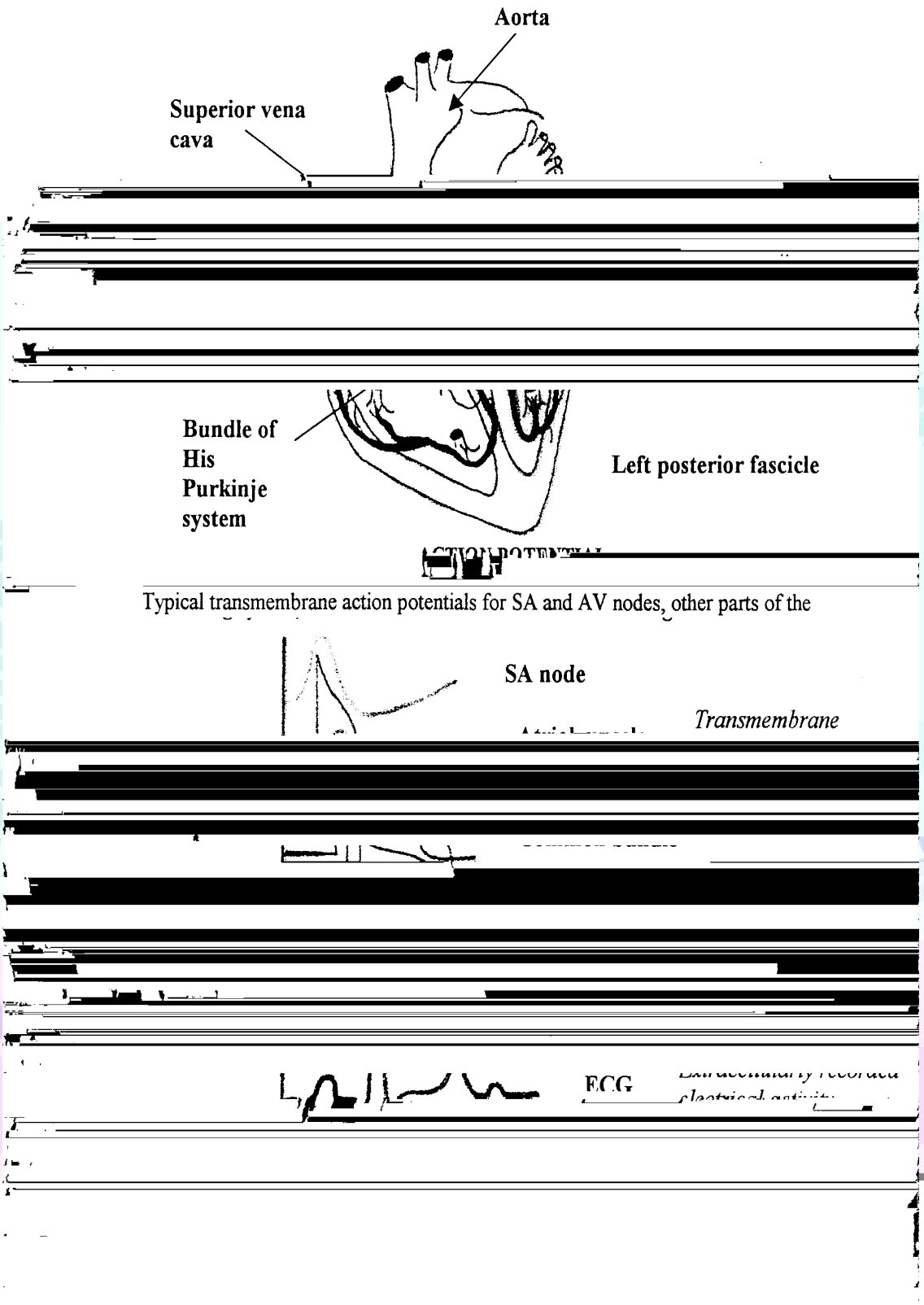

Figure 46. Conducting systems of the heart


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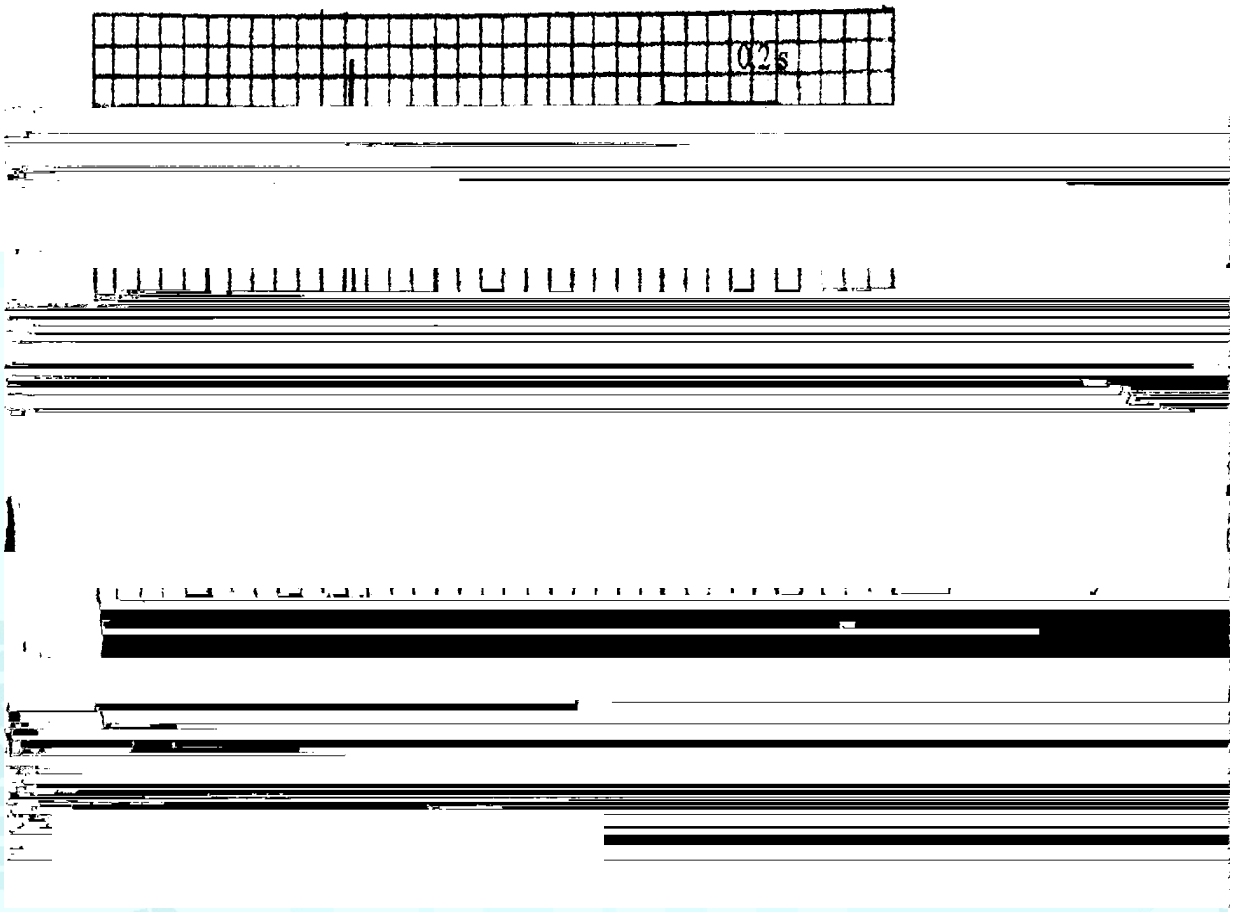
- It has a shorter duration than the ‘P’ wave, because depolarization spreads very quickly through the purkinje network.
- The large QRS complex completely masks obliterates any record of atrial repolarization, which occurs at this time.
- Prolongation of QRS complex: indicates delayed conduction through the ventricles, is often caused by ventricular hypertrophy, with its increased muscle mass, and also increases the voltage of the QRS complex. Another cause is conduction block of one of the bundle branches.

: it is an important parameter of the ECG; it is the time taken from the start of depolarization of the atria to the beginning of ventricular depolarization. Normal interval 0.12- 0.20 sec.



An ECG provides information on heart rate and rhythm, conduction velocity, and even the condition of tissues

Within the heart. The interpretation of an ECG begins with the following questions:

Heart rate is normally timed from the beginning of one P wave to the beginning of the next P wave, or from

Peak to peak of the QRS complexes. A faster rate is called tachycardia, and a slower rate is called bradycardia.

An irregular rhythm, or arrhythmia, can result from a benign extra beat or from more serious conditions such
as atrial fibrillation, in which the SA node has lost control of pace making.

Normally, the voltages in the three standard bipolar limb leads, as measured from the peak of the R wave
to the bottom of the S wave, vary between 0.5mV and 2.0mV, with lead III usually recording the lowest and
Lead II, the highest. However, these relations are not invariably true even in the normal heart. In general,
When the sum of the voltages of all the QRS complexes of the three standard leads is greater than 4mV, one
considers that the patient has a high-voltage ECG.

High-voltage ECG is common in ***ventricular hypertrophy***. Low-voltage ECG is found in cardiac ***myopathies***, ***fluid in the pericardium***, ***pulmonary emphysema*** etc.

After determining the heart rate and rhythm, and voltage of ECG, the next stage in analyzing an ECG is to look at the relationship of the various waves. Does a QRS complex follow each P wave and is the PR segment constant in
length? If not, a problem with conduction of signals through the AV node may exist. In ***heart block***,
action potentials from the SA node sometimes fail to be transmitted through the AV node to the ventricles.
In these conditions, one or more P waves may occur without initiating a QRS complex.

The more difficult aspects of interpreting an ECG include looking for subtle changes such as
alterations in the shape or duration of various waves or segments.

The cardiac cycle is the period from the end of one heart contraction (Systole) and relaxation (diastole) to the end of next systole and diastole. (See figure 48). Cardiac contraction is preceded by electrical changes initiated by the pacemaker of the heart, the sino-atrial node. The contraction of the heart generates pressures within the heart that regulates the opening and closing of the valves and consequently directs the blood flow through the heart and the arteries. Electrical changes are recorded on the electrocardiogram, and the heart sounds are recorded on a phonocardiogram. Similar events occur in the right and left side of the heart, but ventricular and atrial pressures are lower in the right heart. At a heart rate of 75 beats/min, the total cycle time is about 800 milliseconds, a systolic time of 250 - 300 msec, a diastolic time of 500 - 550 msec.

Systole is contraction of the heart, relaxation is diastole. Each of the four chambers of the heart contract and relax rhythmically, filling with blood during diastole, ejecting the blood during systole. The right and left heart contract and relax simultaneously, ejecting equal blood volume at the same time, but with different pressures.

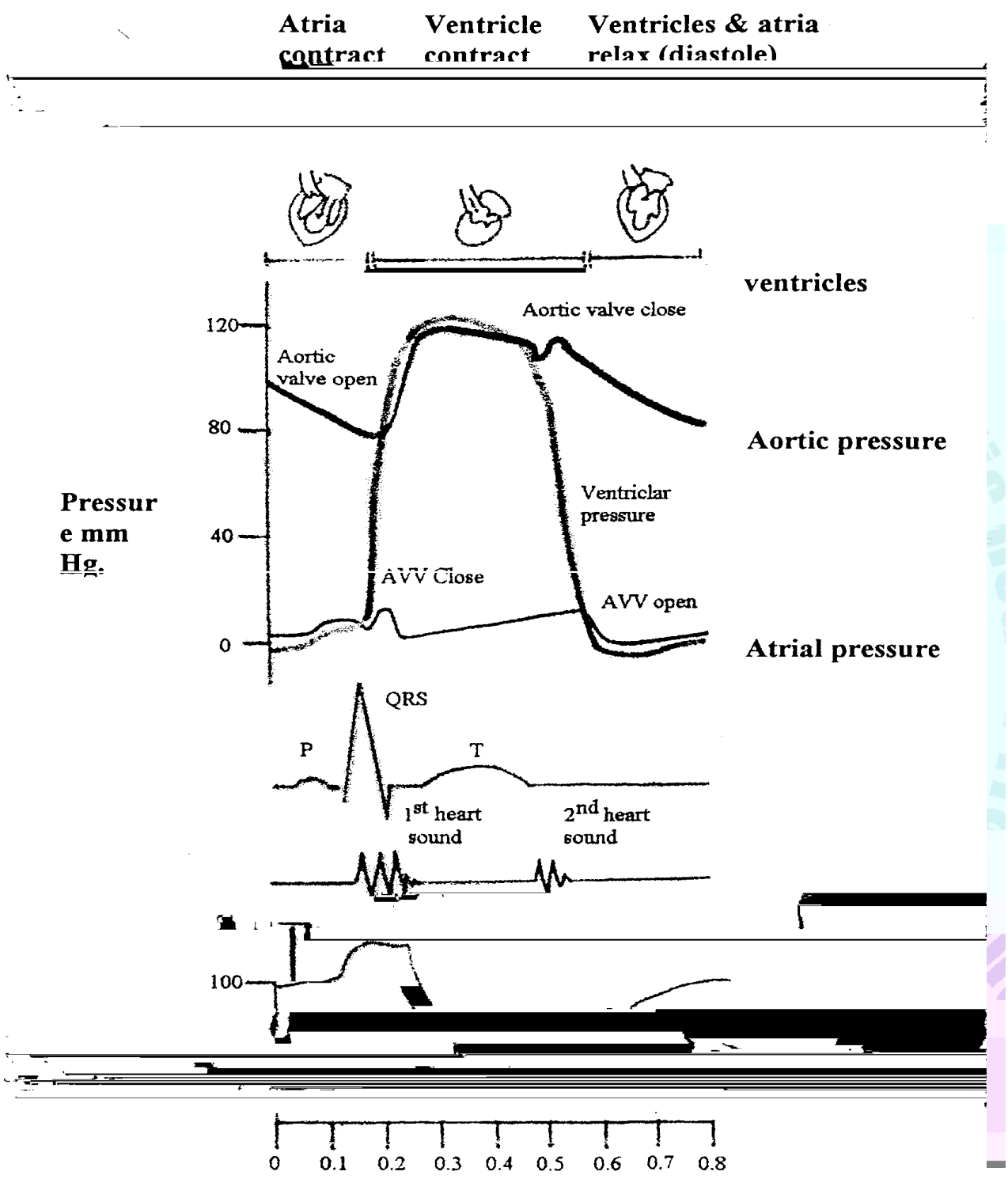


Figure 48. The cardiac cycle

The atria have a minor role during normal resting conditions but contribute significantly to the filling of the ventricles during exercise. The thin-walled atria receive blood continuously from the superior and inferior vena cavae. 70% of ventricular blood volume flows directly through the opened atrioventricular valves into the ventricles. Atrial systole initiated by depolarization occurs late in ventricular diastole and adds 30% to total ventricular filling. Pressure in left atria reaches 7 - 8 mmHg, that in the right atrium to 4 - 6 mm Hg, during atrial contraction. Just prior to ventricular systole, rising pressure in the ventricles closes the atrioventricular valves (AVV). During this AVV closure, the atria continue to fill with blood from great veins, resulting in an increase in atrial pressure.

At the end of ventricular systole, the ventricular pressure falls abruptly when blood is ejected into the aorta and pulmonary artery. At this stage, arterial pressures are higher than ventricular, snapping closed the semilunar valves. For a period of 0.03 - 0.06 seconds, AV valves remain closed, and ventricles begin relaxation. This phase of ventricular relaxation without volume change is called isovolumetric relaxation period. Ventricular pressure falls below atrial pressure, causing AV valves to open again. Opening of the valves results in rapid blood flow into the ventricles. This is the passive rapid filling phase of ventricular diastole. In the later diastole phase, the filling of the ventricles is aided by atrial contraction - active rapid filling phase. At the end of diastole, ventricles contain about 120 ml of blood - known as end – diastolic volume (EDV) in each ventricle. Ventricular systole begins with depolarization of the ventricles. The high ventricular pressure closes the AV valves producing the first heart sound. There is a period when ventricles are contracting, there is no change in ventricular volume and is known as isovolumertic contraction period (0.02 to 0.03 second).

During this phase of contraction, the pressure rises in both ventricles, forcing open the semilunar valve. About two-thirds of the ventricular blood is rapidly ejected into the arteries in the first third of systole, the rest of the blood is ejected slowly during the

second two-thirds of systole. The volume of blood remaining in each ventricle at the end of systole is the end-systolic volume, about 50 ml of blood. Therefore the stroke volume of normal heart in resting conditions is 120-50 =70 ml.

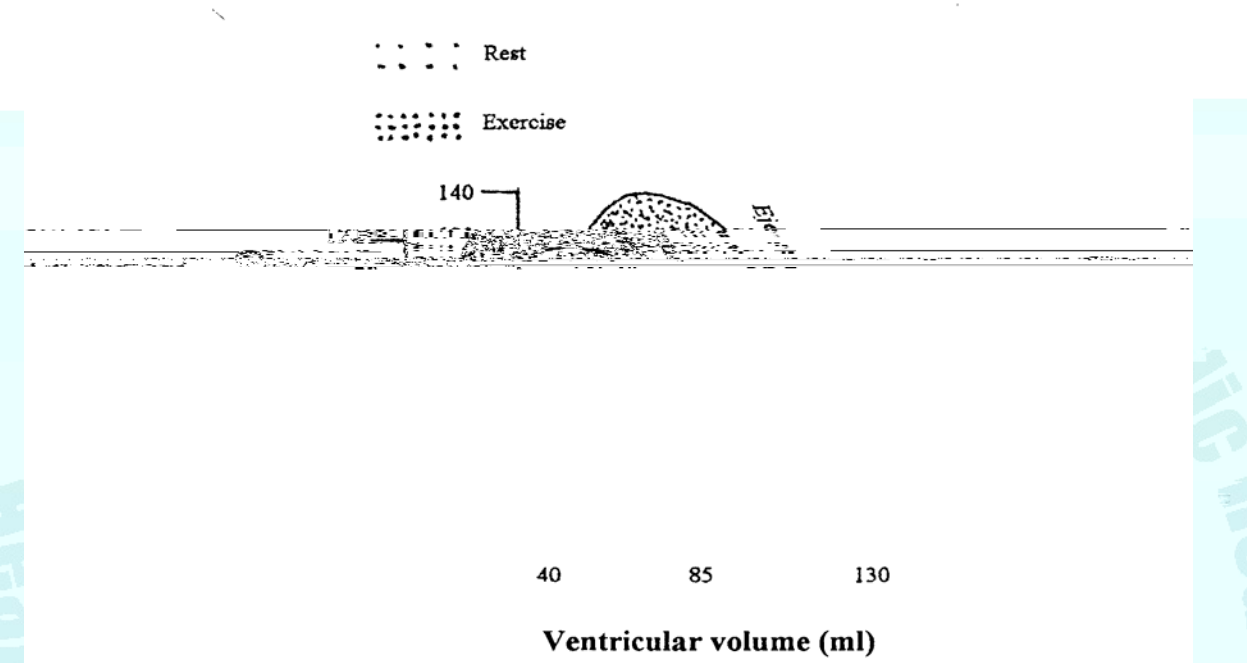


Figure 49. Pressure – Volue Loop of the Cardiac Cycles at Rest and During Exercise.

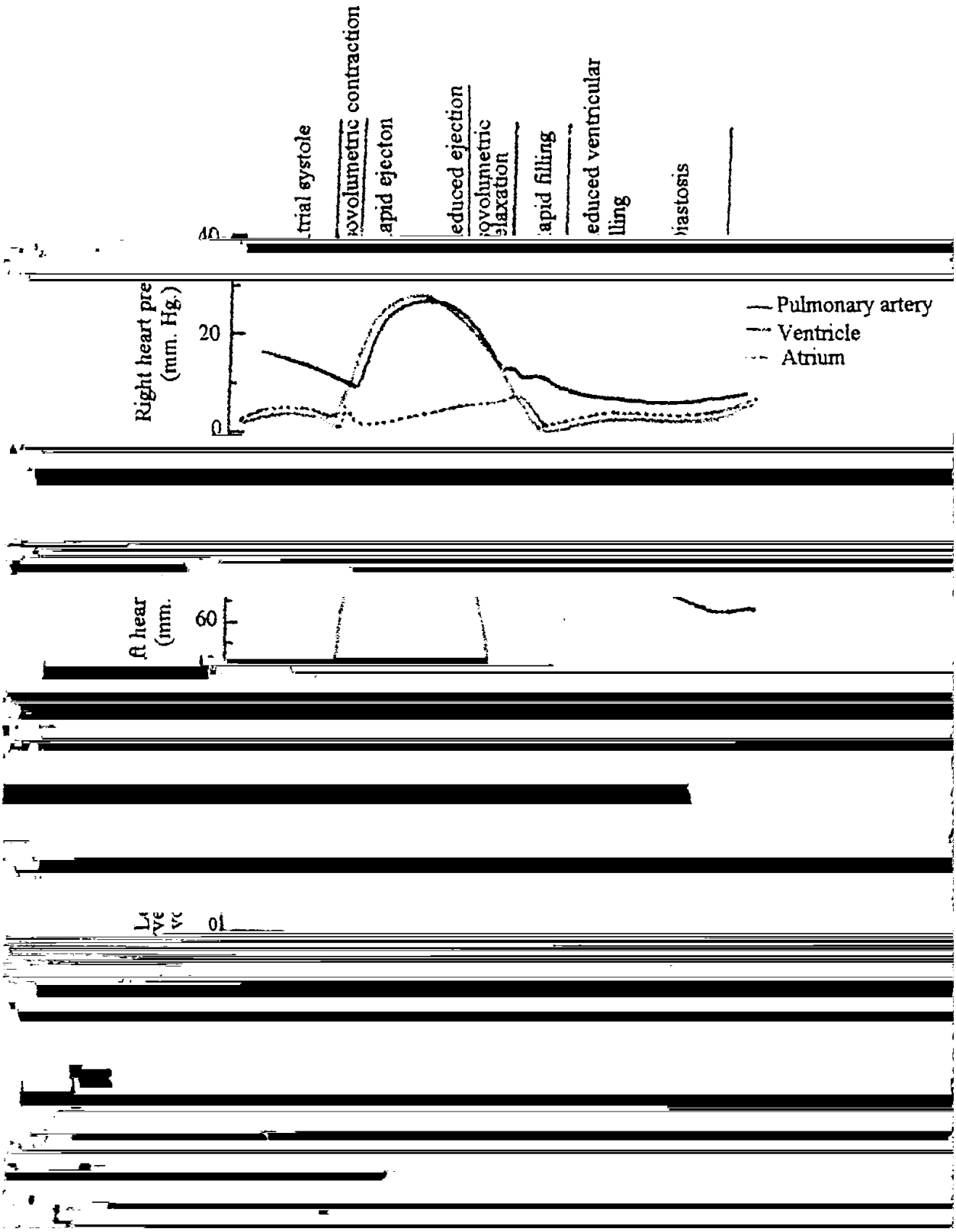


Figure 50. Correlation of events in the cardiac cycle

Heard by a stethoscope

Frequency: 100Hz

Duration: 0.11s.

Cause: Closure of the semilunar valves.

Generally, not heard by a stethoscope

Recorded by phonocardiogram only one-third to one half of all persons

Very low frequency

Cause: Rushing of blood into the relaxing ventricles during early diastole

Generally not heard by a stethoscope

Recorded by phonocardiogram only one-fourth of all persons

Very low frequency (about 20 Hz)

Cause: Rushing of blood into the aorta and pulmonary artery from the contracting ventricles.

Just as the ECG gives important information about the electrical operation of the heart, heart sounds provide valuable information about its mechanical operation. A heart murmur is an abnormal sound that consists of a flow noise that is heard before, between, or after the lubb-dupp or that may mask the normal heart sounds.

Narrowing of the mitral valve by scar formation or a congenital defect

The science of ***hemodynamics*** concerns the relation between ***blood flow***, ***pressure***, and ***resistance***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For fluid flowing through a tube, resistance is influenced by three components: the length of the tube (L), the radius of the tube (r), and the viscosity (ɖ) of the fluid flowing through the tube. The flowing equation, derived by the French physician ***Jean Leonard Marie Poiseuille***, shows the relationship between these factors:

$$R = \frac{8 L \eta}{\pi r^4}$$

Because the value of 8/´ is a constant, the relationship can be rewritten as:

$$R \propto \frac{L \eta}{r^4}$$

This expression says that resistance increases as the length of the tube and the viscosity of the fluid increase but decreases as the radius increases. How significant are length, viscosity, and radius to blood flow in a normal individual? The length of the systemic circulation is determined by the natomy of the system and is essentially constant. The viscosity of blood is determined by the ratio of red blood cells to plasma and by how much protein is in the plasma. Normally, viscosity is constant, and small changes in either length or viscosity have little effect on resistance. This leaves changes in the radius of the blood vessels as the main contributor to variable resistance in the systemic circulation. When the radius of a blood vessel doubles, the resistance increases by 16-fold. Thus, a small change in the radius of a tube will have a large effect on the flow of a liquid through that tube. A decrease in blood vessel diameter is known as vasoconstriction. An increase in diameter of blood vessels is called vasodilation.

The venous system completes the circulatory system; blood from the capillaries is drained into the veins for carrying it back to heart. Thus, veins serve as a blood reservoir, as well as transport passage back to the heart. Veins have large lumen, offering very little resistance to blood flow.

Smaller veins converge into fewer but larger radii vessels, the velocity of blood flow increases as the blood moves toward the heart. Veins also serve as a large blood reservoir and because their storage capacity, they are called as “capacitance vessels”. Veins have large lumen, thinner walls with less smooth muscle than do arteries. As they have abundant collagen tissue, veins have little elasticity in comparison to arteries. Because of these properties, veins are highly distensible or stretchable, and have little elastic recoil. They distend well to accommodate additional amount of blood with only a little rise in venous pressure. Veins with extra amount of blood simply stretch to accommodate without tendency to recoil. Recoil tendency in arteries, drives the blood forward.

When demands for blood are low, the veins can store extra blood as ‘reserve’, because of passive dispensability. In resting condition, the veins contain more than 60% of the total blood volume.

When the stored blood is needed, e.g. during exercise, sympathetic stimulation and other extrinsic factors, drive the extra blood from the veins to the heart so that it could be pumped to the active tissue.

As per Frank- Starling’s Law, increased venous return induces an increase in stroke volume of the heart. If too much blood pools into the veins, cardiac output is abnormally diminished. Therefore, a balance exists between the capacity of the veins, the extent of venous return, and the cardiac output. If more blood remains in the veins instead of being returned to the heart, such storage reduces the effective circulating volume. On the contrary, if venous capacity reduces, more blood returns to the heart, and continues circulating. Therefore, venous return is determinant of effective circulatory blood volume. The total blood volume is influenced by factors that control total ECF volume,

such as salt and water balance. Venous return refers to the volume of blood entering each atrium per minute from the veins. The flow is proportional to the pressure gradient. Since atrial pressure is '0' mm Hg, a small but adequate driving force/pressure promotes the blood flow through large diameter and low resistance veins. Pressure gradient for VR is systemic filling pressure of about 7 mm Hg resulting in venous return of about 5.5 liter/min; if this pressure falls to 5.2 mmHg, VR fall to about 4 liter/min and at pressure gradient of 5 mm Hg, cardiac output is less than 4 liter/min. During exercise, this systemic filling pressure exceeds 10 mm Hg, increasing VR and CO. If atrial pressure becomes increased due to some pathological conditions, the veins-to-atria pressure gradient decreases, reducing VR and causing the blood to dam up in the venous system, e.g. in congestive heart failure. Other than this driving pressure of 7 mmHg, and driving pressure imparted by cardiac contraction, five other factors enhance venous return (VR): venous vasoconstriction by sympathetic activation, skeletal muscle activity, the effect of vein's venous valves, respiratory activity, and the effect of cardiac suction. Most of these factors influence the pressure gradient between the veins and the heart.

Veins are less muscular, have little muscle tone, but venous smooth muscles are richly supplied with sympathetic adrenergic vasoconstrictor fibers. Sympathetic stimulation produces venous vasoconstriction, elevating venous pressure, which in turn increases the pressure gradient to drive more blood from the veins into the right atrium. Even when constricted, the veins still have large diameter and low resistance. Venoconstriction mobilizes the stored blood, enhancing VR by decreasing venous capacity. Less blood coming from the capillaries remains in the veins but continues to flow toward the heart. It is to be noted that arteriolar vasoconstriction reduces blood flow through these vessels, whereas venoconstriction increases flow through these veins, because of reduced capacitance, squeezes out more of the stored blood in the veins, thus increasing blood flow.

Many large veins in the extremities lie between skeletal muscles, so as muscles contract the veins are compressed; this reduces venous capacity, increases venous pressure, squeezing blood in the veins forward toward the heart. This blood pumping action is known as the ‘skeletal muscle pump’, returning extra blood stored in the veins to the heart, during exercise. In exercise, venoconstriction and sympathetic activity also accompanying exercise, further enhances venous return.

The skeletal muscle pump also opposes the gravitational effect on the venous system. When a person is lying down in a bed, the force of gravity is uniformly applied. However, when a person stands erect, gravitational effects are not uniform. The vessels below the heart level are subjected to pressure caused by the weight of the column of blood extending from the heart to the level of the vessel.

This increase in pressure has two consequences; the distensible veins give way under the increased hydrostatic pressure, further distending them, so that their capacity to accommodate blood is increased. Arteries are less distensible, so they do not expand


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is transient drop in the atrial pressure, thus increasing vein-to-atria pressure gradient, so that venous return is facilitated. During ventricular relaxation, a transient negative pressure is created in the ventricle, so that blood is 'sucked in' from the atria and veins; thus the negative ventricular pressure increasing the vein-to-atria-to-ventricles pressure gradient, further enhancing venous return. So heart functions as a "suction pump" for its own filling.

Cardiac output is the amount of blood ejected by either ventricle per minute. The volume of blood returning to the left atrium from the lungs is the same volume, which was released by the right ventricle to the lungs; the output of the right and left ventricles is normally the same.

Cardiac output of a young adult female 67 kg, reclining = about 5L/min. "male of same age & wt = 10% more = 5.5 L/min.

Cardiac Reserve: Cardiac reserve is the difference between the CO at rest and the maximum amount the heart is capable of pumping per minute. Cardiac output is affected by age, changes in posture, and exercise. It may be 20 –25 L/min in exercise and in very severe strenuous exercise in a trained athlete 35 – 40 L/min.

During anytime, the volume of blood flowing through the pulmonary circulation is the same as flowing through the systemic circulation. The two determinants of cardiac output are heart rate (beats/min) and stroke volume (SV) i.e. volume of blood pumped/beat or stroke.

The average HR= 70 beats/min (established by SA Node rhythmicity)

- " SV =70 ml/beat
- " CO = 70 x 70 = 4900 ml/min or close to 5 liter/min

The body's total blood volume averages 5 to 5.5 liters, each ventricle pumps the equivalent amount of blood/minute; right ventricle to the lungs and the left through the systemic circulation.

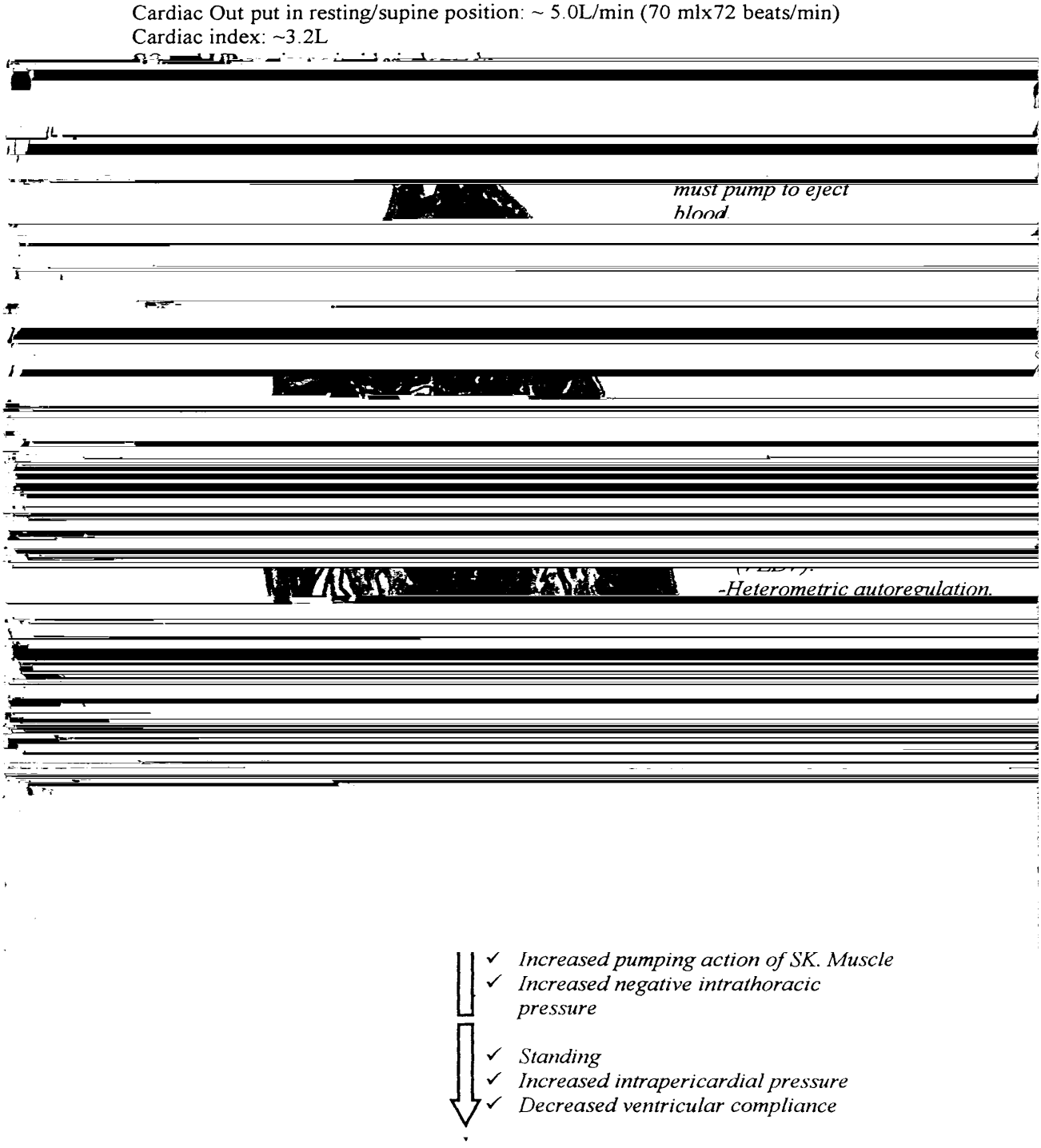

Figure 53. Factors affecting cardiac output.

The parasympathetic nervous system influence on the SA Node is to decrease heart rate; acetylcholine- mediated effect on the permeability of the SA node reducing spontaneous action potential through the following effects;

- Increased potassium permeability hyperpolarizes the SA node membrane because of increased potassium ions efflux, making the inside more negative.
- This increased potassium permeability also opposes the automatic reduction in potassium permeability that initiates depolarization of the membrane to threshold. Thus SA node reaches threshold more slowly and fires signals less frequently, reducing the heart rate. Parasympathetic activation on the AV node reduces its excitability, prolonging the impulse transmission to the ventricles as a result of increased potassium permeability (hyperpolarization), thereby retarding the excitation of AV node. Atrial contraction is weakened by a reduction in the slow inward current carried by calcium, reducing the plateau phase. The parasympathetic has little effect on ventricular contraction. Thus, the heart beats slowly, atrial contraction is weaker, the time between atrial and ventricular contraction is stretched out. These actions are beneficial because parasympathetic controls heart activity in quiet relaxed condition of rest when body is not demanding increase in cardiac output. This is achieved by vagal tone at rest (with heart rate at rest being 70 beats/min, though the inherent rhythmic rate of the SA Node is about 100 beats/ minute.

The sympathetic nervous system controls heart rate in emergency or exercise situation, when there is need for more blood flow; heart rate is increased through effect on the

- Sympathetic stimulation decreases AV node delay, by enhancing the slow, inward calcium ion current.
- Sympathetic stimulation speeds up the spread of the action potential throughout the specialized conduction tissue/pathway
- Sympathetic stimulation increases contractile strength in the atria and ventricles so that heart beats more forcefully and squeezes out more blood; this is by increasing calcium ions permeability, enhancing the slow calcium ions influx and enhancing calcium-dependent excitation-contraction coupling process.

The overall effect of sympathetic stimulation is to increase heart rate, decrease conduction time, and increase force of myocardial contraction. Therefore, parasympathetic and sympathetic effects on heart are antagonistic. Under resting condition parasympathetic dominates. Heart rate is increased by simultaneous stimulation of sympathetic and inhibition of parasympathetic activity. A decrease in heart rate by stimulating parasympathetic and inhibiting sympathetic activity. These two autonomic branches to the heart in turn are primarily controlled by the cardiovascular control centers in the brain stem. Medullary epinephrine too acts on the heart in a manner similar to postganglionic sympathetic neurotransmitter norepinephrine, thus, reinforcing the direct effects of the sympathetic nerves.

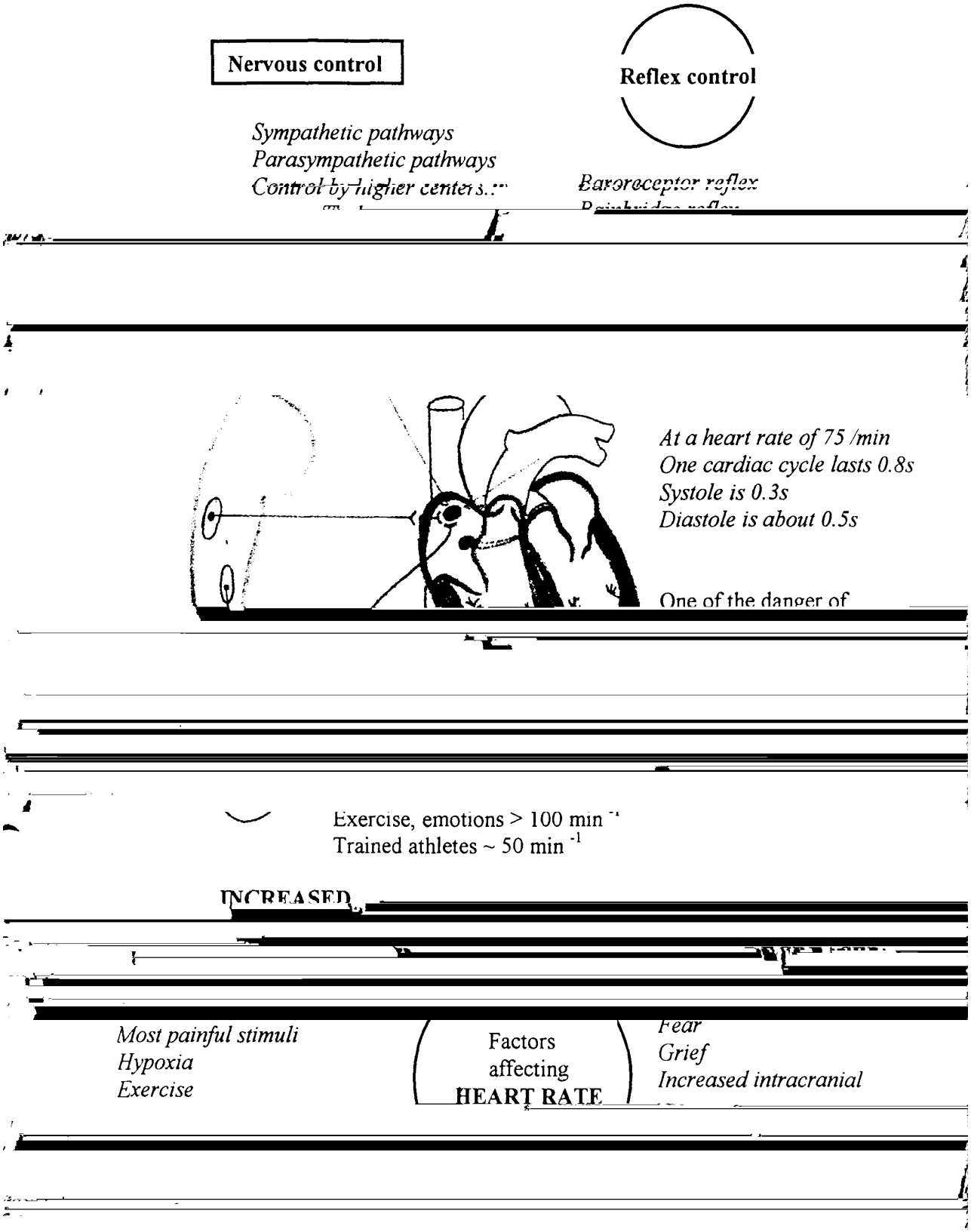

Figure 54. Regulation of the Heart rate.

High blood pressure increases the workload of the heart. During systole, ventricles need to generate sufficient pressure to [illegible]

Figure 55. Factors affecting end-diastolic volume.

Exercise is the most effective way to increase cardiac output. Increase in heart rate, stroke volume, and venous return all contribute to the augmented cardiac output.

- In acute exercise, sympathetic stimulation of the heart and blood vessels and increased venous return from the active muscles are the dominant factors regulating the increase in cardiac output.
- The sympathetic nervous system affects both the inotropic and chronotropic characteristics of the heart
- As a result of the sympathetic stimulat

- Increase in heart rate during exercise is chiefly due to sympathetic stimulation, while there is reduction in vagal nerve discharge.
- During and just before the start of strenuous exercise, there is a marked vasoconstriction of blood vessels in the splanchnic area, shunting blood from the viscera into the thoracic region and increasing venous return to the heart.
- During exercise, sympathetic stimulation of the smooth muscles of the blood vessels increase peripheral resistance and venous return
- The actively contracting muscles during exercise exert pressure on the veins, and, aided by the venous valves, the blood is forced back toward the heart. The end-diastolic volume of the heart is increased by the volume of the blood with which it is filled, stroke volume is increased by Frank -Starling mechanism and the cardiac output is improved. The cardiovascular centers in the brain integrate these responses of the heart and blood vessels.

turn increase contributing to increase in cardiac output, the extent of contribution varies significantly in trained and untrained individuals

- The athlete's heart is usually larger than that of sedentary individuals. Constant and regular training, with the increased workload against which the heart contracts, results in heart muscle compensatory hypertrophy, an increase in size, increase in contractile proteins, myoglobin, and cellular enzyme systems. These biochemical changes increase the inotropic force of the heart, increasing stroke volume and permitting the athlete to achieve the same cardiac output with a slower heart rate.

- The heart rate in an athlete at rest may be as low as 45-50 due to vagal tone, but the increased stroke volume of 100 -110 ml/beat results in normal cardiac output of about

and contributes, along with greater contractile force of the hypertrophied heart, to an enhanced cardiac output.

- In trained athletes, increased stroke volume also appears to help increase in cardiac output. In untrained persons, increased cardiac output is achieved through increased heart rate.

One of the most important adaptations in the bipedal life is the ability to maintain blood pressure in the standing position, despite the fact that the heart and head are

develops if more than 40% of total blood volume is lost if the bleeding occurs more slowly from one to several hours.

High altitude promotes increased red cell production and causes a mild polycythemia; people living at more than 4700 m have red cell count of 6-8 million per cu mm of blood. Acclimatization to high altitude also increases vascularity of the tissues that lowers total peripheral resistance and tries to counteract high red cell count and increased peripheral resistance. Cardiac output is only slightly increased.
In plycythemia vera, the bone marrow becomes malignant and hematocrit may rise from a normal value of 40 – 45% to even 70 –80% blood viscosity rises sharply, peripheral resistance increases, and cardiac output falls.

Anemia decreases viscosity, and together with the vasodilatation due to tissue hypoxia, causes a fall in total peripheral resistance and an increase in cardiac output, so that tissue at rest get enough oxygen, But heart has no reserve to use for the demands of exercise and severe exercise may result in heart failure.

The cardiovascular system is designed to provide widely varying metabolic needs under changing physiological circumstances, without overburdening the heart. Two mechanisms i.e. local control of blood flow matching the metabolic needs - autoregulation and 'neural control' of the resistance of peripheral arterioles, accomplish the response of the vascular system. These two factors:

- Control blood flow and consequently regulate the cardiac output
-

a special function. The organization is not the same, e.g., in the brain, the lungs, and the spleen.

The vessels included in the microcirculation are:

- Terminal arterioles
- Meta -arterioles
- Arterioles
- Arteriovenous anastomoses
- Capillaries
- Post capillary venules

The terminal arterioles are narrow muscular vessels, having a diameter of 35-50 microns and conduct blood directly into the meta arterioles; both the terminal arterioles are the resistance vessels of the microcirculation.

- Are the thin-walled exchange vessels forming a network linkage between narrow meta arterioles and wide-lumen venules.
- Have low velocity of blood flow (0.5 - 0.7 mm/sec but a very large surface area of (e.g. in skeletal muscle 2000 capillaries/mm^2)
- Is the site for the exchange of fluid, nutrients, gases; blood flows only for a very brief period (2 - 5 sec in a capillary 1 - 2 mm long).
- Diameter varies with the functional state of the tissue; narrow in inactive tissue with little or no blood flow; there is an autoregulation of blood flow in the tissue are narrower they pass through capillaries.
- Are of three types, according to their structure and function; all capillaries have single layer of endothelial cells on a thin basement membrane of glycoprotein and do not have muscles or elastic fibers.

(skeletal muscle): entire circumference is made up of one endothelial cell, ends overlapping each other, forming a tight seal; many intracellular vesicles take part in transport of materials.

: Have a very thin area of endothelial membrane stretched between adjacent endothelial cells. These fenestrations are not open holes but are closed by a thin diaphragm; these types are found in the capillary tuft /glomerulus of the kidney, in endocrine glands, and in the intestine providing very high permeability. There is no diaphragm between the adjacent endothelial cells that ensures rapid passage of substances through the capillaries e.g. in the kidney.

are more wide, more irregular in size and shape than capillaries; sinusoid structure is present in liver and the spleen; in the liver, the sinusoids are lined by an incomplete layer of fenestrated endothelial cell, which increases permeability still preventing passage of many small molecules, such as albumin. Liver sinusoids are also lined by macrophages.

Postcapillary venules collect blood from the capillaries, have no muscle and elastic tissue like the capillaries; are wider than the capillaries (15-20 microns); some exchange seems to occur in these vessels; these vessels are very susceptible to inflammation.

According to the Poiseuille's Law, viscosity is one of the parameter of resistances to flow. Laminar flow is a characteristic of blood flow in large vessels of the circulation; the laminae move parallel to each other in longitudinally oriented concentric sleeves, each sleeve moving at a different rate. Not all the layers move at the same rate, but rather at different rates. The viscosity of blood depends on the hematocrit. In leukemia and polycythemia, blood viscosity may rise markedly, increasing systemic and pulmonary resistance and consequently raising blood pressure. In anemia, viscosity falls.

The bore of the vessel also affects viscosity; it decreases as the vessel diameter falls below 150 micron. Blood viscosity may be half in capillaries to the large arteries. This

is increase in viscosity as blood velocity decreases, an effect probably due to increased adherence of the red cells to each other.

If the velocity of flow is very high, or if the blood has to pass an obstruction vessel, flow becomes turbulent so that eddy currents are formed. Turbulence increases vascular resistance significantly. It is important in determining blood pressure.

The mean velocity of blood flow is inversely proportional to the cross-sectional area provide that the total volume of fluid flowing through each segment is constant.

Blood volume is very unevenly distributed through the various vascular segments even though the volume flowing through is relatively constant. The veins have more than 75% of total blood volume. Thick, elastic arteries and arterioles contain 18%, capillaries hold only 3-4 percent of blood volume, while the heart contains about 7% blood pressure is almost inversely proportional to volume distribution and vascular resistance. In the large aorta resistance is very low and the MABP is about 100 mmHg. There is little change in pressure in large arteries, but resistance increases rapidly in small arteries, causing the pressure to drop to about 70 mm Hg at the beginning of the arterioles. The arterioles have the greatest resistance of the systemic circulation, so that by the time blood reaches the capillaries, pressure has dropped to about 30 mmHg. Arteriolar resistance is profoundly affected by sympathetic stimulation.

- The applied pressure (by inflated cuff) is transmitted through the tissues of the arm

method usually gives readings of SBP about 25mmHg lower than the 'true' SBP given by the direct method. The DBP reading by the indirect method is on average 8mmHg higher. Although indirect sphygmomanometry does not give an accurate (absolute) measurement of either SBP or DBP, yet the indirect method is of great practical value in medicine.

Many attempts have been made to define normal values for blood pressure but all such efforts have been unsatisfactory. That mythological polymath "every schoolboy" knows that 'normal' human blood pressure is 120/80mmHg. For an adult under certain conditions he would be right, but it is quite wrong to adopt 120/80 mmHg as the normal standard for a resting child, a pregnant woman in midterm or an elderly man.

The mean arterial pressure is the average of all the pressures measured millisecond over a period of time. It is not equal to the average of systolic and diastolic pressure because the pressure remains nearer to the diastolic pressure than to the systolic pressure during the greater part of the cardiac cycle. MAP is defined as being approximately equal to the diastolic pressure plus

One-third of the pulse pressure:

relative density of mercury); this is 90mmHg, so arterial pressure in the foot is increased to approximately 180mmHg above atmosphere pressure. Conversely, pressure is reduced in the arteries above the heart level and is only 60mmHg or so in human brain during standing.

Upon moving from lying to standing, arterial pressure changes at heart level due to changes in cardiac output and peripheral resistance. A transient fall in aortic pressure (which can produce a passing dizziness) is followed by a small but sustained reflex rise.

Anger, apprehension, fear, stress, and excitement are all potent 'pressor' stimuli, i.e. they elevate blood pressure. Even a telephone conversation raises pressure by around 10mmHg. Compared with the relaxed states, while attending a meeting often raise it by 20mmHg. Since a visit to the doctor is stressful for many patients, a solitary high pressure measurement is not itself prValsalvaul feune tress


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least in the heart, brain, and kidney. Vasomotor tone is the tension basically to maintain arterial blood pressure; increase in tone increases blood pressure; decrease in tone lowers blood pressure.

In order to maintain an adequate coronary and cerebral blood flow while supplying extra blood to the muscles during heavy exercise, blood pressure must be maintained or increased and blood shifted from the splanchnic and renal areas to the active muscles by changes in the resistance of these vascular beds. This is due to changes in the caliber of the blood vessels.

brain, causing vasodilatation, ensuring that these vital organs are not deprived of blood during stressful situations that induces vasoconstriction elsewhere.

The blood vessels of the skeletal muscles also receive sympathetic cholinergic postganglionic fibers stimulating cholinergic receptors, resulting in vasodilatation, just prior to strenuous exercise, shunting blood to the muscles that will be most active.

Postganglionic cholinergic parasympathetic fibers appear to be significant in few tissues; the genital erectile tissues (penis and clitoris) and clitoris glands, such as the salivary glands, where acetylcholine evokes production of vasodilator bradykinin,

The regulation of blood flow thorough the microcirculation is influenced by neural factors as well as some provocative substances that modify vasomotor tone. Some of these vasoactive substances reach the tissues through the circulating blood and others are locally produced by the tissues themselves. Together the neural and vasoactive factors balance vasoconstrictor and vasodilation in specific vascular beds.

Norepinephrine though present in small concentration is generalized vasoconstrictor; its effect is more important as a neurotransmitter at nerve endings. Epinephrine act either as a vasoconstrictor or as vasodilator depending on their concentration, the previous vasomotor tone, and the specific receptors present on the smooth muscle cells of a particular region. It is vasodilator in the skeletal muscle and liver and the heart, elsewhere it has a vasoconstrictor effect.

The hypothalamic peptide vasopressin is vasoconstrictor. Angiotensin II found in blood is another very potent generalized vasoconstrictor. Damaged tissues produce histamine, which are an amine and a very potent vasodilator substance. Most of the histamine is released from mast cells and eosinophils. In damaged tissues histamine causes vasodilatation and a marked increase in capillary permeability and tissue edema. Many tissues, such as brain and the gastrointestinal tract release different peptides, such as glucagons.

These peptides cause vasodilatation. Another peptide bradykinin is very potent vasodilator and also increases capillary permeability. Bradykinin also cause release of local prostaglandin that act either as vasodilator or as vasoconstrictor. Serotonin, released by activated platelets, is a vasoconstrictor that also releases nor epinephrine from sympathetic nerve endings.

Almost all of them are vasodilators, produced by actively metabolizing tissues, which themselves ensure increased blood flow in active tissues. These substances include: hydrogen, and potassium ions, inorganic phosp cra, wcarbo daioxde seo


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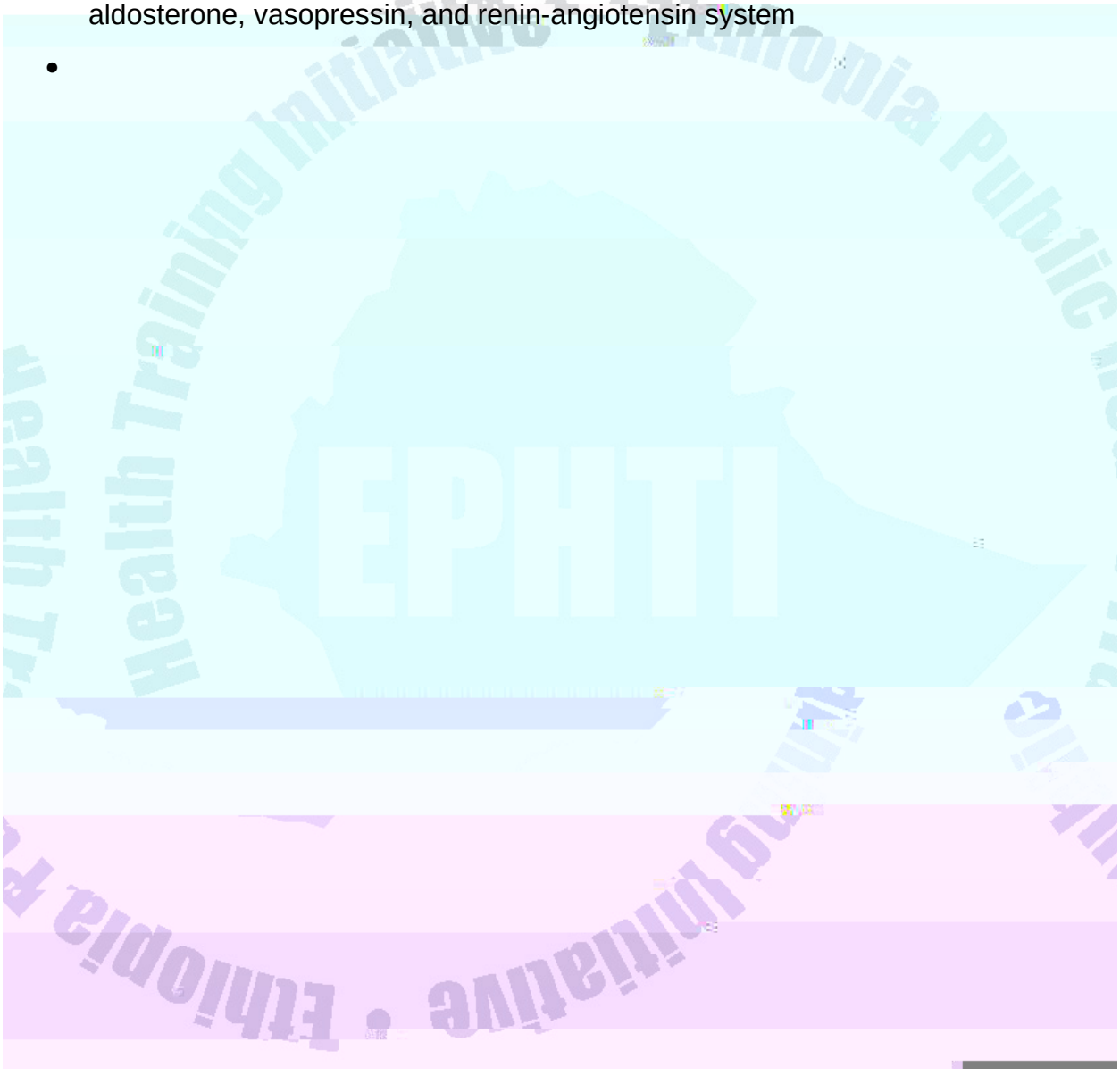
These features are evident in fear, rage, or excitement. Regulation of ABP is accomplished by controlling cardiac out put, total peripheral resistance, & blood volume. Mean ABP Is the main driving force for propelling blood to the tissues. It has to be maintained for the following reasons:

- It must be high enough ensuring sufficient driving pressure in the capillaries where exchange of fluid occurs across the wall;
- Without sufficient pressure, brain & other tissues will not get enough blood flow, no matter what local auto regulation are made;
- This pressure must not be too high to create extra work-load for the heart & increase the risk of rupturing blood vessels.

The two determinants of ABP are cardiac output and total peripheral vascular resistance & number of factors that in turn, determine CO & TPR. Cardiac output primarily influences the SBP & the TPR is a major determinant for DBP.

Same neural & humoral factors are involved in short-term blood pressure regulation vily6t

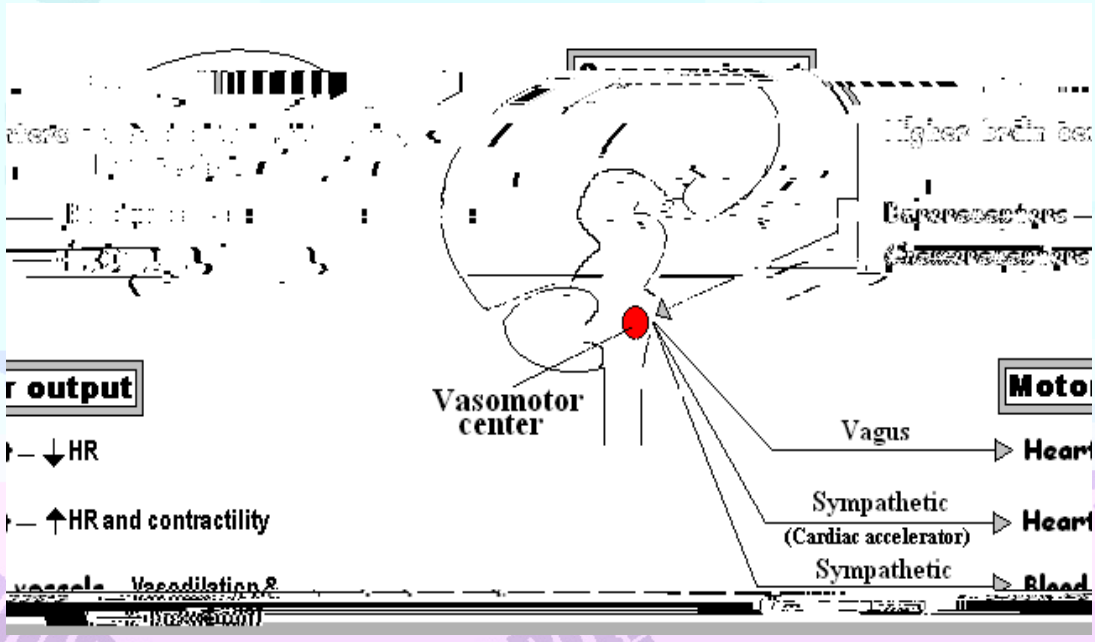
- VR increases by sympathetic-induced venoconstriction. the skeletal pump, the respiratory pump, & the cardiac suction.
- The effective circulating blood volume too influences CO
- Short-term shift between vascular & interstitial fluid compartment
- Long- term: salt balance & water balance, which is hormonally controlled by aldosterone, vasopressin, and renin-angiotensin system
-



receptors are fine nerve endings present in the arterial wall that are stimulated by tension/stretch of the arterial wall evolved by blood pressure.

consists of diffuse group of cells in the lower third of the pons and upper part of medulla.

- Vasoconstrictor area lies in the medulla and cells in this region continuously fire sympathetic vasoconstrictor nerves to maintain vasomotor tone (arteriolar tone)
- Vasodilator area is not clearly defined and may be acting chiefly to inhibit the vasoconstrictor area, there by allowing vasodilatation.



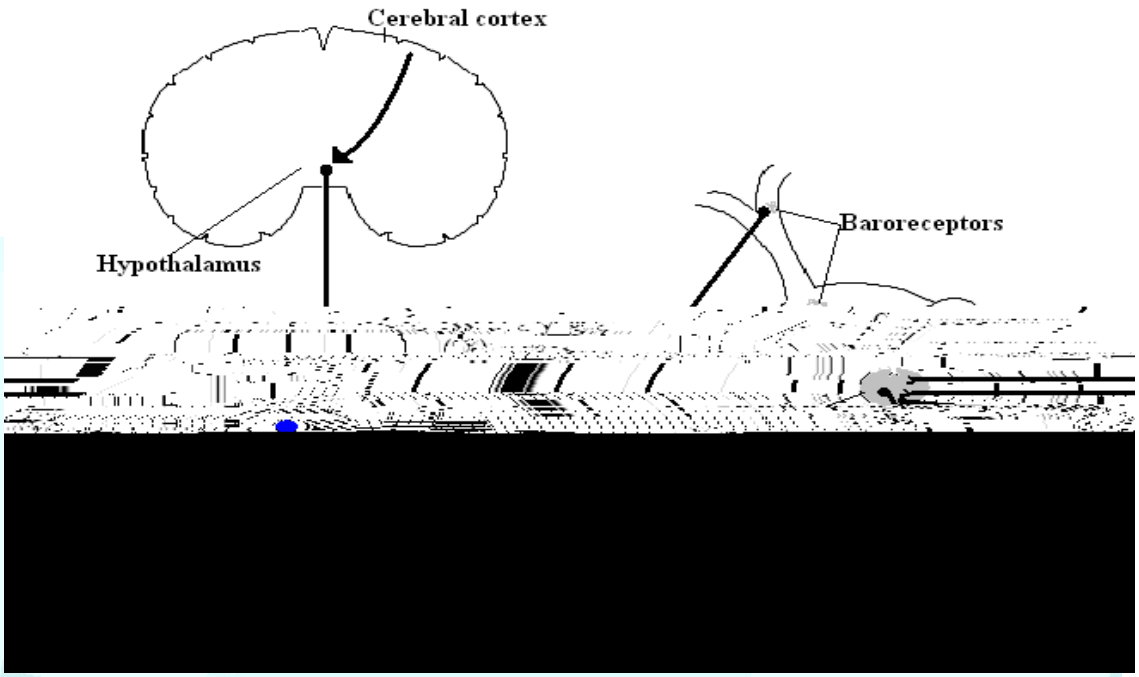


Figure 56, A&B. Vasomotor center: its location, input from the higher centers and output to the effector.

The cardiac center also consists of two functionally different areas. The cardiac inhibitory center lies in medulla and includes the dorsal nucleus of vagus. It slows the heart rate and decreases the contractility of the heart through the impulses sent through the efferent fibers of the vagii.

These areas functions reciprocally. They are completely autonomous. They are

lungs, arterial chemoreceptors (Carotid and aortic bodies), and input from skeletal muscles.

The high-pressure baroreceptors are the most important source of peripheral input. Afferent pathway from bar receptors to cardiac center:

skeletal muscle which promote immediate increase in blood flow to the muscles to be used, sympathetic vasoconstriction else where which increase blood pressure, increase

responses influence blood pressure though they primarily are concerned with the regulation of other functions. Some of these influence ABP away from their normal values temporarily, overriding the baro- receptor reflex to achieve a particular goal.

- Left atrial volume (low pressure baroreceptors) and hypothalamic osmoreceptors are primarily important in water and salt balance in the body; thus, they affect the long-term regulation of ABP by controlling the plasma volume (blood volume).
- Chemoreceptors (carotid and aortic bodies) located in the carotid and aortic arteries are sensitive to hypoxia or low levels of pH in the blood. The chemorecepor function is to reflexly increase respiration to bring more oxygen or to blow off acid-forming carbon dioxide, but they also reflexly increase blood pressure by sending stimulatory impulses to the cardiovascular centers.
- Cardiovascular responses associated with certain behavior and emotions are mediated through the cerebral cortex-hypothalamus pathways and appear to be pre-programmed
- Sympathetic fight-or-flight responses
- Characteristic marked increase in cardiac output and blood pressure associated with sexual response.
- Pronounced cardiovascular changes accompanying exercise
- Sustained increase in skeletal muscle blood flow
- Significant increase in cardiac output
- Decrease in total peripheral resistance due to widespread vasodilation
- Modest increase in ABP

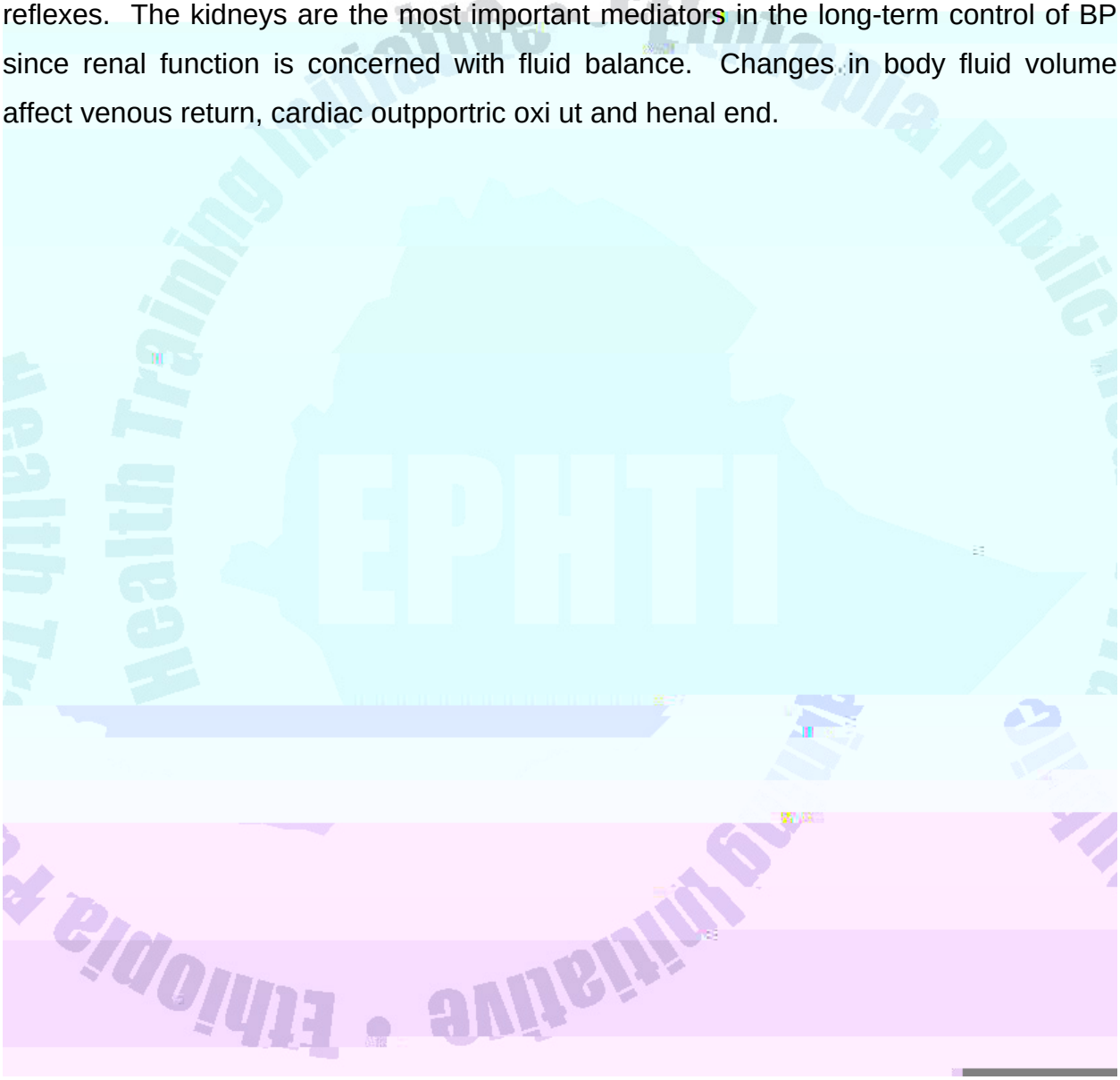
It happens with adaptation of exercise and in early stages

Hypothalamic control over coetaneous arterioles for the purpose of temperature regulation, takes precedence over maintaining ABP. Blood pressure may fall when eliminating excess heat from the body even though baroreceptors reflex is for coetaneous vasoconstriction.

Vasoactive substances released from endothelial cells play a role in the regulation of ABP - endothelium-derived relaxing factor (EDRF) which is nitric oxide (NO).

: Long-term regulation of blood pressure involves many factors in addition to the integrated neural control of cardiovascular reflexes. The kidneys are the most important mediators in the long-term control of BP since renal function is concerned with fluid balance. Changes in body fluid volume

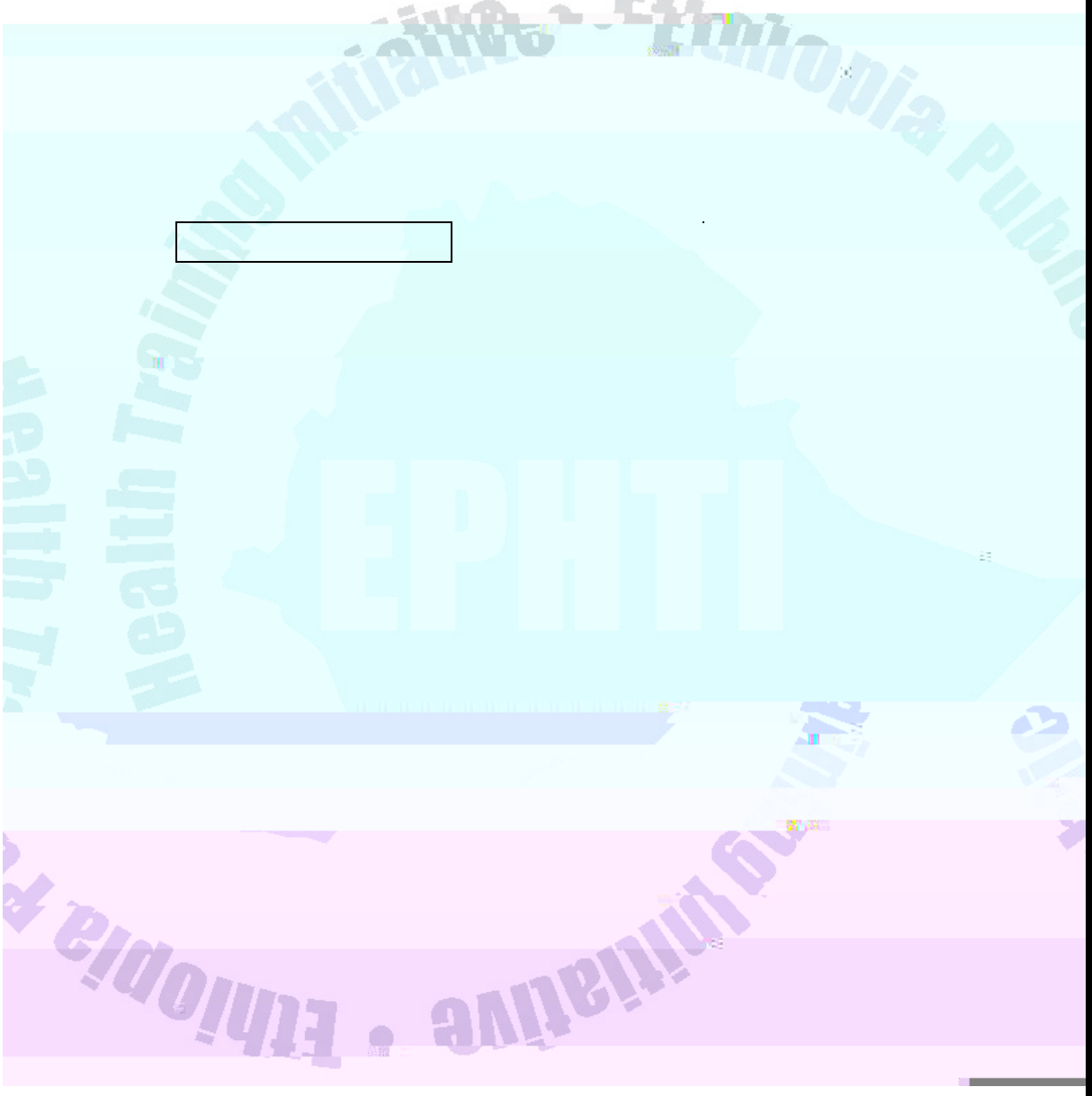
of affect venous return, cardiac outpportric oxi ut and henal end.



:- Renin is secreted by the Juxtaglomerular cells found in the walls of renal afferent arterioles. Its secretion is controlled by the following factors:

- The juxtaglomerular cells not only secrete rennin but also act as baroreceptors responding to these changes in afferent arterioles blood pressure. A fall in systemic blood pressure, reduces the pressure in the afferent arterioles, reduces the wall stretch, and JGC respond by secreting renin.
- In the distal tubule are present specialized cells known as 'macula densa', that act as chemoreceptors, responding to changes in the amount of sodium filtered and /or chloride delivered into the renal tubules. The macula densa responds to sodium excretion and by some unknown mechanism, feedback this information to the juxtaglomerular cells, causing a rise in renin secretion, and corresponding retention - a befitting response to increased sodium excretion in the urine.
- Increased sympathetic stimulation increases renin secretion. It is an indirect effect on the JG cells due to arteriolar vasoconstriction. Circulating catecholamines too would produce rennin secretion.
- Angiotensin, itself exerts a 'negative feedback' effect on rennin secretion.

- Angiotensin-II is the most potent vasoconstrictor, but very short-acting. Its vasoconstrictor effect on arteriolar smooth muscles causes a sharp rise in peripheral resistance and hence arterial blood pressure.
- Angiotensin – It is the most potent stimulus for the release of aldosterone by the zona glomerulosa cells of the adrenal cortex. Aldosterone acts on the distal renal tubule to decrease the amount of NaCl excreted in to the urine. Sodium and water in blood increase. Thus blood volume rises, blood pressure increases, & rennin secretion is inhibited.
- Angiotensin-II stimulates hypothalamus areas controlling thirst and drinking behavior to increase the water intake
- Angiotensin-II stimulates 'Vasomotor centers in the brain' to increase blood pressure via stimulating sympathetic and inhibiting parasympathetic pathways.



‘Shock’ is a popular term used by the layperson to describe a sudden and severe setback due to any reason. But circulatory shock or ‘cardiovascular collapse’ is characterized by a reduction in circulatory blood volume and results in inadequate tissue perfusion. Circulatory shock is the final common pathway for a number of potentially lethal clinical events including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis.

This is due to an absolute reduction in blood volume.

(a) Loss of blood: The fluid lost may be blood and may be lost from the body, as in hemorrhage. Hemorrhage generally leads to shock if more than 15 to 20% of the blood volume has been lost. With smaller losses, the compensatory mechanisms of the body are generally able to prevent shock.

(b) Loss of water and electrolytes: Alternatively, the fluid lost may be water and electrolytes, as in diarrhea and vomiting.

(c) Loss of plasma: The fluid lost may be plasma, and lost to the circulation but


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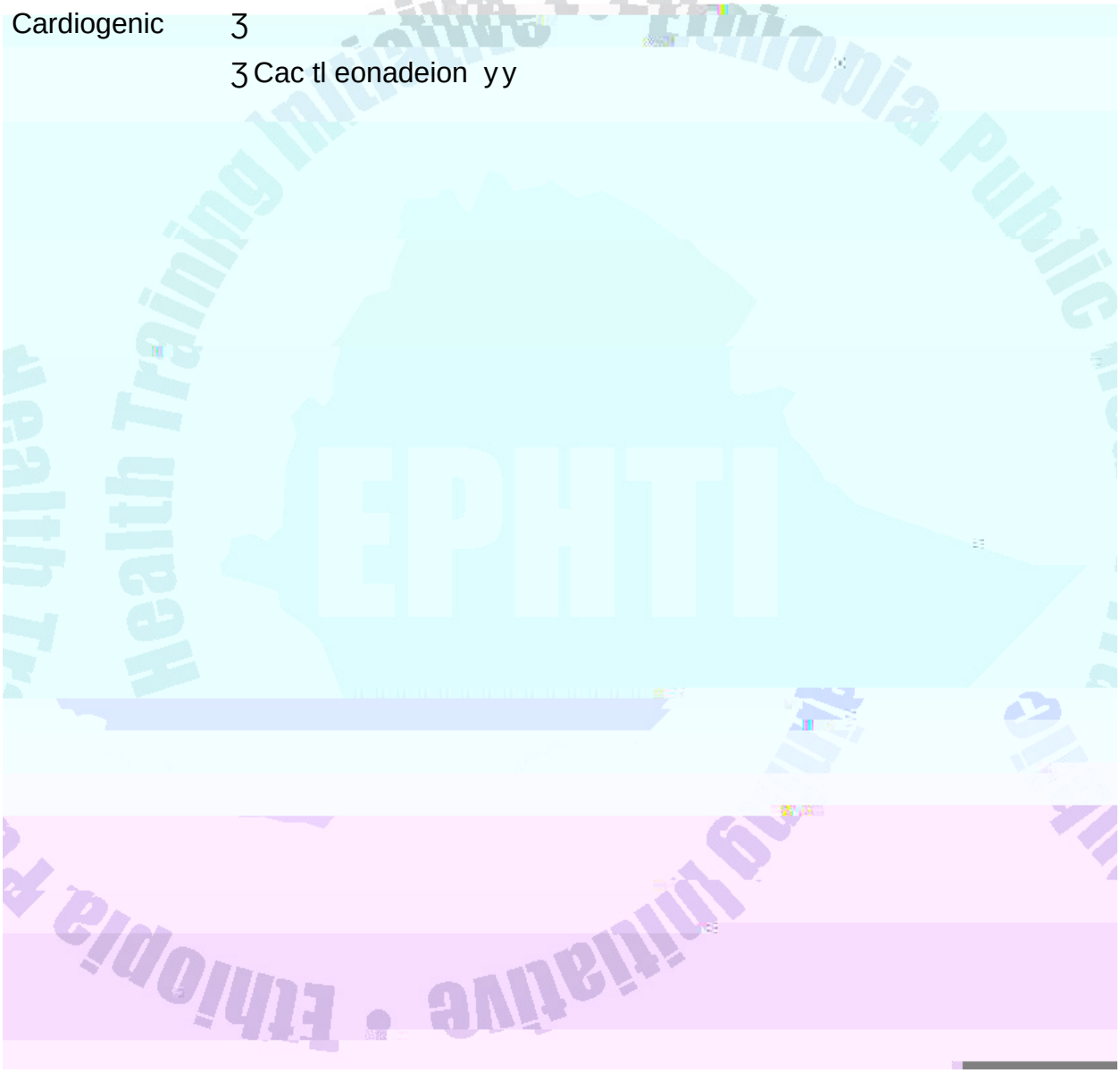
Table 18.Three major types of shock

Type of shock	Clinical examples	Principal mechanisms
Cardiogenic	3 Myocardial infarction 3 Ventricular rupture 3 3 Cac tl eonadeion y y	

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additional salt is added to our food throughout life, the blood pressure will stay constant throughout our life. Since this hypothesis cannot be widely tested on human beings at present stage of our civilization, we have to accept some rise in blood pressure as a part of the aging process. Although the change is gradual, and there is no sharp dividing line between the normal and high blood pressure, an arbitrary dividing line is required for clinical use. The arbitrary upper limits are 140 and 90 mmHg for systolic and diastolic blood pressure respectively. A mean arterial pressure greater than 110 mmHg under resting conditions usually is considered to be hypertensive.

The lethal effects of hypertension are caused mainly in three ways:

(1) Excess workload on the heart leads to early development of congestive heart disease, coronary heart disease, or both, often causing death as a result of heart attack.

(2) Cerebral infarct (“stroke”): The high pressure frequently ruptures a major blood vessel in the brain, followed by death of major portions of the brain; this is a cerebral infarct. Clinically it is called a “stroke.” Depending on what part of the brain is involved, a stroke can cause paralysis, dementia, blindness, or multiple serious brain disorders.08 Tc.0orend

Hemodynamic

Neural

Humoral

Renal

Arterial hypertension occurs when the relationship between blood volume and total peripheral resistance is altered. For many of the secondary forms of hypertension, these factors are reasonably well understood. For example, in renovascular hypertension, renal artery stenosis causes decreased glomerular flow and decreased pressure in the afferent arteriole of the glomerulus. This (1) induces renin secretion, initiating angiotensin II-induced vasoconstriction and increasing peripheral resistance and (2) through aldosterone mechanism increases Na reabsorption and, therefore, blood volume. Several factors may then be postulated to contribute to the primary defects in essential hypertension, encompassing both subtle genetic and environmental influences:

(a) Reduced renal sodium excretion

(b) Vasoconstrictive influences

(c) Environmental factors

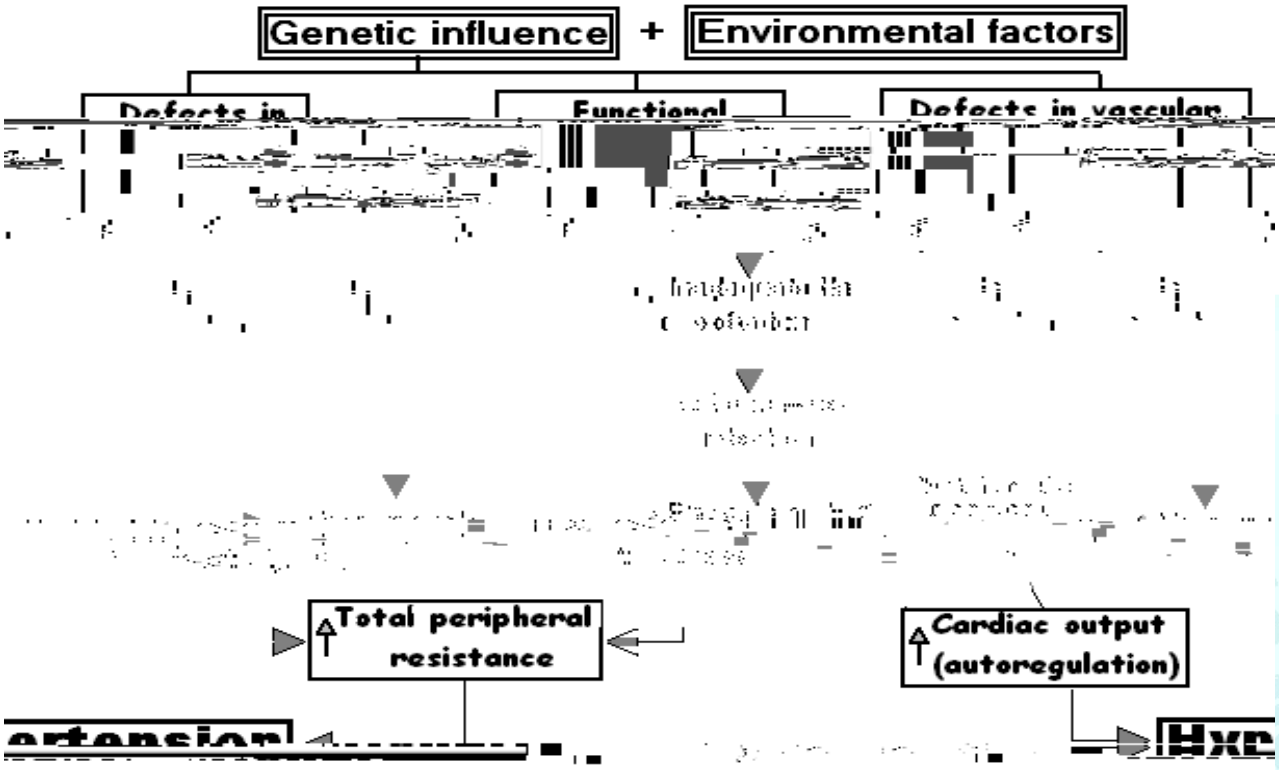

Figure-58 : Hypothetical scheme for the pathogenesis of essential hypertension

Risk factors

(1) Family history

(2) Advancing age

(3) Race

(4) High salt intake

(5) Obesity

(6) Excess alcohol consumption

(9) Use of oral contraceptive drugs

Only 5% to 10% of hypertensive cases are currently classified as secondary hypertension- that is, hypertension due to another disease condition. The disease states that most frequently give rise to secondary hypertension are:

(1) Renal disease
(2) Vascular disorders
(3) Endocrine disorders
(4) Acute brain lesion.

Acute glomerulonephritis
Chronic renal disease
Polycystic disease
Renal artery stenosis
Renal vasculitis
Renin-producing tumors

Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism)
Exogenous hormones (glucocorticoids, estrogen, sympathomimetics)
Pheochromocytoma
Acromegaly
Hypothyroidism (myxedema)
Hyperthyroidism
Pregnancy-induced

Coarctation of aorta
Polyarteritis
Increased intravascular volume
Increased cardiac output
Rigidity of the aorta

Psychogenic

Increased intracranial pressure

Sleep apnea

Acute stress, including surgery

Davenport HW. The ABC of acid-base chemistry

Dougherty WM. Introduction to haematology

Gordon AS. Blood cell physiology

Platte WR. Color atlas and Textbook of haematology

Berne RM and MN Levy. Cardiovascular Physiology; 6th ed St Louis: C.V. Mosby, 1991.

Folkow B and E Neil. Circulation

Guyton AC, CE Jonesand TG Coleman. Circulatory physiology, cardiac output and its regulation.

Randall W. Neural regulation of the heart

Smith JJ and JP Kampine. Circulatory physiology, the essentials.

Describe the functional structure of haemoglobin and its degradation related to bilirubin metabolism.

Discuss the regulation of erythropoiesis

Discribe the functions of different types of leukocytes

Discuss leucopoiesis

What are physiological responses in hemostasis? - Role of platelets; Intrinsic, extrinsic and final common pathway in coagulation; Fibrinolysis.

Discuss the balance of clotting and anti-clotting mechanism

Describe conduction tissue of the heart and origin and spread of cardiac impulse

Describe the events of cardiac cycle

Discuss cardiac cycle:- Factors influencing cardiac output ; venous return; Factors influencing heart rate, myocardial contractility and stroke volume.

Discuss the regulation of arterial blood pressure: Short term control; long term control; role of hormones.

Discuss microcirculation of blood flow: Myogenic and metabolic autoregulation

Atrioventricular node: a small bundle of specialized cardiac cells located at the junction of the atria and ventricle serving as the only site of the electric contact between the atria and ventricle.

Atrioventricular valve: Value that permits the flow of blood from the atria to the ventricle during filling of the heart but prevents back flow from the ventricles to the atria during the emptying of the heart.

Atrium (Atria, plural): an upper chamber of the heart that receives blood from the veins and transfers it to the ventricle.

Autonomic Nervous system: the portion of the different division of the peripheral nervous system that innervates smooth muscles and cardiac muscle and exocrine glands; composed of two divisions: the sympathetic and parasympathetic nervous system.

Axon hillock: the first portion of a neuronal axon, the site of action potential in most neurons.

Baroreceptor reflex: an autonomically mediated reflex response that influence the heart and blood vessels to oppose change in mean arterial blood pressure.

Bundle of His: a tract of specialized cardiac cells that rapidly transmits an action potential down the interventricular septum of the heart.

Baroreceptor: receptor located within the circulatory system that monitors blood pressure.

B- lymphocytes (B cells): white blood cells that produce antibodies against specific targets.

Basophils: white blood cells that release histamine in allergic responses and heparin that removes fat particles from the blood.

Body system: a collection of organs that perform related functions essential for survival of the whole body, e.g. the digestive system.

Calmodulin: intracellular calcium-binding protein that upon activation is important in smooth muscle contraction.

Cardiac cycle: one period of systole and diastole.

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Endothelial derived relaxing factor (EDRF): a local chemical mediator CNO, nitric oxide, released from the endothelia cells lining an arteriole that diffuses locally to cause relaxation of the arteriolar smooth muscle in the vicinity.

Endothelium: the thin single celled layer of epithelial cells that lines the entire circulatory system.

End-plate potential (EPP): The gradual receptor potential that occurs at motor end plate of skeletal muscle in response to binding of acetylecholine

End-systolic volume (ESV): the volume of blood in the ventricle at the end of systole, when emptying is complete.

Eosinophils: white blood cells that are important in allergic response in combating parasitic infections.

Erythropoiesis: Red cell production by the bone marrow

Erythropoietin: the hormone released from the kidneys in response to hypoxia; stimulating Erythrocyte production.

Excitable Tissue: Tissue capable of producing electrical signals when excited includes muscle and nerve.

Graded potential: a local change in membrane potential that occurs in varying grades of magnitude; serves as short distance electric signals in Excitable Tissues.

Granulocytes: Leukocytes that contain granules such as neutrophils, eosinophils and basophils.

Heart failure: an inability of the cardiac output to keep pace with the body's demands for supplies and for removal of wastes.

Helper T- cells: T- cells enhancing the activity of other immune response effector cells.

Hematocrit: Percentage of blood cell volume

Hemoglobin: A large iron-bearing molecule transporting O_2 and CO_2.

Hemostasis: the stoppage of bleeding from injured vessel.

Hyperpolarization: an increase in membrane potential from resting potential, becoming even more negative.

Hypertension: sustained, above normal mean arterial blood pressure.

Hypotension: sustained, below normal mean arterial blood pressure.

Hypoxia: insufficient oxygen at cellular level.

Integrating center: A region that determines efferent output based on processing of afferent input

Interleukin-I: Multipurpose chemical mediator released from macrophages

Interleukin-II: a chemical mediator secreted by T-helper cells that augument the activities of all T cells.

Internal environment: The body extracellular fluid region having plasma and interstitial fluid.

Left ventricle: the heart chamber that pumps blood in to the systematic circulation.

Lymphocytes: white blood cells that provide immune defense against target cells.

Lysosome: Cell organelles having powerful hydrolytic enzymes that destroy unwanted material within the cell.

Macrophage: large tissue bound phagocytic cells

Mean arterial blood pressure: the pressure responsible for driving blood forward through the arteries in to the tissues throughout the cardiac cycle.

Repolarization: return of membrane potential to resting potential following depolarization.

Ribosomes: special plexus that synthesize proteins.

Right atrium: the heart chamber that receive venous blood from the systemic circulation.

Right Ventricle: the heart chamber that pumps blood in to the pulmonary circulation.

Saltatory condition: propagation of action potential in a myelinated fiber with the impulse jumping from one node of Ranvier to another.

Sarcoplasmic reticulum: reservoir of ionic calcium

Second messenger: an intracellular chemical messenger activated by extracellular chemical that triggers preprogramed biochemical events, resulting in control of cellular activity.

Signal transduction: The sequence of events, which carry signals from first chemical messenger conveyed to the cell.

Sinoatrial (SA) node: a small specialized autorhythmic region in the right atrial wall of the heart that has the fastest rate of the spontaneous depolarization and serves as the normal pace maker of the heart.

Stroke volume (SV): the volume of blood pumped out of each ventricle with each contraction or beat of the heart.

Synapse: specialized junction between two neurons.

T-lymphocytes: White cells involved in immune response.

Vasoconstriction: the narrowing of a blood vessel lumen as a result of contraction of the vascular circular smooth muscle.

Vasodilatation: the enlargement of a blood vessel lumen as a result of relaxation of the vascular circular smooth muscle.

Vein: A vessel that carries blood toward the heart.

Venous return: the volume of blood returned to each atrium per minute from the veins.

Ventricle: a lower chamber of the heart that pumps blood in to the arteries.

ECG: electro cardiogram

EDV: end diastolic volume

EPSP: Excitatory post-synaptic potential

IPSP: inhibitory post-synaptic potential

After this chapter the student is expected to:

- relate the structural organization of the respiratory system to its function
- describe the functional importance of the intraplueral fluid , the parietal and visceral pleura
-

prostaglandins and epinephrine. The lungs are also responsible for protecting the body from inhaled particles.

Function of the respiratory system is the exchange of O_2 and CO_2 between the external environment and cells of the body.

Functionally, the respiratory air passages are divided into two zones: a conductive zone and a respiratory zone. The airway tree consists of a series of highly branched hollow tubes thatdecrease in diameter and become more numerous at each branching. Trachea, the main airwayin turn branches into two bronchi, one of which enters each lung. Within each lung, these bronchi branch many times into progressively smaller bronchi, which in turn branch into terminal bronchioles analogous to twigs of a tree. The terminal bronchioles redivide to form respiratory bronchioles, which end as alveoli, analogous to leaves on a tree. (see fig. 59)

The conducting zone includes all of the anatomical structures through which air passes before reaching the respiratory zone. The conducting zone includes all of the anatomical structures through which air passes before reaching the respiratory zone. The conducting zone carries gas to and from the alveoli, i.e., it exchanges air between the alveoli and atmosphere. The conducting zone of the respiratory system, in summary consists of the following parts:

Mouth Ÿ nose Ÿ pharynx Ÿ larynx Ÿ trachea Ÿ primary bronchi Ÿ all successive branches of bronchioles including terminal bronchioles.

Regardless of the temperature and humidity of the atmosphere, when the inspired air reaches the respiratory zone it is at a body temperature of 37^{o} C (body temperature) and it is saturated with water vapor. This ensures that a constant internal body temperature will be maintained and that delicate lung tissue will be protected from desiccation.

Mucous secreted by the cells

Figure 59. Structure of the airway

Pulmonary blood flow is the cardiac output of the right heart. It is delivered to the lungs via the pulmonary artery. Pulmonary capillaries form dense network around the alveoli. Pulmonary blood flow is not distributed evenly in the lungs because of gravitational effects. When a person is standing, blood flow is lowest at apex (top) and higher at base (bottom) of lungs. When a person is in supine (lying down), position gravitational effects disappear. As in other organs, regulation of blood flow is accomplished by altering arteriolar resistance

Bronchial circulation is the blood supply to the conducting airways & is a small fraction of total pulmonary blood flow.

. (see figure 60)

volume expired or inspired with each breath at rest


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even may increase. In obstructive lung disease (e.g. asthma), FEV_1 is reduced more than FVC and ratio of FEV_1/FVC is decreased. (see fig. 61)

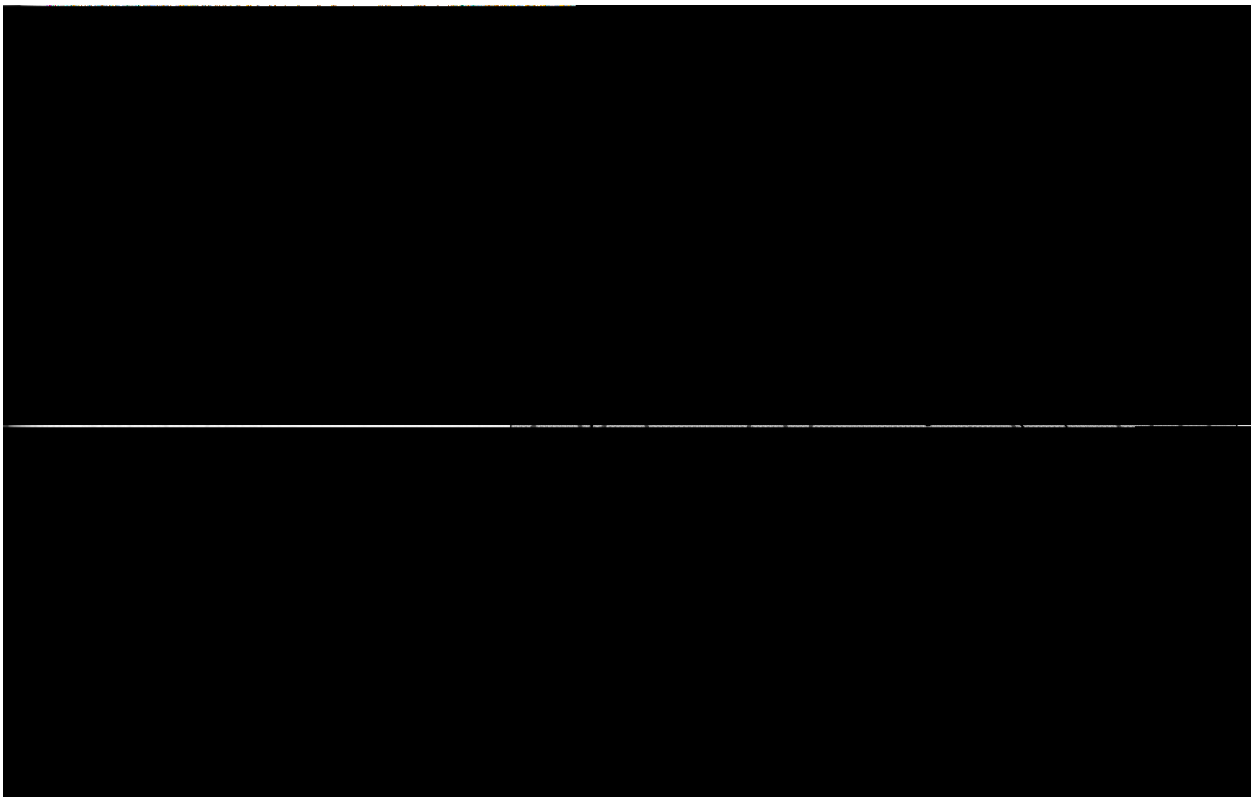

Figure 60. Lung volumes and capacities.

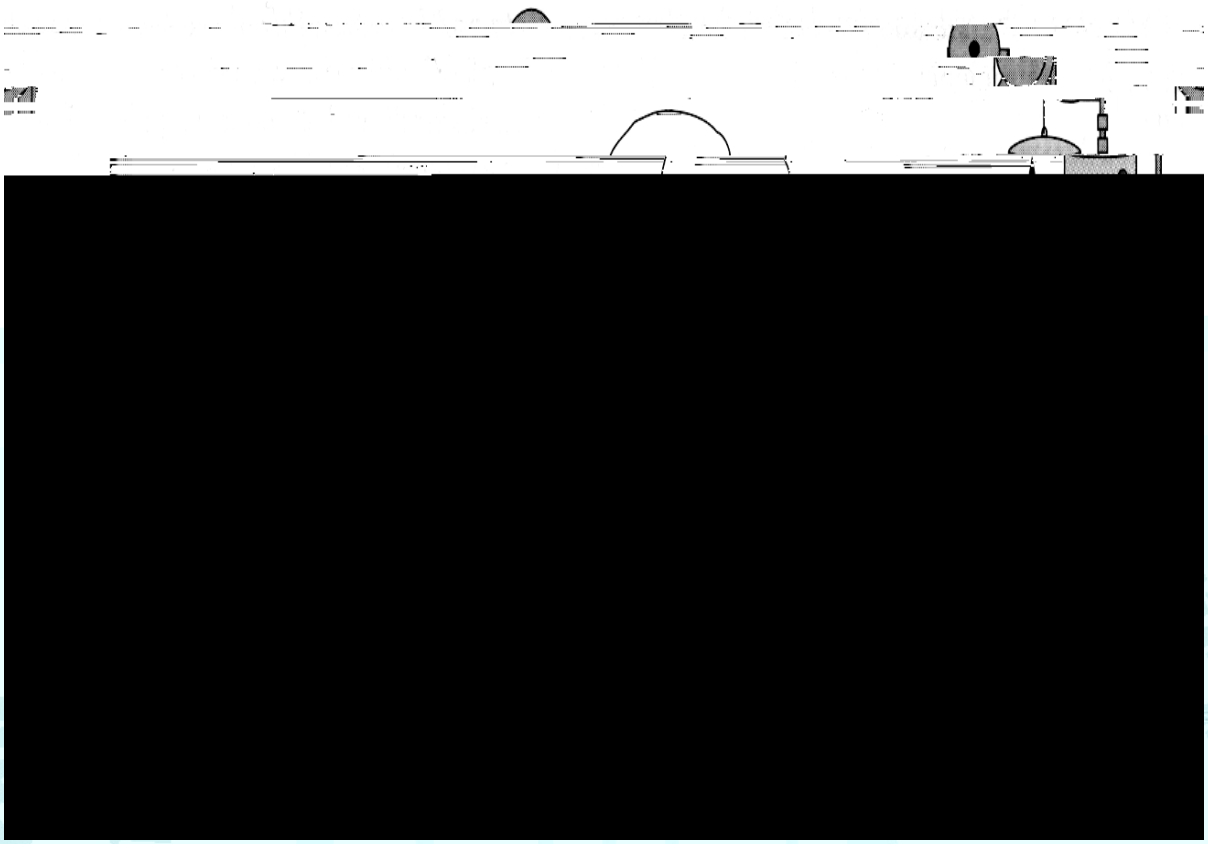

Figure 61. Measurement of lung volumes and capacities. Note that FRC and RV can't be measured by spirometer alone

: The volume of the airways and lungs that does not participate in gas exchange

: Volume of the conducting airways (does not include respiratory bronchioles and alveoli). If TV is 500ml, the entire volume does not reach alveoli for gas exchange. A portion fills conducting airways; this is ~ 150ml (dead space vol.) in TV of 500ml.

is volume of lungs that does not participate in gas exchange (wasted ventilation)

Physiologic dead space includes the anatomic dead space plus a functional dead space in the alveoli, (i.e. alveoli that do not participate in gas exchange). The functional dead space can be thought of as the alveoli that do not participate in gas exchange. The most important reason that the alveoli do not participate in gas exchange is an imbalance or

inequality of ventilation and perfusion in which ventilated alveoli are not perfuse by capillary blood.

In normal person, physiologic dead space is nearly equal to the anatomic dead space where alveolar ventilation and blood flow are well matched.

If physiologic dead space is greater, there is imbalance of ventilation and perfusion.

Ventilation rates: Volume of air moved into and out of the lungs per unit time.

Minute ventilation = V_T x breaths /min

Where V_T=tidal volume (ml)

Alveolar ventilation = minute ventilation corrected for the physiologic dead space

$V_A = (V_T - V_D)$ X breathes/min

Where

V_A= alveolar ventilation (ml/min)

V_T= Tidal volume (ml)

V_D= Physiologic dead space (ml)

:

: The diaphragm is the most important inspiratory muscle. When diaphragm contracts, abdominal contents are pushed downward and the ribs are lifted upward and outward. These changes increase intrathoracic volume and lowers intrathoracic pressure. This initiates flow of air into the lungs. During exercise, when breathing frequency and TV increases, external intercostals muscles and accessory muscles are used for more vigorous inspiration.

: Expiration is normally passive. During exercise or in diseases, in which airway resistance is increased (e.g.

important. Compliance of lung and chest wall are inversely correlated with their elastic properties (elastance)

: Increase in lung compliance may occur due to loss of elastic fibers (e.g. emphysema, old age). Decrease in lung compliance increases the tendency of lung to collapse, e.g. in fibrosis

Small size of alveoli is difficult to keep them open because of surface tension.
Surfactant line alveoli and reduce surface tension. Thus surfactant keeps alveoli open.
Atelectasis- collapsed alveoli due to reduced surfactant.
Surfactant is synthesized by TypeII alveolar cell. Surfactant is lacking in premature infants, causing neonatal respiratory distress syndrome.

Normal breathing cycle is shown in figure 62. Breathing cycle is divided into 3 phases

.

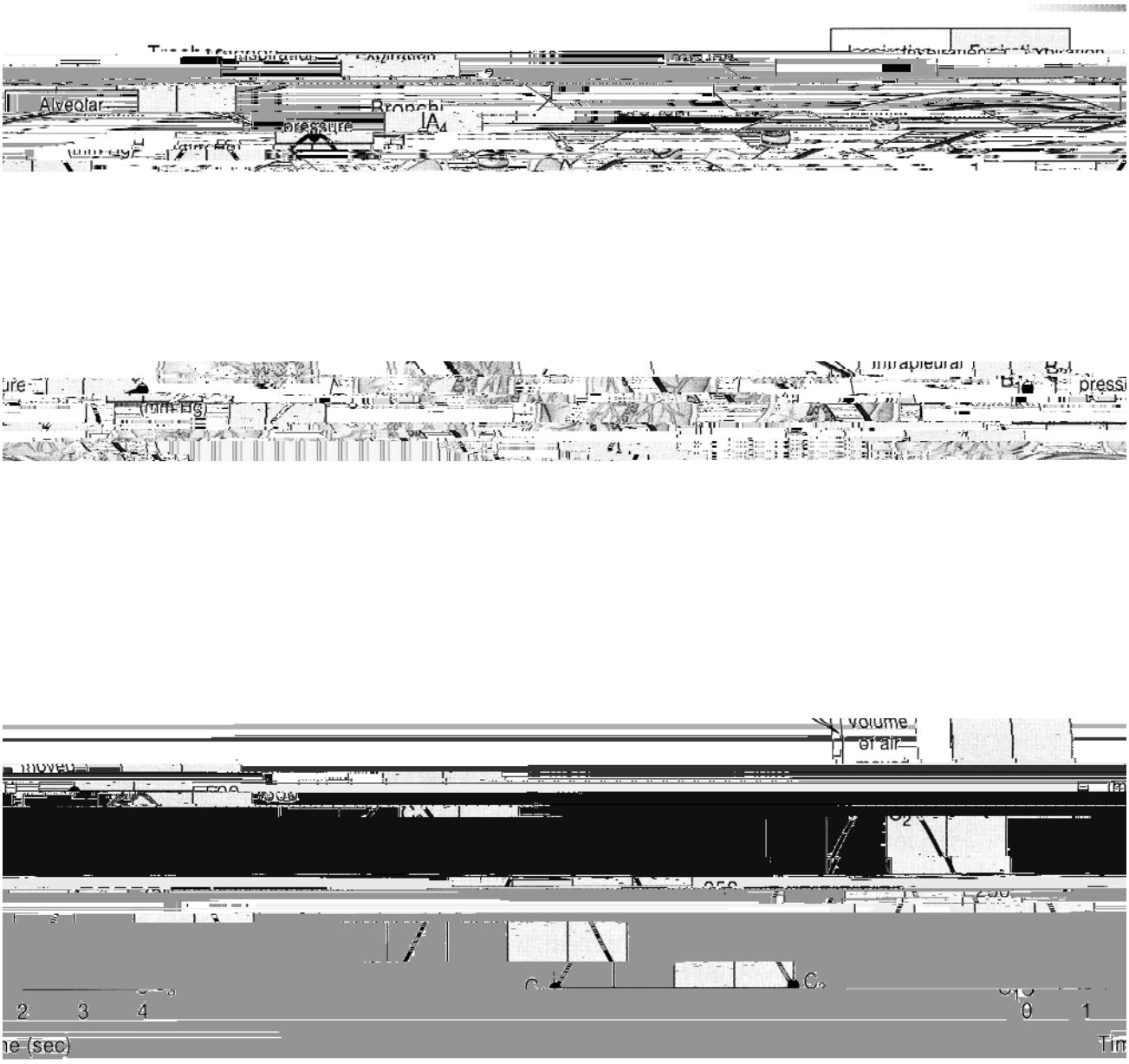

Figure 62. Volumes and pressures during the normal breathing cycle. Intrapleural and alveolar pressure are given in reference to atmospheric pressure

. This is a period between breathing cycles. No air is moving into or out of the lungs. Alveolar pressure equals atmospheric pressure. Intrapleural pressure is negative (~ -5cmH_2O) because opposing forces of lungs trying to collapse and chest wall trying to expand creates negative pressure in intrapleural space. The expanding force on the

lungs and airways at rest is + 5cmH_2O (alveolar or airway pressure minus intraplural pressure)

The diaphragm contracts, causing volume of thorax to increase. Both airway and alveolar pressure becomes negative (i.e. less than atmospheric). Now pressure gradient is created between atmosphere, airways and alveoli. Air flows into the lungs until the pressure

gradient is dissipated. Intrapleural pressure becomes even more negative than at rest. The reason is as lung volume increases, elastic recoil strength of lungs increases.

Airway an alveolar pressure becomes negative as volume of thorax increase.

The two effects together cause intrapleural pressure to be more negative (~ -8cmH_2O).

: Expiration is normally passive. Alveolar pressure becomes positive (higher than atmospheric) because the elastic forces of the lung compress air in the alveoli. When alveolar pressure is greater than atmospheric, air flows out of lungs. Following expiration, volume in the lung decreases and intrapleural pressure returns to its resting volume (i.e.-5cmH_2O). Pneumothorax occurs when air is introduced into intrapleural space (e.g. hole by sharp object). In such a case there is no counterbalancing expanding force, thus lung collapses.

.

Refers to energy expended to:

- Expand elastic tissues of chest wall and lungs (compliance work)
- Overcome viscosity of inelastic structures of chest wall and lungs (tissue resistance work).
- Move air against resistance of airways.(airway resistance work)

Work of breathing accounts 2-3% of body's total energy expenditure.

Gas exchange in the respiratory system refers to diffusion of oxygen and carbon dioxide in the lungs and in the peripheral tissues. Oxygen is transferred from alveolar gas into pulmonary capillary blood and, ultimately it is delivered to the tissues, where it diffuses from systemic capillary blood into the cells. Carbon dioxide is delivered from the tissues

to venous blood, (to pulmonary capillary blood), and is transferred to alveolar gas to be expired.

At sea level, barometric pressure (P_B) = 760mmHg, and percentage of gas at dry air is 78% N_2, 21% O_2, 1% inert gas and 0.04% CO_2.

Dalton's law of partial pressure states that each gas contributes to the total pressure in direct proportion to its relative concentration.

Partial pressure of any gas can therefore be calculated.

$P_{X=}P_BXF$

P_X=partial pressure of gas (mmHg)

P_B=barometric pressure (mmHg)

F= fractional concentration of gas

Thus P_{N2} (at see level) = ~ 600 mmHg

PO_2 (at see level) = 160mmHg

As air traverses the conduction system to enter the gas exchange area, temperature and humidity of gas approaches body temp and 100% humidity. The partial pressure (PX) of gas in the alveolus changes.

Thus, P_X= (P_B-PH_2O) XF

PH_2

Thus, $C_X = P_x$ X solubility

Where

C_x= conc. of dissolved gas (ml gas/100 ml blood)

P_X= Partial pressure of gas (mmHg)

Solubility= solubility of gas in blood, ml gas/100ml blood/mmHg.

Eg. The solubility of O_2 is 0.003ml/100ml blood /mmHg

Transfer of gases across capillary wall is by simple diffusion.

Rate of transfer by diffusion is directly proportional to driving force, diffusion coefficient and surface area available for diffusion, but inversely proportional to thickness of membrane barrier.

Thus:

$$V_x = \frac{DA\varphi P}{\varphi x}$$

Where V_x= volume of gas transferred

D= diffusion coefficient of the gas

A= surface area

φP= partial pressure difference of the gas

φX = thickness of the membrane

Two special points regarding diffusion of gases are:

-φP is driving force for diffusion of a gas across the membrane (not concentration difference)

For example, if. Po_2 (partial pressure of O_2) of alveolar air= 100mmHg an P_{O2} of mixed venous blood =40mmHg,

φP of O_2= (100-40) =60mmHg

- D is combination of diffusion coefficient (which depends on molecular weight) and solubility of the gas. For example, D for CO_2= 20 time higher than D for O_2. Therefore, Co_2 diffuses 20 times faster than O_2

DL (Vol./mmHg/min/pair of lungs) is volu

Figure 64. Schematic diagrams of an alveolus and pulmonary capillary. Mixed venous blood enters the pulmonary capillary, O_2 is added to pulmonary capillary blood and CO_2 is removed.

:

$P0_2$ = 160mmHg (760x0.21)

P_{CO2} =~0 mmHg

In humidified tracheal air – P_{O2} is reduced, $C0_2$ is “diluted” by water vapor

Thus $P0_2$= 150mmHg (760mmHg- 47mmHg) x 0.2)

PCO_2=0

In alveolar air –Pao_2 (Partial pressure of O_2 in alveoli) =100mmHg. This is less than inspired air and P_{CO2}= 40 mmHg. The reason is O_2 leaves alveolar air and is added to pulmonary capillary blood and CO_2 levels pulmonary capillary blood and enters alveolar air on daily bases, O_2 transfer from alveoli equals O_2 consumption by the body, and CO_2 transfer to alveolar air equals CO_2 production.

Figure 65. Values for PO_2

PaO_2 = 100mmHg

$PaCO_2$= 40 mmHg

Thus, it is in complete equilibrium with alveolar air (see figure 61). Normally, PaO_2 is slightly less than PAO_2 due to physiologic shunt. Physiologic shunt refers to the fraction of pulmonary blood flow that bypasses the alveoli, therefore is not arterialized. Thus $PaO_{2\sim}$ is normally 95 mmHg. Physiologic shunt is increased in pathologic conditions. This is called Ventilation/perfusion defect. A-a difference expresses difference in PO_2 between alveolar gas (A) and systemic arterial blood (a). If shunt is small, then A-a is small (normal), If abnormal, A-a difference increases.

Figure 66 shows changes in PO_2 and PCO_2 in the lungs. In the tissues, O_2 diffuses from systemic capillaries into tissues and CO_2 from tissues into capillaries, thus PVO_2 (PO_2 in venous blood) = 40 mmHg, whereas, $PVCO_2$ (PCO_2 in venous blood) = 46mmHg

As blood reaches the venous system, PO_2 and PCO_2 changes.

Figure 66.Gas transport to the periphery. Uptake of CO_2 and liberation of O_2 in systemic capillaries. Exactly opposite events occur in the pulmonary capillaries

: O_2 is carried in the blood in two forms.

It accounts only 2-3% of the total O_2 content of blood. The solubility of O_2 in blood is 0.003mlO_2/100ml blood/mmHg. Thus for normal PaO2 of 100mmHg, dissolved O_2 = 0.3ml O_2/100ml (100 mmHg x0.003 ml O_2/100ml blood/mmHg. The resting O_2 consumption is 250 ml O_2/min. Thus dissolved O_2 is greatly insufficient. Another transport mechanism is thus required.

97-98% of O_2 is carried bound to Hb. Hb is found inside red cells and has 4 subunits. Each subunit contains heme moiety which is iron-binding porphyrin and polypeptide chain (either α or ɓ). Adult Hb (HbA) has α_2 $ɓ_2$ (2 of subunits have α chain and 2 have ɓ chain)

Each subunit can bind one molecule of O_2, a total of 4 molecules of O_2 for 1 molecule of Hb. When Hb oxygenated it is called Oxyhemoglobin. When Hb is deoxygenated it is called deoxyhemoglobin. For Hb subunits to bind O_2, the iron in heme moieties must be in ferrous state ($Fe^{2+)}$

This is when iron molecule is in ferric (Fe^{3+}) state thus doesn't bind O_2.

The cause is due to oxidation of Fe^{2+} to Fe^{3+} by nitrites or sulfonamides. This is a Congenital variant

In fetal Hb, the two ɓ chains are replaced by ϒ chains (ϒ$_2$31 d7veHbF):

O_2 binding capacity is the maximum amount of O_2 that can be bound to Hb per volume of blood. 1gm Hb binds 1.34 ml O_2. The normal conc. of Hb in blood is 15gm/100ml. Therefore, O_2 binding captaincy=20.1ml O_2/100ml blood (15gm/100ml x 1.34 ml O_2 /gm Hb)

O_2 content= actual amount of O_2 per volume of blood

= (O_2-binding capacity X% saturation of Hb) +dissolved O_2

Where

O_2 content=actual O_2 in blood (ml O_2/100ml blood)

O_2 binding capacity = maximum O_2 bound to Hb

(ml O_2/100 ml blood) at 100% saturation

Percentage saturation= % of heme groups bound to O_2

Dissolved O_2 = un bound O_2 in blood (mlO_2/100ml blood).

Each molecule of Hb binds to 4 molecules of O_2, which is 100% saturation.

If 3 molecules of O_2 bind - 75% saturation

If 2 " " " " - 50% "

if 1 " " " " - 25% "

Figure 67. O_2-Hemoglobin dissociation curve P_{50} is the PO_2

The sigmoid shape of O_2-Hb dissociation curve helps explain: why O_2 is loaded into pulmonary capillary blood from alveoli and unloaded from systemic capillaries into the tissues. At the highest volumes of PO_2 (i.e. in alveolar gas), affinity of Hb for O_2 is highest; at the lower volume of PO_2 (i.e. in mixed venous blood) affinity for oxygen is lower. Alveolar air, pulmonary capillary blood and systemic arterial blood all have a PO_2 of 100mmHg. The graph shown in figure 68 corresponds to 100% saturation and (affinity of Hg for O_2 highest). On the other hand, mixed venous blood has P_{O2}=40 mmHg (because O_2 diffused from systemic capillaries into tissues), which corresponds to 75% saturation and lower affinity of Hb for O_2

These changes in affinity facilitates- loading of OT2for O

P_{O2} is 100mmHg. Hb is nearly 100% saturated. Due to positive coaperativity, affinity of Hb for O_2 is the highest, which corresponds to flat portion of curve (figure 68). PA_{O2} is higher than $Pa_{O2.}$ Therefore, O_2 diffuses into the pulmonary capillary blood. The flat position of curve extends from 100mmHg to 60mmHg (see figure 67). This means, human can tolerate substantial decreases in alveolar P_{O2} to 60mmHg (e.g. caused by decreases in atmosphere pressure) without compromising the O_2-carrying capacity of Hb.

P_{O2} is 40mmHg. Hb is 75% saturated and the affinity for O_2 is decreased. O_2 is not tightly bound which facilitates unloading of O_2 in the tissues. Partial pressure gradient for O_2 diffusion into tissue is maintained in two ways:

-Tissues consume O_2 keeping PO_2 law

-Low affinity for O_2 insures O_2 will be unloaded from Hb

Thus O_2 diffusion from blood to tissues maintained.

Occur when there is decreased affinity of Hb for O_2 (see figure.69). P_{50} increases and unloading of O_2 in the tissues is facilitated.

:

: When metabolic activity of the tissues Increase production of CO_2 increases. An increase in tissue PCO_2 causes an increase H^+ and a decrease pH. This mechanism ensures that O_2 delivery to the tissues can meet O_2 demand (e.g. in exercising skeletal muscle).

Bohr effect states that an increased H^+ concentration causes a right shift of the O_2-Hb dissociation curve which causes Hb to unload O_2 more readily in the tissues.

. Increases in temperature also cause right shift, and facilitate unloading of oxygen in the tissues.

2,3-DPG binds to β

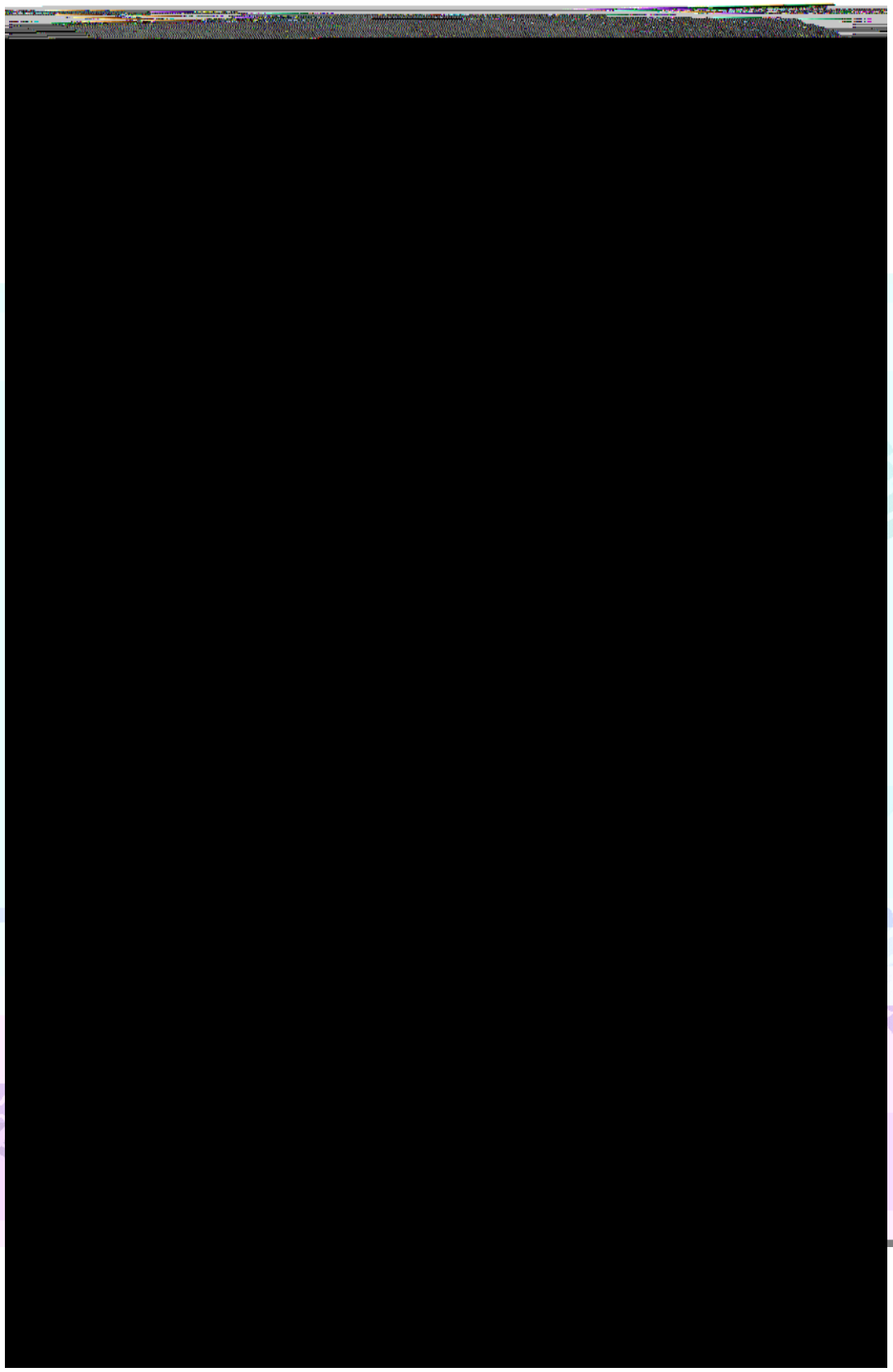

Figure 69 A. shift of the O_2-Hb dissociation curve.


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When tissue metabolism decreases, less heat is produced and less O_2 is unloaded to the tissues.

This reflects decreased tissue metabolism, causing a left shift of the curve and less oxygen to be unloaded in the tissues.

All the effects on the oxygen- hemoglobin dissociation curve discussed above have involved right or left shifts, with no change in oxygen binding capacity. The effect of CO is different: it decreases O_{2-} binding capacity and also causes left shift (see figure 70). Co binds to Hb with affinity 250 times that of O_2.

Co+Hb = carboxyhemoglobin (COHb.)

In the presence of CO, O_2 can't bind to heme group that are bound to CO. Thus O_2-binding capacity of Hb decreases. The final effect is decreased O_2 delivery to the tissues. CO also causes left shift, because heme not bound to CO have increased affinity for O_2. P_{5o} decreased, and unloading becomes difficult.

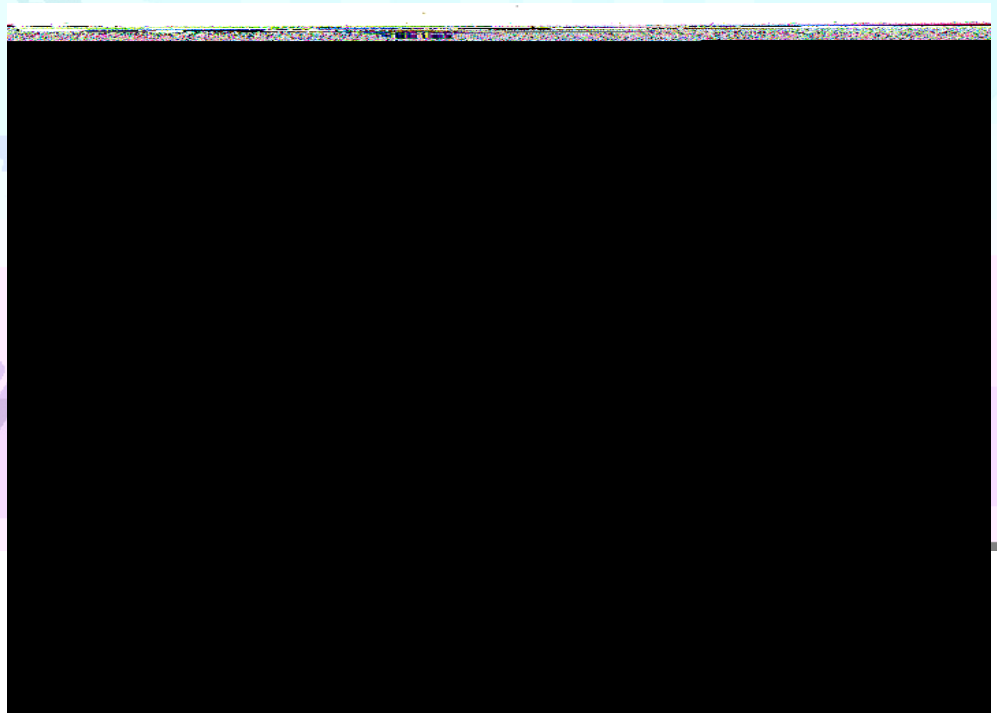

Figure 70. Effect of carbon monoxide on the oxygen –hemoglobin dissociation curve.

About 5% of the total CO_2 in the blood is transported dissolved.

Solubility of CO_2= 0.03mlCO_2/100ml blood/mmHg.

Dissolved CO_2 in arterial blood = 40mmHg x0.03mlCO_2/100ml blood/mmHg)

= 1.2ml/100ml blood

CO_2 binds to terminal aminogroups on proteins (eg. Hb and plasma proteins such as albumin). When CO2 is bound to Hb, it is

Figure 71. Transport of CO_2 in blood, CO_2 and H

5. The $HCO3^-$ produced is exchanged for Cl^- (to maintain change balance).

Cl^- HCO_3^- exchange is called Cl^- shift (chloride shift). In the lungs the reaction is reversed (not shown in figure 13). When RBC enters pulmonary capillaries, O_2 diffuses into cell and combines with Hb, which releases CO_2 (Haldane effect)

Breathing is an involuntary process that is controlled by the medulla and pons of the brainstem. The frequency of normal, involuntary breathing is controlled by three groups of neurons or brainstem centers.

- modullarly respiratory center: are located in the reticular formation, and are composed of Inspiratory center (dorsal respiratory group) and Expiratory center (Ventral respiratory group)
- The Inspiratory center controls basic rhythm by setting the frequency of inspiration. This group of neurons receives sensory input from Peripheral chemoreceptors via glossopharyngeal (CN IX) and Vagus (CN X) and from ` mechanoreceptors in lung via the vagus nerve

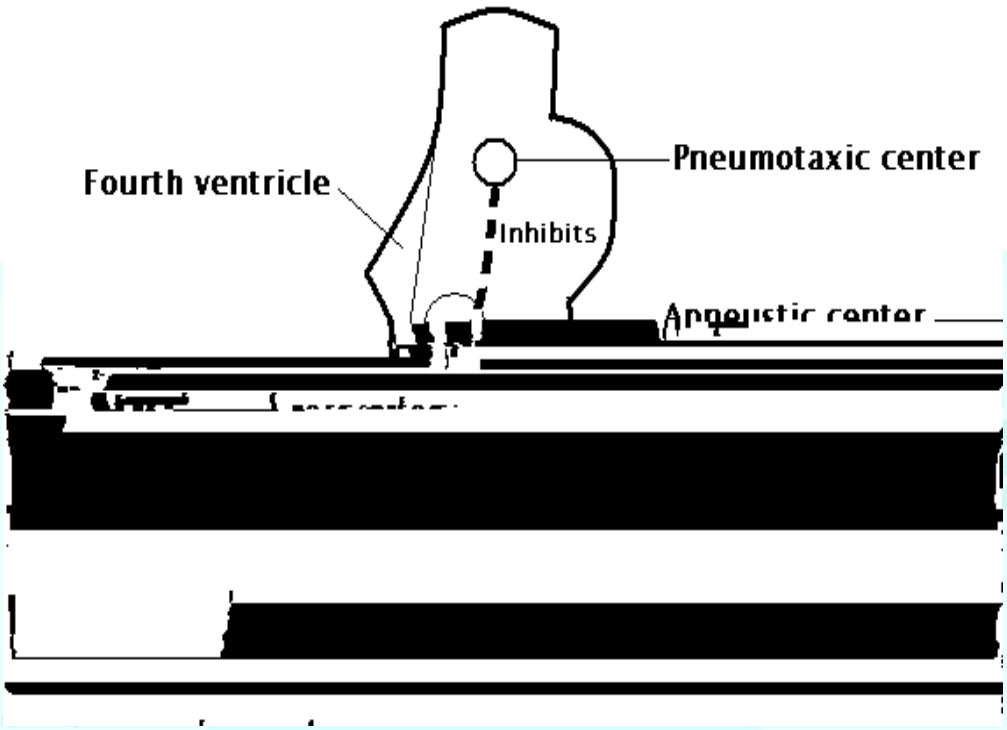

Figure 72. Organization of the respiratory center

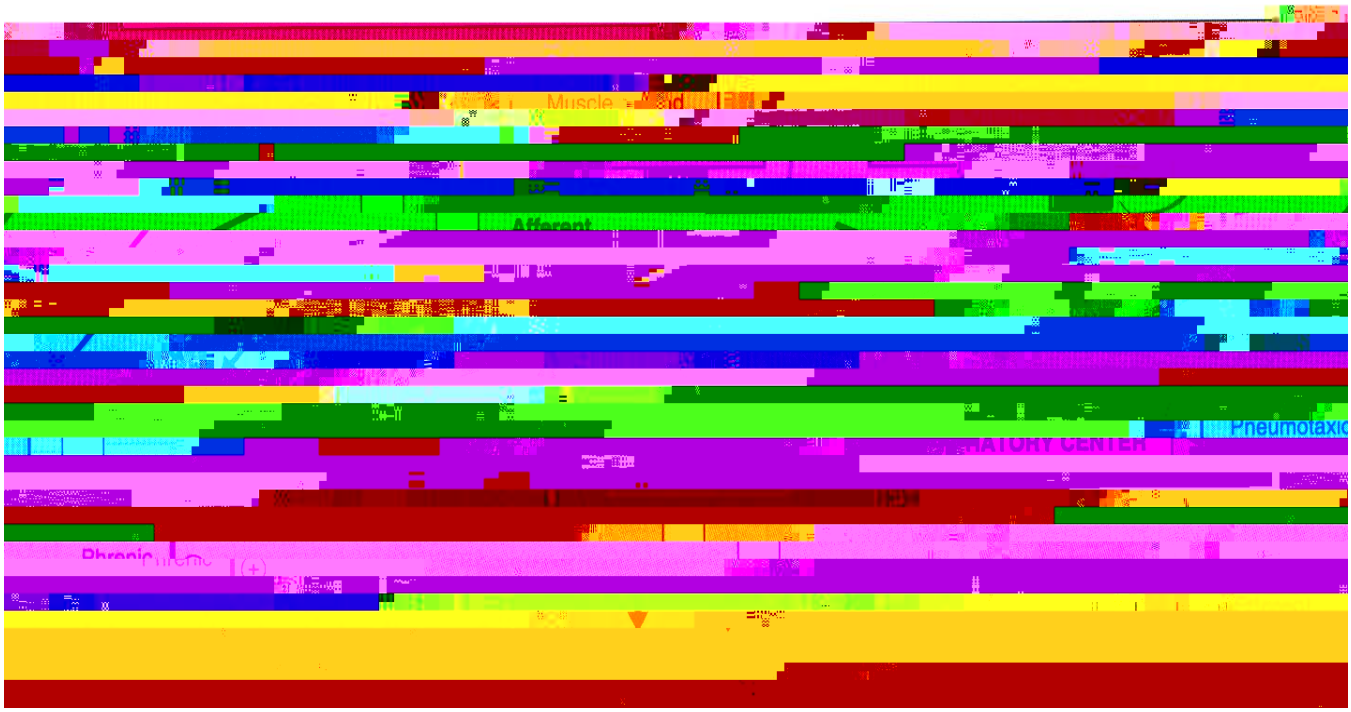

Figure 73. Brainstem control of breathing. Afferent (sensory) information reaches the medullary inspiratory center Via central and peripheral chemoreceptors and via

The brain stem controls breathing by processing sensory (afferent) information and sending motor (efferent) information to the diaphragm. The most important sensory information is PaO

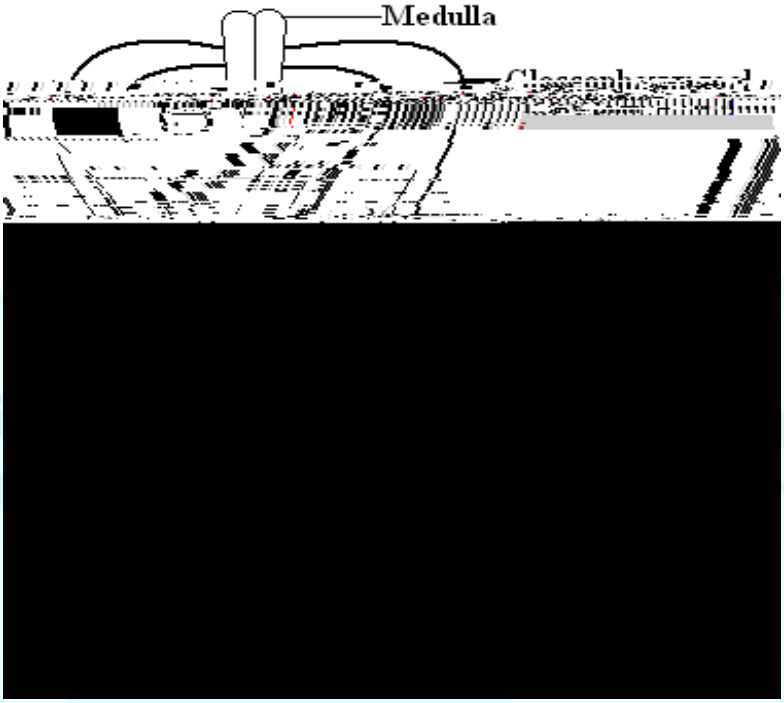

Figure 74: Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies

: (see fig. 74)

-

If the oxygen content of the blood is reduced, there may be insufficient O_2 to support the aerobic metabolism of the tissues. This condition is known as hypoxia. Hypoxia, if severe enough, can cause death of cells throughout the body. In less severe degree it results:

(1) , sometimes culminating in coma.

(2) .

Types of hypoxia

Depending on the cause, hypoxia is generally divided into four categories- hypoxic, anemic, stagnant, and histotoxic

If the alveolar P_{O2} is low the arterial P_{O2} will inevitably follow and so will O_2 content. As a result, or O_2 is extracted from the blood to support the oxidative metabolism of the tissues. This is quite common following ascent to high altitude as the barometric pressure and P_{O2} falls with increasing altitude.

Hypoventilation will lead to a reduced alveolar P_{O2} and an increased P_{CO2} (hypercapnia).

Examples

Respiratory depression due to drug overdose (barbiturate poisoning)

Severe weakness of the muscles that support respiration e.g. myasthenia gravis

Airway obstruction

Examples

Fibrosis of the lung parenchyma

Pulmonary edema

If the ventilation-perfusion ratio (V_A:V_Q) is low in a significant portion of the lung, this will lead to hypoxic hypoxia.


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P_{O2} is abnormally high.

Examples:

Cyanide poisoning

Beriberi

Oxygen therapy

Oxygen therapy may be required for respiratory failure due to lung disease or poisoning.

Oxygen may be administered in many ways:

The simplest way is to connect a cannula to an oxygen cylinder and insert it into one or both nostrils. This raises the concentration of oxygen in the inspired air but generally not to 100%, which may be a boon if the hypoxic drive is important to maintain the ventilation of the patient.

By this method the patient is allowed to breathe either pure oxygen or high concentrations of oxygen from a mask.

Another method for giving oxygen is through a mechanical ventilator. Patients who remain unconscious for fairly long periods of long time are given an ***endotracheal or tracheostomy tube***, which are connected to a ventilator.


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In this type of hypoxia, the tissue metabolic enzyme system is simply incapable of using the oxygenthat is delivered. Therefore, oxygen therapy is of hardly any measurable benefit.

The term cyanosis means blueness of the skin, and its cause is excessive amounts of deoxygenated hemoglobin in the skin blood vessels, especially in the capillaries.

This deoxygenated hemoglobin has an intense dark blue-purple color that is transmitted through the skin. In general, definite cyanosis appears whenever the arterial blood contains more than 5g deoxygenated hemoglobin in each 100ml of blood. The common sites where cyanosis is observed are ***lips***, ***nailbeds***, ***ear lobes***, ***cheeks***, and ***mucous membranes of the oral cavity***.

A person with ***anemia*** almost never becomes cyanotic because there is not enough hemoglobin for 5g to be deoxygenated in 100ml of arterial blood. Conversely, in a person with excess red blood cells, as occurs in ***polycythemia vera***, the great excess of available hemoglobin that can become deoxygenated leads frequently to cyanosis, even under otherwise normal conditions.

Pulmonary edema refers to the condition in which fluid accumulates in the interstitial spaces and alveoli of the lungs. Acute pulmonary edema is a life-threatening condition

---

(a) Left heart failure:

(b) Infectious agents, toxic gases, and drug reactions

(c) Rapid infusion of intravenous fluids or a blood transfusion

The term chronic obstructive pulmonary disease (COPD) denotes a group of respiratory disorders Characterized by small airway obstruction and reduction in expiratory flow rate. The most prevalent of these disorders are ***emphysema*** and ***chronic bronchitis***. Other forms of COPD are ***bronchiectasis*** and ***cystic fibrosis***. Since the most common cause of COPD is smoking, the disease is largely preventable. Unfortunately, clinical findings are completely absent during the early stages of the COPD and by the time, symptoms appear, the disease is usually well advanced. The mechanisms of airway obstruction in COPD are usually multiple, which include a reduction in the elasticity of the lung structures, bronchoconstriction, and chronic inflammation. In COPD the time required for FVC is increased, the $FEV_{1.0}$ is decreased, and $FEV_{1.0}$/FVC is decreased.

These and other measurements of expiratory flow are determined by spirometry and are used in the diagnosis of COPD.

Emphysema is characterized by a loss of lung elasticity and abnormal dilation of the air spaces distal to the terminal bronchioles with destruction of the alveolar walls and capillary beds.
There is hyperinflation of the lungs, and breath sounds are decreased.

In chronic bronchitis airway obstruction is caused by inflammation of both major and small airways. It is more common in men than in women, but changing smoking habits may soon change this disproportion. It usually first appear in the fourth to fifth decades of the life.


EPHTI

(b) : It is also common in subjects who have rapidly climbed to a high altitude.

Cheyne-Stokes breathing is due to sluggishness of chemical regulation of respiration. The result is alternate apnea and hyperventilation.