Physiology of calcium
Thus, the plasma and interstitial fluids have a normal ionic calcium ion concentration of about 1.16 mmol/L (or 2.4 mEq/L, because it is a divalent ion), a level only one-half the total plasma calcium concentration. This ionic calcium is the form that is important for most functions of calcium in the body, including the effect of calcium on the heart, the nervous system, and bone formation.

Increases in calcium ion concentration above normal (hypercalcemia) cause

1. progressive depression of the nervous system (depressive effects begin to appear when the blood level of calcium rises above about 12 mg/dl)
2. reflex activities of the central nervous system are sluggish;
3. decreases the QT interval of the heart
4. lack of appetite
5. constipation;

Conversely, decreases in calcium concentration (hypocalcemia) cause the nervous system to become more excited about 6 mg/dl. The result is hypocalcemic tetany, which is characterized by extensive spasms of skeletal muscle (carpopedal spasm), involving especially the muscles of the extremities. Laryngospasm can become so severe that the airway is obstructed and fatal asphyxia is produced. It is usually lethal at about 4 mg/dl.

The possible mechanism behind hypocalcemic tetany (pathophysiology):

1. Hypocalcemia
2. No complete closure of Na channels at rest
3. Na leak into the cell from ECF
4. Intracellular become less negative and approaching more to threshold (more excitable)
   So less amount of dis required to initiate depolarization
5. Slight stimuli cause action potential
Positive Chvostek’s Sign

Positive Trousseau’s Sign

Trousseau's sign

Carpopedal Spasm

- Hypocalcemia demonstrated by muscle spasm of hands and feet.
The extent of Ca\(^{2+}\) binding by plasma proteins (i.e. the free Ca\(^{2+}\) level) is proportional to:

1. **the plasma protein level** (example pregnancy)
2. **Other electrolytes**
3. **pH**.

Thus, for example, symptoms of tetany appear if the patient have higher plasma protein or hyperventilates.

```
Hyperventilates
\n\nMore wash of blood CO2
\n\nAlkalosis (respiratory alkalosis)
\n\nPlasma protein are more ionized when pH is high
\n\nIncrease Ca binding to plasma protein
\n\nHypocalcemia even though normal level of plasma protein
```
Physiology of phosphate:

Total body phosphorus is 500 to 800 g (16.1–25.8 mol) distributed as:

1. Approximately 85–90% of the body’s phosphate is stored in bones,
2. 14 to 15 percent is in the cells, and
3. less than 1 percent is in the extracellular fluid.

Total plasma phosphorus is about 12 mg/dL (because it is difficult to calculate inorganic phosphate),

1. two-thirds of this total in organic compounds

Phosphate is found in ATP, cyclic adenosine monophosphate (cAMP), 2,3-diphosphoglycerate, many proteins, and other vital compounds in the body.

2. the remaining inorganic phosphorus (Pi) mostly in PO$_4^{3-}$, HPO$_4^{2-}$, and H$_2$PO$_4^{-}$.

The amount of phosphorus normally entering bone is about 3 mg (97 μmol)/kg/d, with an equal amount leaving via reabsorption

Phosphorylation and dephosphorylation of proteins are involved in the regulation of cell function. Therefore, it is not surprising that, like calcium, phosphate metabolism is closely regulated.

extracellular fluid ↓pH (acidic) ➢ ↑H$_2$PO$_4^{-}$ + ↓HPO$_4^{2-}$ whereas the opposite occurs when the extracellular fluid becomes alkaline
Inorganic phosphorus (Pi) in the plasma is filtered in the glomeruli, and 85–90% of the filtered Pi is reabsorbed.

**Inorganic phosphorus active transport in the proximal tubule of the kidney:**
Inorganic phosphorus active transport in the proximal tubule accounts for most of the reabsorption and involves two cotransporters, NaPi-IIa (Na:Pi, 1:3) and NaPi-IIc (Na:Pi, 1:2). NaPi-IIa is powerfully inhibited by parathyroid hormone, which causes its internalization and degradation of NaPi-IIa and NaPi-IIc, thus a reduction in renal Pi reabsorption.

---

**Diagram:**
- **FGF-23** stimulates Pi reabsorption.
- **PTH** decreases Pi reabsorption.
- **FGFR1** and **Klotho** are receptors for FGF-23.
- **NaPi-IIa** and **NaPi-IIc** are NaPi cotransporters with different stoichiometries.
- **PTH** interacts with the **PTH receptor (PTHR)** to regulate Pi reabsorption.
- **Increase Pi reabsorption: Phosphate deficiency, Growth Hormone**
- **Decrease Pi reabsorption: Parathyroid Hormone, High Pi intake, Fibroblast growth factor 23**
Pi is absorbed in the duodenum and small intestine. Uptake occurs by a transporter related to those in the kidney, NaPi-IIb (1:2); that takes advantage of the low intracellular sodium concentration established by the Na\(_{\text{+}}\), K ATPase on the basolateral membrane of intestinal epithelial cells to load Pi against its concentration gradient. However, the pathway by which Pi exits into the bloodstream is not known. Many stimuli that increase Ca\(_{\text{2+}}\) absorption, including 1,25-dihydroxycholecalciferol, also increase Pi absorption via increased NaPi-IIb expression.
Vitamin D
The active transport of Ca\(^{2+}\) and PO\(_{4}^{-}\) from the intestine is increased by a metabolite of vitamin D. The term “vitamin D” is used to refer to a group of closely related sterols produced by the action of ultraviolet light on certain pro-vitamins.

Vitamin D\(_{3}\), which is also called cholecalciferol, is produced in the skin of mammals from 7-dehydrocholesterol by the action of sunlight. The reaction involves the rapid formation of pre-vitamin D\(_{3}\), which is then converted more slowly to vitamin D\(_{3}\).

Vitamin D\(_{3}\) and its hydroxylated derivatives are transported in the plasma bound to a globulin vitamin D binding protein (DBP). Vitamin D\(_{3}\) is also ingested in the animal diet source or ingested from plant diet source and converted to (D\(_{2}\) or ergo-calciferol). In the liver, vitamin D\(_{3}\) is converted to 25-hydroxy-cholecalciferol (calcidiol, 25-OHD\(_{3}\)). The process is limited because the 25-hydroxycholecalciferol has a feedback inhibitory effect on the conversion reactions. This feedback effect is extremely important for two reasons. First, the feedback mechanism precisely regulates the concentration of 25-hydroxycholecalciferol in the plasma, the intake of vitamin D\(_{3}\) can increase many times and yet the concentration of 25-hydroxycholecalciferol remains nearly normal.
This high degree of feedback control prevents excessive action of vitamin D when intake of vitamin D3 is altered over a wide range.

Second, this controlled conversion of vitamin D3 to 25-hydroxycholecalciferol conserves the vitamin D stored in the liver for future use. Once vitamin D3 is converted, the 25-hydroxycholecalciferol persists in the body for only a few weeks, whereas in the vitamin D form, it can be stored in the liver for many months. The 25-hydroxycholecalciferol is converted in the cells of the proximal tubules of the kidneys to the more active metabolite 1,25-dihydroxycholecalciferol, which is also called calcitriol or 1,25-(OH)2D3 (is by far the most active form of vitamin D) effect. Therefore, in the absence of the kidneys, vitamin D loses almost all its effectiveness.

1,25-Di-hydroxycholecalciferol is also made in the placenta, in keratinocytes in the skin, and in macrophages. Vitamin D3 is also ingested in the animal diet source or ingested from plant diet source and converted to (D2 or ergocalciferol). In the liver by the aid of 25-hydroxylase will be converted to 25-hydroxyeryocalciferol. 25-hydroxy-eryocalciferol will be converted to 1, 25, di-hydroxybycholecalciferol the aid of 1 alpha-hydroxylase.
Regulation of synthesis of 1,25-dihydroxycholecalciferol (calcitriol):

Primary regulator:
1. Parathyroid hormone (PTH)
The conversion of 25-hydroxycholecalciferol to 1, 25-dihydroxycholecalciferol requires PTH. **In the absence of PTH, almost none of the 1, 25-dihydroxycholecalciferol is formed.** Therefore, PTH exerts a potent influence in determining the functional effects of vitamin D in the body.

2. Calcium level:
   - ↑ Calcium ▶ ↓ parathyroid hormone production ▶
     a. ↓ 1α-hydroxylase ▶ decrease conversion 25-hydroxy-cholecalciferol to 1, 25 dihydroxy-cholecalciferol
     b. ↑ 24-hydroxylase ▶ increase conversion 25-hydroxy-cholecalciferol to 24, 25 dihydroxy-cholecalciferol

3. Phosphate level:
   - ↑ phosphate level ▶ ↓ 1α-hydroxylase (so decrease production of 1,25-hydroxy-cholecalciferol). The reverse is also true.

4. 1,25-di-hydroxy-cholecalciferol
   - ↑ 1,25-di-hydroxy-cholecalciferol ▶ ↓ 1α-hydroxylase ▶ decrease conversion 25-hydroxy-cholecalciferol to 1, 25 dihydroxy-cholecalciferol (direct negative feedback effect). The reverse is also true

Secondary regulator:
Prolactin, estrogen, androgen, progesterone, insulin, growth hormone, human chorionic somatomammotropin (HCS), thyroid hormone, and calcitonin all increase 1, 25-hydroxy-cholecalciferol, while hyperthyroidism is associated with a decrease in 1,25-hydroxy-cholecalciferol.
Intestinal Epithelia can absorb Ca\(^{2+}\) by para-cellular and trans-cellular transport.

Passive and paracellular Ca\(^{2+}\) transport takes place across the tight junctions and is driven by the electrochemical gradient for Ca\(^{2+}\).

The active form of vitamin D (1,25-(OH)\(_2\)D\(_3\)) stimulates the individual steps of trans-cellular Ca\(^{2+}\) transport by increasing the expression levels of

1. the luminal Ca\(^{2+}\) channels,
2. calbindins D9k,
3. the extrusion systems.

Active and transcellular Ca\(^{2+}\) transport is carried out as a three-step process.

1. After entry of Ca\(^{2+}\) through the (hetero) tetrameric epithelial Ca\(^{2+}\) channels, TRPV5 and TRPV6 (transient receptor potential vanilloid type 6 (TRPV6)),
2. Ca\(^{2+}\) bound to calbindin diffuses to the basolateral membrane.
3. At the basolateral membrane, Ca\(^{2+}\) is extruded via an
   a. ATP-dependent Ca\(^{2+}\)-ATPase (PMCA1b: The plasma membrane calcium pump type 1b)
   b. Na/Ca\(^{2+}\) exchanger (NCX1).

In this way, there is net Ca\(^{2+}\) absorption from the luminal space to the extracellular compartment.
Since the discovery of α-Klotho, it was found to play a role in Bone metabolism, aging processes, Nephrology, Immunology, etc. α-Klotho is found in two forms

A. α Klotho transmembrane protein

The Klotho family consists of three single-pass transmembrane proteins (αKlotho, βKlotho and γKlotho). Each of them combines with fibroblast growth factor (FGF) receptors (FGFRs) to form receptor complexes for various FGF’s. αKlotho is a co-receptor for physiological FGF23 signaling. FGF23 thereby

1. Kidney:
   a. Inhibits 1α-hydroxylase, → reducing levels of 1,25-dihydroxycholecalciferol (Calcitriol synthesis)
   b. decreases renal Na-dependent phosphate cotransporters (NaPi-IIa and NaPi-IIc) expression

   Increase phosphate excretion (Negative phosphate balance)

2. Parathyroid gland
   Inhibit parathyroid hormone
   reducing levels of 1,25-dihydroxycholecalciferol (Calcitriol synthesis).
b. α Klotho protein

α Klotho protein also plays a FGF23-independent role in phosphate homeostasis. Animal experimental studies and clinical observations have demonstrated that

1. **α Klotho deficiency** ➔ severe hyperphosphatemia, accelerated aging, decreased bone mineral density, calcifications, and hypercalcemia;
2. moderate elevation of **α Klotho** reduces serum phosphate
3. extremely high **α Klotho** induces hypophosphatemia and high-FGF23.

α Klotho maintains circulating phosphate in a narrow range by

1. modulating intestinal phosphate absorption,
2. urinary phosphate excretion by the kidney,
3. phosphate distribution into bone rather than soft tissue in concerted interaction with other calico-phosphotropic hormones such as PTH, FGF23, calcitriol

The role of **α Klotho** in maintenance of phosphate homeostasis is mediated by

1. direct suppression of Na-dependent phosphate cotransporters (NaPi-II) in target organs.
2. α-Klotho plays an important role in stabilizing the membrane localization of proteins important in calcium and phosphate (re)absorption, such as TRPV5 (transient receptor potential vanilloid type 5) and Na-K ATPase

It is already known that **α Klotho** levels in blood decrease with age. Low **α Klotho** levels are often associated with age-related diseases.
The functions of 1,25-dihydroxycholecalciferol

- are coordinated to increase both [Ca$$^{2+}$$] and [phosphate] in ECF to mineralize new bone.

a. Increases intestinal Ca$$^{2+}$$ absorption (directly or indirectly through increase PTH)
b. Increases intestinal phosphate absorption.
c. Increases renal re-absorption of Ca$$^{2+}$$ and phosphate, analogous to its actions on the intestine.

The actions of vitamin D on bone will be:

a. Small quantity of 1,25-hydroxy-cholecalciferol promote bone calcification by maintaining normal quantity of calcium and phosphate.
b. Extreme quantity of 1,25-hydroxy-cholecalciferol causes absorption of bone.
c. In the absence of 1,25-hydroxy-cholecalciferol, the effect of parathyroid hormone in causing bone absorption is greatly reduced.
d. Increasing osteoclast activity
   ↓ dietary calcium  ➤ ↓ intestinal calcium absorption  ➤ 1,25(OH)2D binds to osteoblasts ➤
   ↑ osteoclast activity  ➤ release of skeletal calcium.
Other effects of Vitamin D

1. Vitamin D exhibits local (paracrine) effects on cell proliferation and differentiation and immune function.

2. Research has shown that vitamin D might play an important role in regulating mood and warding off depression.

3. Most cells in the body express vitamin D receptor (VDR) and 1α-hydroxylase, thereby permitting local production of 1,25(OH)2D, which has therapeutic implications. For example, Topical 1,25 (OH)2D is used to treat psoriasis.

Ongoing studies are aiming to clarify the role of 1,25 (OH)2D in the treatment of cancer and immune disorders, including rheumatoid arthritis (RA).

Failure of skin synthesis of vitamin D can be caused by:
1. Aging (synthesis is reduced by 75% at age 70)
2. Skin pigmentation (melanin absorb UV photon and prolong exposure time require for synthesis)
3. Body fat (excess body fat takes up and store newly synthesized Vitamin D)
4. Regular sunscreen, clothing atmospheric pollution, sun avoidance all decrease amount of exposure to sun
Parathyroid hormone (PTH) effects:

1. PTH acts directly on bone to increase bone resorption and mobilize Ca^{2+} and phosphate.

PTH has two effects to mobilize calcium and phosphate from bone. One is a rapid phase that begins in minutes and increases progressively for several hours. This phase results from activation of the already existing bone cells (mainly the osteocytes) to promote calcium and phosphate release.

The second phase is a much slower one, requiring several days or even weeks to become fully developed.

On a longer time scale, PTH stimulates both osteoblasts and osteoclasts.

PTH results from proliferation of the osteoclasts, followed by greatly increased osteoclastic resorption of the bone itself, not merely release of the calcium and phosphate salts from the bone.

2. PTH increases phosphate excretion in the urine and thereby depresses plasma phosphate levels. This **phosphaturic action** is due to a decrease in reabsorption of phosphate via effects on NaPi-IIa in the proximal tubules, as discussed previously.

The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.
PTH

a. ↑ renal tubular reabsorption of calcium

Plasma Ca\(^{2+}\) is filtered in the kidneys, but 98–99% of the filtered Ca\(^{2+}\) is reabsorbed.

About 60% of the reabsorption occur in the proximal tubules and the remainder in the ascending limb of the loop of Henle and the distal tubule.

The increased calcium reabsorption occurs mainly in the late distal tubules, the early collecting ducts, and possibly the ascending loop of Henle to a lesser extent.

Although Ca\(^{2+}\) excretion in the urine is often increased in hyperparathyroidism because the increase in the load of filtered calcium overwhelms the effect on reabsorption

b. ↓ phosphate reabsorption.
Model of calcium reabsorption in the distal convoluted tubule (DCT).

Apical calcium transport is mediated by Transient Receptor Potential channel subfamily V member 5 (TRPV5) channels, which can be activated by the \( \beta \)-glucuronidase Klotho (Reduced production of this protein has been observed in patients with chronic renal failure (CRF), and this may be one of the factors underlying the degenerative processes (e.g., arteriosclerosis, osteoporosis, and skin atrophy) Cytosolic calcium is immediately bound by calbindin-D28K, which shuttles calcium to the basolateral aspect of the DCT cell, where it can be transported out by the type 1 sodium calcium exchanger (NCX1) or calcium ATPases. These processes are tightly regulated by hormones, such as parathyroid hormone and vitamin D
4. PTH also increases the formation of 1,25-dihydroxycholecalciferol
   a. ↑calcium absorption from the intestine
   b. ↑phosphate absorption from the intestine
5. PTH
   a. ↑reabsorption of magnesium ions and hydrogen ions
   b. ↓reabsorption of sodium, potassium, and amino acid ions in much the same way that it affects phosphate.

Control of parathyroid secretion by calcium ion concentration
Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes; if the decreased calcium concentration persists, the glands will hypertrophy, sometimes fivefold or more.

The parathyroid glands become greatly enlarged in persons with:
1. rickets,
2. pregnancy,
3. lactation
The parathyroid glands become *greatly depressed* in persons with

1. excess quantities of calcium in the diet,
2. increased vitamin D in the diet
3. bone resorption caused by factors other than PTH (e.g., *disuse of the bones*)

Changes in extracellular fluid calcium ion concentration are detected by a calcium-sensing receptor in parathyroid cell membranes. Mild decreases in serum \([\text{Mg}^{2+}]\) stimulate PTH secretion. Severe decreases in serum \([\text{Mg}^{2+}]\) inhibit PTH secretion and produce symptoms of hypo-parathyroidism (e.g., hypocalcemia).
Parathyroid hormone related protein (PTHrP), Parathyroid hormone related protein (PTHrP), is produced by many different tissues in the body. Parathyroid hormone related protein has 140 amino acid residues. Parathyroid hormone related protein bind the same receptor of PTH this why it has same activates of PTH. 

Parathyroid hormone related protein actions

1. Parathyroid hormone related protein has a marked effect on the growth and development of cartilage in utero
2. Parathyroid hormone related protein
   a. stimulated cartilage cells proliferate
   b. Inhibit cartilage cells terminal differentiation
3. Parathyroid hormone related protein expressed in the brain, where evidence indicates that it inhibits excitotoxic damage to developing neurons.
4. Parathyroid hormone related protein is involved in Ca$^{2+}$ transport in the placenta.
5. Parathyroid hormone related protein is also found in keratinocytes in the skin, in smooth muscle, and in the teeth, where it is present in the enamel epithelium that caps each tooth.

In the absence of Parathyroid hormone related protein teeth cannot erupt. 
6. Parathyroid hormone related protein play a role of hypercalcemia in malignancy such as lung cancer.
Calcitonin

In mammals, calcitonin is produced by the parafollicular cells of the thyroid gland, which are also known as the clear or C cells. Human calcitonin has a molecular weight of 3500 and contains 32 amino acid residues.

Calcitonin gene-related peptide (CGRP; is a polypeptide that exists in two forms in humans: CGRPα and CGRPβ) and the calcium-lowering hormone calcitonin are both products of the calcitonin gene. In the thyroid gland, splicing produces the mRNA that codes for calcitonin, whereas in the brain, alternative splicing produces the mRNA that codes for CGRPα where it acts as neurotransmitter. CGRP has little effect on Ca^{2+} metabolism, and calcitonin is only a weak vasodilator. Secretion of calcitonin is increased when the thyroid gland is exposed to plasma calcium level of approximately 9.5 mg/dL.
Above this level, plasma calcitonin is directly proportionate to plasma calcium. Calcitonin secretion also stimulate by β-adrenergic agonists, dopamine, and estrogens. Gastrin, cholecystokinin (CCK), glucagon, and secretin have all been reported to stimulate calcitonin secretion, with gastrin being the most potent stimulus. Thus, the plasma calcitonin level is elevated in Zollinger–Ellison syndrome and in pernicious anemia. However, the dose of gastrin needed to stimulate calcitonin secretion is supra-physiological and not seen after eating in normal individuals, so dietary calcium in the intestine probably does not induce secretion of a calcium lowering hormone prior to the calcium being absorbed. In any event, the actions of calcitonin are short-lived because it has a half-life of less than 10 min in humans.

**Calcitonin actions:**

Calcitonin exact physiologic role is uncertain.

Calcitonin receptors are found in bones and the kidneys.

a. Calcitonin lowers circulating calcium levels by inhibiting bone resorption by inhibits the activity of osteoclasts in vitro.

b. Calcitonin increases Ca2+ excretion in the urine.

Calcitonin content of the human thyroid is low. After thyroidectomy, bone density and plasma Ca2+ level are normal as long as the parathyroid glands are intact.
There are only transient abnormalities of Ca\textsuperscript{2+} metabolism when a Ca\textsuperscript{2+} load is injected after thyroidectomy. This may be explained in part by secretion of calcitonin from tissues other than the thyroid. However, there is general agreement that the hormone has little long term effect on the plasma Ca\textsuperscript{2+} level in adult animals and humans. Further, unlike PTH and 1,25-dihydroxycholecalciferol, calcitonin does not appear to be involved in phosphate homeostasis. Moreover, patients with medullary carcinoma of the thyroid have a very high circulating calcitonin level but no symptoms directly attributable to the hormone, and their bones are essentially normal. No syndrome due to calcitonin deficiency has been described. More hormone is secreted in young individuals, and it may play a role in skeletal development. In addition, it may protect the bones of the mother from excess calcium loss during pregnancy. Bone formation in the infant and lactation are major drains on Ca\textsuperscript{2+} stores, and plasma concentrations of 1,25-dihydroxycholecalciferol are elevated in pregnancy. They would cause bone loss in the mother if bone resorption were not simultaneously inhibited by an increase in the plasma calcitonin level.
SUMMARY

1. PTH
   - ↑ plasma Ca\(^{2+}\) by mobilizing this ion from bone.
   - ↑ Ca\(^{2+}\) reabsorption in the kidney, but this may be offset by the increase in filtered Ca\(^{2+}\).
   - ↑ the formation of 1,25-dihydroxycholecalciferol.

2. 1,25-Dihydroxycholecalciferol
   - ↑ Ca\(^{2+}\) absorption from the intestine
   - ↑ Ca\(^{2+}\) reabsorption in the kidneys.

3. Calcitonin
   - ↓ bone resorption
   - ↑ the amount of Ca\(^{2+}\) in the urine.
Growth hormone increases calcium excretion in the urine and increases intestinal absorption of Ca\(^{2+}\), and this effect may be greater than the effect on excretion, with a resultant positive calcium balance.

Insulin-like growth factor I (IGF-I) generated by the action of growth hormone stimulates protein synthesis in bone.

Thyroid hormones may cause hypercalcemia, hypercalciuria, and, in some instances, osteoporosis.

Estrogens prevent osteoporosis by inhibiting the stimulatory effects of certain cytokines on osteoclasts.

Insulin increases bone formation, and there is significant bone loss in untreated diabetes.

Glucocorticoids

a. lower plasma Ca\(^{2+}\) levels by inhibiting osteoclast formation and activity,

The decrease in plasma Ca\(^{2+}\) concentration also increases the secretion of PTH, and bone resorption is facilitated.

b. over long periods they cause osteoporosis by decreasing bone formation and increasing bone resorption.

c. decrease bone formation by inhibiting protein synthesis in osteoblasts.

d. decrease the absorption of Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) from the intestine

e. increase the renal excretion of these ions.
Physiology of the teeth:

Function of different parts of the teeth:
The tooth can be divided into crown (which is the portion that protrudes out from the gum into the mouth),
The root (which is the portion within the bony socket of the jaw).
The collar between the crown and the root where the tooth is surrounded by the gum is called the neck.
• Enamel:
  - It forms the outer surface of the tooth
  - It is formed by special epithelial cells called ameloblast.
  - It is formed before tooth eruption, once the tooth is erupted, no more enamel is formed.
  - It is composed of very large and very dense crystals of hydroxyapatite with adsorbed carbonate, magnesium, sodium, potassium, and other ions imbedded in the fine meshwork of strong and almost insoluble protein fibers that are similar in physical characteristics (but not chemically identical) to the keratin of hair. Fluorapatite (Ca$_{10}$(PO$_4$)$_6$F$_2$) is fluoride modification of hydroxyapatite, which is often used therapeutically in order to prevent caries.
  - Crystalline structure of salts makes the enamel extremely hard.
  - The special protein fiber meshwork, although constituting only about 1% of the enamel mass, makes enamel resistant to acids, enzymes, and other corrosive agents because this protein is one most insoluble and resistant protein known.
Dentin:

- It is made up *principally of hydroxyapatite crystals similar to those in the bone but much denser*. The calcium salts in dentin makes it extremely resistant to compression force.

- Hydroxyapatite crystals are imbedded in a strong meshwork of collagen fibers (i.e. the principle constituent of dentin is much the same as those of bone). The collagen fibers makes it tough and resistant to tensional force.

- Dentin does not contain any osteoblast, osteocytes, osteoclasts, or spaces for blood vessels or nerve.

- Dentin nourishment is by a layer of cells called odontoblast, which line the inner surface along the wall of the pulp cavity.
- Cementum:
  - It is bony substance secreted by cells of the periodontal membrane, which lines the tooth socket.
  - Many collagen fibers pass directly from the bone of the jaw, through the periodontal membrane, and then into the cementum (periodontal ligament). These collagen fibers and the cementum hold the tooth in place.
  - The cementum becomes thicker and stronger with age and with exposure to excessive strain causing the teeth to become more firmly seated in the jaws.
• Pulp (or endodontium):

😊 It is the tooth cavity which is composed of connective tissue with abundant supply of nerve fibers, blood vessels and lymphatic.

😊 The cell lining the surface of the pulp cavity are the odontoblast, which, during the formative years of the tooth, lay down the dentin but at the same time encroach more and more on the pulp cavity, make it smaller. In later life, the dentin stops growing and the pulp cavity remains essentially constant in size.

😊 The odontoblast send projections into small dentinal tubules that penetrate all the way through the dentin: they are important for exchange of calcium, phosphate with the dentin.
Dentition:

Human develop two sets of teeth during a lifetime. The first teeth are called the (deciduous teeth, or milk teeth), and they number 20 in human. They erupt between the 7th month and the 2nd year of life, and they last until the 6th to the 13th year. After each deciduous tooth is lost, a permanent tooth replaces it and additional 8 to 12 molars appear posteriorly in the jaws, making the total number of permanent teeth 28 to 32, depending on whether the four wisdom teeth finally appear.
Mineral exchange in teeth:

The salts of teeth, like those of bone, are composed of hydroxyapatite with adsorbed carbonates and various cations bound together in a heard crystalline substance.

New salt are constantly being deposited while old salts are being reabsorbed from the teeth, as occurs in bone.

Deposition and reabsorption occur mainly in the dentin and cementum and to a very limited extent in the enamel.

The rate of absorption and deposition of minerals in the cementum is about equal to that in the surrounding bone of the jaw,

the rate of deposition and absorption of minerals in dentin is only 1/3 that of bone.

In the enamel, these processes occur mostly by diffusion exchange of mineral with saliva instead of with the fluid of the pulp cavity.

The cementum has characteristics almost identical to those of usual bone, including the presence of osteoblast and osteoclast, whereas dentin does not have these characteristics.