1. **Briefly describe the calcium complex found in bones and teeth.**

   About 98% of the calcium in adults is located in the skeleton and teeth, where it is combined with phosphates to form a crystal lattice of mineral salts. The remaining calcium is largely found in the extracellular fluid compartments.

   The most abundant mineral salt is calcium phosphate [$Ca_3(PO_4)_2$]. It combines with another mineral salt, calcium hydroxide [$Ca(OH)_2$], to form crystals of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. As the crystals form, they combine with still other mineral salts, such as calcium carbonate ($CaCO_3$), and ions such as magnesium, fluoride, potassium, and sulfate. As these mineral salts are deposited in the framework formed by the collagen fibers of the extracellular matrix, they crystallize and the tissue hardens.

   Hydroxyapatite: A major component and an essential ingredient of normal bone and teeth. Hydroxyapatite makes up bone mineral and the matrix of teeth. It is hydroxyapatite that gives bones and teeth their rigidity.

   Hydroxyapatite molecules can group together (crystalize) to form microscopic clumps. If these tiny crystals of hydroxyapatite are deposited by mistake in or around joints, they may cause inflammation of the joints and nearby tissues, such as tendons and ligaments, particularly causing rotator cuff problems in the shoulder.

2. **Give the normal serum concentration of calcium ion.**

   Normal serum calcium ranges from 8.5 to 10.4 mg/dL (4.25–5.2 mEq/L, 2.1–2.6 mM) and includes three components: ionized (~50%), protein-bound (~40%, predominantly to albumin; a decrease in albumin of 1.0 g/dL from the normal value of 4.0 g/dL typically decreases total serum calcium by ~0.8 mg/dL), and complexed to anions such as phosphate and citrate (~10%).

3. **Give the roles and functions of calcium in the body.**

   Besides contributing to the hardness of bones and teeth, Calcium plays important roles in blood clotting, neurotransmitter release, maintenance of muscle tone, and excitability of nervous and muscle tissue.
   Whenever the skin becomes broken, the sticky platelets contained in the blood form clots to stop blood flow. Calcium works together with vitamin K and a protein called fibrinogen in the clotting cascade. Without adequate levels of calcium and vitamin K, blood will take longer to clot, and if both nutrients are missing, it might cause severe hemorrhage.
   As soon as blood from a wound is exposed to the air, the platelets disintegrate and react with fibrinogen to create fibrin: a mass of tiny threads. This triggers a whole series of reactions that rely on adequate levels of calcium and vitamin K to work. The fibrin hardens very quickly to form a scab over the wound.
   The role of the calcium inside the nervous system extends from the initiation of a nerve signal to action taking place. Calcium signals an impulse to a muscle cell and continues to be useful until the contraction i complete.
   Approximately 99% of body Ca is found in bone, where it serves a key structural role as a component of hydroxyapatite.

4. **Describe how PTH regulates and maintains the concentration of calcium in the body.**

   PTH secretion operates via a negative feedback system. If some stimulus causes the blood Ca^{2+} level to decrease, parathyroid gland cells (receptors) detect this change and increase their production of a molecule known as cyclic adenosine monophosphate (cyclic AMP). The gene for PTH within the nucleus of a parathyroid gland cell (the control center) detects the intracellular increase in cyclic AMP (the input). As a result, PTH synthesis speeds up, and more PTH (the output) is released into the blood. The presence of higher levels of PTH increases the number and activity of osteoclasts (effectors), which step

up the pace of bone resorption. The resulting release of Ca^{2+} from bone into blood returns the blood Ca^{2+} level to normal. PTH also acts on the kidneys (effectors) to decrease loss of Ca^{2+} in the urine, so more is retained in the blood. And PTH stimulates formation of calcitriol (the active form of vitamin D), a hormone that promotes absorption of calcium from foods in the gastrointestinal tract into the blood. Both of these actions also help elevate blood Ca^{2+} level.

The blood calcium level directly controls the secretion of both calcitonin and parathyroid hormone via negative feedback loops that do not involve the pituitary gland:

- A higher-than-normal level of calcium ions (Ca^{2+}) in the blood stimulates parafollicular cells of the thyroid gland to release more calcitonin.
- Calcitonin inhibits the activity of osteoclasts, thereby decreasing the blood Ca^{2+} level.
- A lower-than-normal level of Ca^{2+} in the blood stimulates chief cells of the parathyroid gland to release more PTH.
- PTH promotes resorption of bone extracellular matrix, which releases Ca^{2+} into the blood and slows loss of Ca^{2+} in the urine, raising the blood level of Ca^{2+}.
- PTH also stimulates the kidneys to synthesize calcitriol, the active form of vitamin D.
- Calcitriol stimulates increased absorption of Ca^{2+} from foods in the gastrointestinal tract, which helps increase the blood level of Ca^{2+}.

5.

a) What are the consequences of excessive activity of PTH?

Hyperparathyroidism, an elevated level of parathyroid hormone, most often is due to a tumor of one of the parathyroid glands. An elevated level of **PTH causes excessive resorption of bone matrix, raising the blood levels of calcium and phosphate ions and causing bones to become soft and easily fractured.**
Primary hyperparathyroidism causes **hypercalcemia and an increase in calcium in the urine filtrate, resulting in hypercalcuria and the potential for development of kidney stones.**
In early renal failure, an increase in PTH **results from decreased serum calcium and activated vitamin D levels. As the disease progresses, there is a decrease in vitamin D and calcium receptors, making the parathyroid glands more resistant to vitamin D and calcium**. At this point, elevated phosphate levels induce hyperplasia of the parathyroid glands independent of calcium and activated vitamin D.

b) What will be the consequences of hypoparathyroidism?
Hypoparathyroidism- too little parathyroid hormone—leads to a deficiency of blood Ca^{2+}, which **causes neurons and muscle fibers to depolarize and produce action potentials spontaneously. This leads to twitches, spasms, and tetany (maintained contraction) of skeletal muscle**. The leading cause of hypoparathyroidism is accidental damage to the parathyroid glands or to their blood supply during thyroidectomy surgery.

Manifestations of acute hypoparathyroidism that result from a decrease in serum calcium include tetany with **muscle cramps, carpopedal spasm, and convulsions.** Paresthesias, such as **tingling of the circumoral area and in the hands and feet, are almost always present. There may be prolongation of the QT interval caused by low calcium levels, resistance to digitalis, hypotension, and refractory heart failure**. Symptoms of chronic deficiency include lethargy, anxiety state, and personality changes. There may be **blurring of vision caused by cataracts, which develop during an extended period of time. Extrapyramidal signs, such as those seen with Parkinson's disease, may occur because of calcification of the basal ganglia.**

In PTH deficiency (idiopathic or surgical hypoparathyroidism) or an abnormal target tissue response to PTH (pseudohypoparathyroidism), **serum calcium falls and serum phosphate rises.**

6. Differentiate between hypocalcemia from hypercalcemia. Site causes of these conditions.

Hypocalcemia	Hypercalcemia
Laboratory Serum calcium <8.5 mg/dL	**Laboratory** Serum calcium >10.5 mg/dL
	Inability to Concentrate Urine and Exposure of Kidney to Increased Concentration of Calcium Polyuria Increased thirst Flank pain Signs of acute renal insufficiency Signs of kidney stones
Neural and Muscle Effects (Increased Excitability) Paresthesias, especially numbness and tingling Skeletal muscle cramps Abdominal muscle spasms and cramps Hyperactive reflexes Carpopedal spasm Tetany Laryngeal spasm	**Neural and Muscle Effects (Decreased Excitability)** Muscle weakness Ataxia, loss of muscle tone Lethargy Personality and behavioral changes Stupor and coma
Cardiovascular Effects Hypotension Signs of cardiac insufficiency Decreased response to drugs that act by calcium-mediated mechanisms Prolongation of the QT interval predisposes to ventricular dysrhythmias	**Cardiovascular Effects** Hypertension Shortening of the QT interval Atrioventricular block
Skeletal Effects (Chronic Deficiency) Osteomalacia Bone pain	**Gastrointestinal Effects** Anorexia Nausea, vomiting Constipation

Hypocalcemia

The causes of hypocalcemia can be divided into three categories: (1) impaired ability to mobilize calcium bone stores, (2) abnormal losses of calcium from the kidney, and (3) increased protein binding or chelation such that greater proportions of calcium are in the nonionized form. A pseudohypocalcemia is caused by hypoalbuminemia. It results in a decrease in protein-bound, rather than ionized, calcium and usually is asymptomatic. Calcium deficit caused by dietary deficiency exerts its effects on bone stores, rather than extracellular calcium levels.

Hypocalcemia can be caused by hypoparathyroidism, vitamin D deficiency, osteobalstic metastasis, steatorrhea, Cushing's syndrome and hyperphosphatemia.

Hypercalcemia

The most common causes of hypercalcemia are increased bone resorption caused by neoplasms or hyperparathyroidism. Hypercalcemia is a common complication of cancer, occurring in approximately 10% to 20% of persons with advanced disease. A number of malignant tumors, including carcinoma of the lungs, have been associated with hypercalcemia. Some tumors destroy the bone, but others produce humoral agents that stimulate osteoclastic activity, increase bone resorption, or inhibit bone formation.
Less common causes of hypercalcemia are prolonged immobilization, increased intestinal absorption of calcium, and excessive doses of vitamin D. Prolonged immobilization and lack of weight bearing cause

demineralization of bone and release of calcium into the bloodstream. Intestinal absorption of calcium can be increased by excessive doses of vitamin D or as a result of a condition called the milk-alkali syndrome. The milk-alkali syndrome is caused by excessive ingestion of calcium (often in the form of milk) and absorbable antacids. Because of the advent of nonabsorbable antacids, the condition is seen less frequently than in the past, but it may occur in women who are overzealous in taking calcium preparations for osteoporosis prevention.
A variety of drugs elevate calcium levels. The use of lithium to treat bipolar disorders has caused hypercalcemia and hyperparathyroidism. The thiazide diuretics increase calcium reabsorption in the distal convoluted tubule of the kidney. Although the thiazide diuretics seldom cause hypercalcemia, they can unmask hypercalcemia from other causes such as underlying bone disorders and conditions that increase bone resorption.

Hypercalcemia can be found in hyperparathyroidism, hypervitaminosis D, and some bone neoplastic diseases.

7. Give several food sources of calcium.

Sources of calcium include:

- milk, cheese and other dairy foods
- green leafy vegetables – such as broccoli, cabbage and okra, but not spinach
- soya beans
- tofu
- soya drinks with added calcium
- nuts
- bread and anything made with fortified flour
- fish where you eat the bones – such as sardines and pilchards
- cereals

8. Describe the cellular transport of calcium in and out of the cell.

Calcium is removed from cells by two basic mechanisms. The first mechanism involves an ATP-dependent Ca++ pump that actively removes calcium from the cell (see figure at right). The second mechanism is the sodium-calcium exchanger. The exact mechanism by which this exchanger works is unclear. It is known that calcium and sodium can move in either direction across the sarcolemma. Furthermore, three sodium ions are exchanged for each calcium, therefore a small (few millivolt) electrogenic potential is generated by this exchanger. The direction of movement of these ions (either inward or outward) depends upon the membrane potential and the chemical gradient for the ions. When the membrane potential is negative (e.g., in resting cells), the exchanger transports Ca++ out as Na+ enters the cell. When the cell is depolarized and has a positive membrane potential, the exchanger works in the opposite direction (i.e., Na+ leaves and Ca++ enters the cell). Therefore, during ventricular systole when the myocytes are depolarized, Ca++ enters the cell through this exchanger. In contrast, during ventricular diastole when the cells are repolarized, Ca++ leaves the cell through this exchanger.
We also know that an increase in intracellular sodium concentration leads to an increase in intracellular calcium concentration through this exchange. This has important physiological implications. One example of this occurring is when the activity of the Na+/K+-ATPase pump is decreased. This energy requiring, ATP-dependent pump transports sodium out of the cell and potassium into the cell. When the activity of this pump is reduced, for example, by cellular hypoxia (which causes ATP levels to fall) or by chemical inhibitors of this pump such as digitalis, then intracellular Na+ concentrations increase. One way to envision how this affects Ca++ exchange is that the increased intracellular Na+ reduces the concentration gradient of Na+ across the sarcolemma, which reduces the inward movement of Na+ down its concentration gradient via the exchanger. This, in turn, reduces the outward movement and exchange of Ca++, which leads to an accumulation of intracellular calcium.

9. Discuss the function of calcium ion in:

a. Dysrhythmias

Intracellular calcium dynamics in cardiac cells have been recognized as an important contributor in life-threatening ventricular arrhythmia (ventricular tachycardia and ventricular fibrillation) as well as increasingly prevalent atrial arrhythmias (atrial fibrillation [AF] and flutter).

The alternation of the action potential and the calcium transient can be in-phase or out-of-phase, both within the same cell or throughout the tissue. Out-of-phase alternation at the cellular level, electromechanical discordance, and at the tissue level, spatial discordance, promotes arrhythmias. Sarcoplasmic reticulum calcium uptake and release regulate the heart rates at which the alternans occur and further that there is a complex interaction between regimes for electromechanical and spatial discordance.

The proteins governing calcium-induced calcium release (CICR) are arranged in a complex spatial pattern with respect to the T-tubule in the cardiac cell. These proteins include the L-type calcium channels as well as ryanodine receptors (RyR) and the SERCA (sarco/endoplasmic reticulum Ca^{2+}-ATPase) pump, which are responsible for the release from and uptake of calcium back into the sarcoplasmic reticulum.

b. Hypertension

Intracellular calcium plays a crucial role in the regulation of cardiovascular functions: An increased influx of calcium into the vascular smooth muscle cells leads to an augmental muscular tone and therefore to an increased vascular resistance and rise in blood pressure.

The role of calcium in clinical hypertension can be best understood by a hierarchal model in which the blood pressure effects of a dietary signal depend on alterations of hormonal systems specific for that signal. These alterations mediate both the cellular recognition of these signals as well as the resultant clinical responses to them. In the case of both dietary calcium and dietary salt, these systems appear to include calcium regulating hormones having direct, calcium-dependent vasoactive properties, and which are linked to the activity of the renin-angiotensin system. Altered salt and calcium intake exert reciprocal linked effects on these hormone systems and on blood pressure. These reflect altered cellular calcium uptake from the extracellular space, salt-induced calcium hormones stimulating and calcium-induced suppression of these hormones inhibiting extracellular calcium uptake.

10. Discuss the role of the calcium-channel blockers in dysrhythmias and hypertension.

Calcium channel blockers prevent calcium from entering cells of the heart and blood vessel walls, resulting in lower blood pressure. Calcium channel blockers, also called calcium antagonists, relax and widen blood vessels by affecting the muscle cells in the arterial walls.

Some calcium channel blockers have the added benefit of slowing your heart rate, which can further reduce blood pressure, relieve chest pain (angina) and control an irregular heartbeat.

Currently approved calcium-channel blockers (CCBs) bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes). These channels are responsible for regulating the influx of calcium into muscle cells, which in turn stimulates smooth muscle contraction and cardiac myocyte contraction. In cardiac nodal tissue, L-type calcium channels play an important role in pacemaker currents and in phase 0 of the action potentials. Therefore, by blocking calcium entry into the cell, CCBs cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity within the heart (negative dromotropy), particularly at the atrioventricular node.

By causing vascular smooth muscle relaxation, CCBs decrease systemic vascular resistance, which lowers arterial blood pressure. These drugs primarily affect arterial resistance vessels, with only minimal effects on venous capacitance vessels.

The antiarrhythmic properties (Class IV antiarrhythmics) of CCBs are related to their ability to decrease the firing rate of aberrant pacemaker sites within the heart, but more importantly are related to their ability

to decrease conduction velocity and prolong repolarization, especially at the atrioventricular node. This latter action at the atrioventricular node helps to block reentry mechanisms, which can cause supraventricular tachycardia.

The calcium-channel blockers represent a group of organic chemical structures that share the ability to inhibit Ca2+ entry into excitable cells. In coronary and peripheral arterial smooth muscle and the heart, inhibition of Ca2+ entry blunts the ability of Ca2+ to serve as an intracellular messenger. Thus, calcium-channel blockers are smooth-muscle dilators and have a negative inotropic effect on the working myocardial cells of the atria and ventricles. Calcium-channel blockers also have effects on impulse formation and conduction in some regions of the heart. A fast, Na+-dependent ionic current is responsible for the upstroke of the action potential in the working cells of the atria and ventricles and in the rapidly conducting cells of the His-Purkinje system, so that the calcium-channel blockers do not inhibit conduction in these cells. In the sinoatrial and atrioventricular nodes, where depolarization is due primarily to a Ca2+-dependent slow inward current, the calcium-channel blockers slow the sinus pacemaker and inhibit atrioventricular conduction. The actions of different calcium-channel blockers are not always similar; for example, nifedipine is much more potent as an inhibitor of calcium channels in smooth muscle than in the heart, whereas verapamil and diltiazem are approximately equipotent in heart and vascular smooth muscle. It is likely that the calcium-channel blockers reach their specific binding sites in membranes by first dissolving in the phospholipid bilayer, after which they may interact with hydrophobic regions of proteins that make up, or regulate, these channels.