Blood – Ch. 19

*blood*: specialized, fluid, connective tissue that contains cells suspended in fluid matrix (made up of ground substance \& proteins)

*functions of the blood:*
- transportation of dissolved gases, nutrients, hormones, \& metabolic wastes
- regulation of pH \& electrolyte composition of interstitial fluids throughout body
  - blood absorbs \& neutralizes acids generated by active tissues
  - needs to get rid of protons
- restriction of fluid losses through damaged vessels or at other injury sites
- defense against toxins \& pathogens
- stabilization of body temperature

*composition of blood:*
- *plasma*: extracellular matrix consisting of *plasma proteins* \& ground substance called *serum*
  - slightly denser than water
- *formed elements*: blood cells \& cell fragments that are suspended in plasma
  - *red blood cells*: *erythrocytes*; most abundant blood cells
    - essential for transport of oxygen in blood
  - *white blood cells*: *leukocytes*; less numerous than red blood cells
    - involved in body’s defense mechanism
  - *platelets*: small, membrane-bound packets of cytoplasm that contain enzymes \& other substances important to process of blood clotting; noncellular formed elements
- *whole blood*: plasma \& formed elements together

*blood collection \& analysis*
- *venipuncture*: process of collecting fresh whole blood from superficial vein, such as *median cubital vein* on anterior surface of elbow
  - common sampling technique because:
    - superficial veins are easy to locate
    - walls of veins are thinner than those of comparably sized arteries
    - blood pressure in venous system is relatively low; so puncture wound seals quickly
- *blood smear*: thin film of capillary blood on surface of microscope slide; can be stained with special dyes to show different types of formed elements
- *arterial puncture*: *arterial stick*; may be used for checking efficiency of gas exchange at lungs
- *whole blood*, taken from any source, has same general characteristics:
  - temperature – 38 °C
  - viscosity – 5 times stickier, more cohesive, \& resistant to flow than water
  - pH – averaging 7.4 – slightly alkaline
- *blood volumes* – 4-5 for women, 5-6 for men
  - *hypovolemic*: low blood volume
  - *normovolemic*: normal blood volume
  - *hypervolemic*: high blood volume

**Plasma**
- contributes some 46-63% of volume of whole blood \& is composed of about 92% water
- differences between plasma \& interstitial fluid
  - concentrations of dissolved proteins, because plasma proteins cannot cross capillary walls
  - levels of respiratory gases (oxygen \& carbon dioxide) due to respiratory activities in tissue cells
- plasma proteins: large size \& globular shapes of most blood proteins prevent them from crossing capillary walls \& they remain trapped in circulatory system; in solution
*albumins*: constitute roughly 60% of plasma proteins
*helps to regulate interstitial fluid volume indirectly
*important in transport of fatty acids, thyroid hormones, some steroid hormones, & other substances
*when attached to albumin, solubility of steroid hormones increases

*globulins*: account for about 35% of protein population
*ex: immunoglobulins, transport globulins
*immunoglobulins*: antibiotics, attack foreign proteins & pathogens
*transport globulins*: bind small ions, hormones, & compounds that might otherwise be lost at kidneys or have very low solubility in water
*thyroid-binding globulin & transthyretin*, which transport thyroid hormones;
  *transcortin*, which transports ACTH; & *transcalciferin*, which transport calcitriol
*metalloproetins*, which transport metal ions
*apolipoproteins*, which carry triglycerides & other lipids in blood; called *lipoprotein*
  when bound to lipids
*steroid-binding proteins*, which transport steroid hormones in blood

*fibrinogen*: functions in blood clotting
*accounts for roughly 4% of plasma proteins
*under certain conditions, fibrinogens interact, forming large, insoluble strands of fibrin
*provide basic framework for blood clot
*if conversion of fibrinogen to fibrin occurs in plasma, clotting proteins are removed,
  leaving fluid known as *serum
*clotting process also removes Ca\(^+\) ions & other materials from solution
*peptide hormones, including insulin, prolactin (PRL), & the glycoproteins thyroid-stimulating hormone (TSH), FSH, & LH are normally present in circulating blood (remaining 1% of blood)

*origin of plasma proteins:*
*liver synthesizes & release more than 90% of plasma proteins, including albumin & fibrinogen, most of globulins, & prohormone angiotensinogen
*immunoglobulins* produced by plasma cells – derived from lymphocytes, the primary cells of lymphatic system

**Formed Elements**
*hemopoieses: hematopoieses; process through which formed elements are produced
*blood cells appear in circulation during third week of embryonic development
*embryonic cells differentiate into stem cells; produce blood cells by their divisions
*as skeleton enlarges, predominates after 5th month
*hemocytoblasts: pleuripotent stem cells; divide to produce myeloid stem cells (production of RBC & all WBC except lymphocytes) & lymphoid stem cells (production of lymphocytes)

*red blood cells (RBC):* contain red pigment, hemoglobin
*give whole blood its deep red color (4-6.3 million/uL)
*hematocrin*: percentage of whole blood occupied by cellular elements
*commonly reported as volume of packed red cells (VPRC) or packed cell volume (PCV)
*increases in cases of dehydration, owing to reduction in plasma volume
*ratio of volume of formed elements to total volume of blood
*RBC production stimulated by androgens
*structure
*among most specialized cells of body
*biconcave disc with thin central region & thicker outer margin
*unusual shape has 3 important effects on function:
* gives each RBC relatively large surface area, allowing for faster exchange between interior of cell & surrounding plasma
* oxygen must be released or absorbed quickly as RBC passes through capillaries of lungs or peripheral tissue
* enables RBCs to form stacks, called rouleaux that smooth flow through narrow blood vessels → gas transport
* stacks form & dissociate repeatedly without affecting cells involved
* enables them to bend & flex when entering small capillaries & branches
* cells only retain cytoskeletal elements; lose most organelles during differentiation
* because they lack nucleus & ribosome, circulating RBCs are incapable of dividing & synthesizing structural proteins or enzymes
* as a result, RBCs cannot perform repairs, & life span is relatively short, usually less than 120 days – energy demand are low
* no mitochondria; get energy through anaerobic metabolism of glucose absorbed from surrounding plasma

**hemoglobin (Hb)**: account for over 95% of intracellular proteins
* responsible for cell’s ability to transport oxygen & carbon dioxide
* **structure:**
  * complex quaternary shape; 2 alpha chains & 2 beta chains of polypeptides in each molecule
  * each chain is globular protein subunit that resembles myoglobin in skeletal & cardiac muscle cells
  * each Hb chain contains single molecule of heme: pigment complex that carries 4 molecules of oxygen; a porphyrin: organic compound generally associated with metal ions
  * each heme unit holds iron ions in such a way that iron can interact with oxygen molecule, forming oxyhemoglobin
* **function:**
  * each RBC can potentially carry more than one billion oxygen molecules
  * amount of oxygen bound to Hb depends primarily on oxygen content of plasma
  * when plasma oxygen levels are low, Hb releases oxygen → carbon dioxide levels in plasma are elevated
  * alpha & beta chains of Hb then bind CO₂, forming carboxyhemoglobin; CO₂ binds to protein not heme (CO binds to heme)
  * in capillaries of lungs, plasma oxygen levels are high & CO₂ levels are low
  * upon reaching capillaries, RBCs absorb oxygen, which is then bound to Hb, & release CO₂
  * normal activity levels can be sustained only when tissue oxygen levels are kept within normal limits
* **anemia**: condition when Hb content of RBCs is reduced
  * produces clinical symptoms cuz it interferes with oxygen delivery to peripheral tissues
  * organ function deteriorates due to oxygen starvation

**RBC life span & circulation:**
* erythrocyte is exposed to severe mechanical stress
* travels about 700 miles in 120 days; afterwards either cell membrane ruptures or damage is detected by phagocytic cells, & cell is engulfed
Hemoglobin conservation & recycling:
*Phagocytic cells generally recognize & engulf erythrocytes before they hemolyze, or rupture
*Phagocytes also detect & remove Hb molecules & cell fragments from relatively small number of RBCs that hemolyze in bloodstream
*If Hb released by hemolysis isn’t phagocytized, its components will not be recycled → Hb remains intact only under conditions found inside RBCs
*Hemoglobinuria: condition when urine develops reddish or brownish coloration due to abnormal large numbers of erythrocytes break down in circulation
*Hematuria: presence of intact RBCs in urine, occurs only after kidney damage or damage to vessels along urinary tract
*Once RBC has been engulfed & broken down by phagocyte each component of Hb has different fate:
  * Globular proteins are disassembled into component amino acids, which then are either metabolized by cell or released into circulation for use by other cells
  * Each heme unit is stripped of its iron & converted to biliverdin: a porphyrin derivative with green color
  * Biliverdin is then converted to bilirubin: which has an orange-yellow color, & is released into circulation where it binds to albumin & is transported to liver
  * Liver cells absorb bilirubin & converted to conjugated bilirubin: which is slightly more soluble than bilirubin absorbed by liver; most excreted in bile; small amount reenters circulation, & normally will be removed by kidneys & eliminated in urine
  * Jaundice: condition where circulating levels of conjugated & unconjugated bilirubin climb rapidly due to blockage of bile ducts or the inability of liver to absorb or excrete bilirubin; causes yellow color of skin & eyes
  * Inside large intestine, bacteria convert conjugated bilirubin to urobilinogens & stercobilinogens
  * Some of urobilinogens are absorbed back into circulation & will be subsequently excreted in urine
  * On exposure to oxygen, some of urobilinogens & stercobilinogens convert to urobilins (give urine yellow color) & stercobilins (in combo with urobilins, give feces brownish color)
*Large quantities of iron are toxic to cells, & Fe within body is generally bound to transport or storage proteins – Fe is competitive inhibitor of enzymes
*Fe extracted from heme molecules may be bound & stored within phagocytic cell or released into bloodstream, where it binds to transferrin, plasma protein
*RBCs developing in bone marrow absorb amino acids & transferrins from circulation & use them to synthesize new Hb molecules
*Excess transferrins are removed in liver & spleen, & Fe is stored in 2 special protein-Fe complexes: ferritin & hemosiderin

RBC formation:
*Erythropoiesis: RBC formation; in adult, occurs in red bone marrow, myeloid tissue
*Red marrow: where active blood cell production occurs; located in portions of vertebrae, sternum, ribs, pelvis, & proximal limb bones
*Yellow marrow: fatty tissue in other marrow; under extreme stimulation, areas of yellow marrow can convert to red marrow
stages in RBC maturation:
*hematologists: specialists in blood formation & function

-divisions of hemocytoblasts in red bone marrow produce myeloid stem cells, which in turn divide to produce RBC & several classes of white blood cells, & lymphoid stem cells, which divide to produce various classes of lymphocytes

-cells destined to become RBCs first differentiate into proerythroblasts & then proceed through various stages of erythroblasts: which actively synthesize hemoglobin

-after roughly 4 days of differentiation, erythroblasts, now called normoblast, shed its nucleus & become reticulocyte: contains 80% of hemoglobin of mature RBC

-after 2 days in bone marrow, reticulocyte enters circulation; after 24 hours, reticulocytes complete maturation to become RBC

regulation of erythropoiesis

-for erythropoiesis to proceed normally myeloid tissues must receive adequate supplies of amino acids, Fe, & vitamins required for protein synthesis

-essential coenzymes: B₆, B₁₂, folic acid – necessary for DNA replication (mitosis)

-vitamin B₁₂: obtained from dairy products & meat; its absorption requires presence of intrinsic factor produced in stomach

-pernicious anemia: lack of intrinsic factor in stomach

-stimulated directly by erythropoietin & indirectly by several hormones, including thyroxine, androgens, & growth hormone

-erythropoietin (EPO): “erythropoiesis-stimulating hormone;” glycoprotein that appears in plasma when peripheral tissues, especially kidneys, are exposed to low oxygen concentrations

-hypoxia: state of low tissue oxygen

-EPO released:

-*during anemia

-*when blood flow to kidneys declines

-*during adaptation to high altitudes

-*when respiratory surfaces on lungs are damaged

-*once in circulation, EPO travels to areas on red bone marrow, where it stimulates stem cells & developing erythrocytes

-2 major effects:

-*stimulates increased rates of cell divisions in erythroblasts & in stem cells that produce erythroblasts

-*speeds up maturation of RBCs, primarily by accelerating rate of Hb synthesis

-blood doping: reinfusion of packed RBCs removed at earlier date & stored, with goal of increasing hematocrit to improve performance; creates problems

-blood types

-antigens are materials that can trigger an immune response, a defense mechanism that protects you from infection

-*most antigens are proteins

-*cell membranes contain surface antigens that immune defenses recognize as “normal”

-*surface antigens involved are integral glycoproteins or glycolipids whose characteristics are genetically determined

-*surface antigens are often called agglutinogens
**blood type**: determined by presence or absence of specific surface antigens in RBC cell membranes; A, B, Rh(D)

*Type A*: has antigen A only; contains Anti-B antibodies
*Type B*: has B antigen only; contains Anti-A antibodies
*Type AB*: has both A & B antigens; contains neither Anti-A nor Anti-B antibodies
*Type O*: has neither A nor B antigens; contains both Anti-A & Anti-B antibodies
*Rh-positive*: indicates presence of Rh surface antigen, sometimes called *Rh factor*
*Rh negative*: indicates absence of Rh surface antigen

*immune system will ignore surface antigens on its own RBCs*

*agglutinins*: antibodies contained in plasma that will attack antigens on “foreign” RBCs
*when agglutinins attack, foreign cells clump together, or agglutinate; the process is called agglutination*
*agglutinins cause agglutination but agglutinogens are antigens*

cross-reactions

cross-reaction: when antibody meets specific antigen
*initially RBCs agglutinate, & they may also hemolyze
*clumps & fragments of RBCs under attack form drifting masses that can plug small vessels in kidneys, lungs, heart, or brain, damaging or destroying dependent tissues
*compliment attack proteins – attack any cell that has antibodies on it – goal is to lyse cell, which releases all Hb
*blood types of donor & recipient must be compatible; testing:
*determination of blood type
*cross-match test – involves exposing donor’s RBCs to sample of recipient’s plasma under controlled conditions

**white blood cells (WBC)**: leukocytes; have nuclei & other organelles & lack hemoglobin, unlike RBCs (6000-9000 WBC/uL)
*help defend body against invasion by pathogens, & they remove toxins, wastes, & abnormal or damaged cells

*leukocytes divided into 2 categories on basis of appearance after staining:
*granular leukocytes or granulocytes*: (with abundant stained granules)
*neutrophils, eosinophils, & basophils
*agranular leukocytes or agranulocytes*: (with few if any stained granules)
*monocytes & lymphocytes

**WBC circulation & movement**
*circulate for only short portion of their life
*migrate through loose & defense connective tissues of body
*use bloodstream primarily to travel from one organ to another or for rapid transportation to areas of invasion
*circulating WBCs have 4 characteristics:
capable of amoeboid movement – gliding motion accomplished by flow of cytoplasm into slender cellular process extending in front of cell
*mechanism involves continuous rearrangement of bonds of actin filaments in cytoskeleton
*mechanism requires Ca^{2+} ions & ATP
*mobility allows WBCs to move along walls of blood vessels & outside bloodstream, through surrounding tissues
*can migrate out of bloodstream by squeezing between adjacent endothelial cells in capillary wall, a process known as diapedesis
*attracted to specific chemical stimuli – **positive chemotaxis**: guides WBC to invading pathogens, damaging tissues, & active WBCs
*neutrophils, monocytes, & eosinophils are capable of phagocytosis
*cells may engulf pathogens, cell debris, & other materials
*before becoming phagocytic, monocytes must first leave bloodstream & then differentiate into connective tissue cells known as **macrophages**
*neutrophils & eosinophils are sometimes called **microphages**, to distinguish them from larger macrophages

**general function**
*neutrophils, eosinophils, basophils, & monocytes contribute to body’s **nonspecific defenses**
*defenses are activated by variety of stimuli, but they do not discriminate between one type of threat & another
*lymphocytes are responsible for **specific immunity**: body’s ability to mount counter-attack against particular invading pathogens or foreign proteins on individual basis

**neutrophils**: 50-70% of circulating WBCs
*granules are chemically neutral & thus are difficult to stain with either acidic or basic dyes
*mature neutrophil has very dense, segmented nucleus that forms 2-5 lobes resembling beads on string → **polymorphonuclear leukocytes** (PMNs), “polymorphs”
*cytoplasm is packed with pale granules containing lysosomal enzymes & bactericidal compounds
*highly mobile, & generally first of WBCs to arrive at injury site
*very active cells that specialize in attacking & digesting bacteria that have been “marked” with antibodies or complement proteins, plasma proteins involved in tissue defenses
*will quickly engulf bacterium, & metabolic rate of neutrophil increases dramatically – **respiratory burst** accompanies production of destructive chemical agents, including hydrogen peroxide & superoxide anions – highly reactive chemicals that can kill bacteria
*meanwhile, vesicle holding pathogen fuses with lysosomes that contain digestive enzymes & small peptides called defensins
*process which reduces number of granules in cytoplasm is called **degranulation**
*defensins kill variety of pathogens by combining to form large channels in their cell membranes
*while actively engaged in attacking bacteria, neutrophil releases prostaglandins (contribute to local inflammation by increasing capillary permeability in affected region) & leukotrienes (hormones of immune system that attract phagocytes & help coordinate immune response)
*have short life span (only about 10 hours); when actively engulfing debris or pathogens, they may last 30 minutes or less

**eosinophils**: granules stain darkly with **eosin**, a red dye
*represent 2-4% of circulating WBCs
*similar in size to neutrophils, but combination of deep red granules & bi-lobed nucleus makes eosinophil easy to identify
*attack objects that have already been coated with antibodies
*phagocytic cells & will engulf antibody-marked bacteria, protozoa, or cellular debris
*primary mode of attack is exocytosis of toxic compounds onto surface of their opponents
*important against large multicellular parasites, & they increase in number during parasitic infection
*sensitive to circulating allergens (materials trigger allergies), eosinophils increase in number during allergic reactions as well
*attracted to sites of injury, where they release enzymes that reduce degree of inflammation & control its spread to adjacent tissues
*basophils: have numerous granules that stain darkly with basic dyes
*smaller than neutrophils or eosinophils; relatively rare, accounting for less than 1% of circulation leukocyte population
*migrate to sites of injury & cross capillary endothelium to accumulate within damaged tissues
*there they discharge granules, containing histamine & heparin (chemical that prevents blood clotting) into interstitial fluids
*arrival enhances local inflammation initiated by mast cells
*monocytes: have large nucleus that tends to be oval or kidney bean-shaped
*normally account for 2-8% of circulating leukocytes
*individual monocyte uses bloodstream as highway, remaining in circulation for only about 24 hours before entering peripheral tissue to become tissue macrophage
*upon encountering foreign object too large for single cell to engulf, several macrophages may fuse together to create single phagocytic giant cell
*lymphocytes: slightly larger than RBCs & lack abundant, deeply stained granules
*account for 20-30% of WBC population of blood
*continuously migrate from bloodstream through peripheral tissue, & back to bloodstream
*circulating blood contains 3 classes of lymphocytes:
*T cells: responsible for cellular immunity, defense mechanism against invading foreign cells & tissue, & for coordination of immune response
*activated cytotoxic T cells enter peripheral tissues & destroy foreign cells directly by physical & chemical attack
*regulatory T cells, including helper T cells and suppressor T cells, stimulate or inhibit activities of other lymphocytes
*B cells: responsible for humoral immunity, defense mechanism that involves production & distribution of antibodies that can attack foreign antigens throughout body
*active B cells differentiate into plasma cells, which are specialized for synthesis & secretion of antibodies
*antibodies produced by plasma cells in one location can destroy antigens almost anywhere in body
*NK cells: “large granular lymphocytes;” responsible for immune surveillance, detection & subsequent destruction of abnormal tissue cells – important in preventing cancer
*differential count & changes in WBC profiles
*variety of disorders, including pathogenic infection, inflammation, & allergic reactions, cause characteristic changes in circulating populations of WBCs
*differential count: number of each type of cell in sample of 100 WBCs
*leukopenia: indicates inadequate numbers of WBCs
*leukocytosis: refers to excessive numbers of WBCs
*modest leukocytosis is normal during infection
*extreme – generally indicates presence of some form of leukemia
*WBC production
*stem cells responsible for WBC production originate in bone marrow, with divisions of hemocytoblasts
*myeloid stem cell division creates **progenitor cells**, which give rise to all formed elements except lymphocytes
*divisions of one type of progenitor cell produce RBCs; divisions of second type of progenitor cell produce platelets
*neutrophils, eosinophils, basophils, & monocytes are produced by third type of progenitor cell
*all but monocyte complete development within bone marrow
*monocytes complete development when they become free macrophages in peripheral tissue
*each of other cells goes through characteristic series of maturation stages, proceeding from **blast cells to myelocytes to band cells** before becoming mature WBCs
**lymphopoiesis**: production of lymphocytes by lymphoid stem cells, which migrate from bone marrow to peripheral **lymphoid tissues**, including thymus, spleen, & lymph nodes
**regulation of WBC production**
*prior to maturity, “thymosins” produced by thymus promote differentiation & maintenance of T cells
*in adult, production of B & T lymphocytes (escalates when antigen appears) is regulated primarily by exposure to antigens (foreign proteins, cells, or toxins)
*colony-stimulating factors (CSFs): hormones involved in regulation of other WBC populations
*M-Csf: stimulates activity along monocyte/macrophage line
*G-Csf: stimulates production of granulocytes (neutrophils, eosinophils, & basophils)
*GM-Csf: stimulates production of both granulocytes & monocytes
*Multi-Csf: accelerates production of granulocytes, monocytes, platelets, & erythrocytes
*chemical communication between lymphocytes & other WBC assists in coordination of immune response

**Platelets**
*in nonmammalian vertebrates are nucleated cells called **thrombocytes**
*called platelets in human because they are cell fragments rather than individual cells
*continuously replaced – each one circulates 9-12 days before being removed by phagocytes, mainly in spleen
*roughly 1/3 of platelets in body at any moment are held in spleen & other vascular organs rather than in circulation
*thrombocytopenia: abnormally low platelet count; generally indicates excessive platelet destruction or inadequate platelet production
*thrombocytosis: abnormally high platelet count; generally results from accelerated platelet formation in response to infection, inflammation, or cancer
**functions**:
*one participant in vascular clotting system that also includes plasma proteins & cells & tissues of circulatory network
*transport of chemicals important to clotting process
*by releasing enzymes & other factors at appropriate times, they help initiate & control clotting process
*formation of temporary patch in walls of damaged blood vessels
*clump together at injury site, forming **platelet plug**, which can slow rate of blood loss while clotting occurs
*active contraction after clot formation has occurred
*contain filaments of actin & myosin; after blood clot has formed, contraction of
platelet filaments shrinks clot & reduces size of break in vessel wall
*platelet production
*thrombocytopoiesis: platelet production; occurs in bone marrow
*megakaryocytes: unusual, enormous cells in bone marrow & have large nuclei
*during development & growth, they manufacture structural proteins, enzymes, & membranes
*begin shedding cytoplasm in small membrane-enclosed packets – platelets that enter circulation
*produces about 4000 platelets before nucleus is engulfed by phagocytes
*rate of megakaryocyte activity & platelet formation is regulated by:
*thrombopoietin (TPO): thrombocyte-stimulating factor; peptide hormone that accelerates platelet formation & stimulates production of megakaryocytes
*result is rapid rise in platelet count
*produced in kidneys
*interleukin-6 (IL-6): hormone of immune system; has stimulatory effect on platelet formation
*multi-CSF: stimulates platelet production by promoting formation & growth of megakaryocytes

*Hemostasis
*minimizes blood loss through walls of damaged vessels; maintenance of blood volume
*establishes framework for tissue repairs
*vascular phase – lasts about 30 minutes
*cutting wall of blood vessel triggers contraction in smooth muscle fibers of vessel wall
*contraction produces local vascular spasm that decreases diameter of vessel at site of injury
*changes in endothelium at injury site
*endothelial cells contract & expose underlying basement membrane to bloodstream
*endothelial cells begin releasing chemical factors & local hormones
*also release endothelins: peptide hormones that (1) stimulate smooth muscle contraction & promote vascular spasms & (2) stimulate division of endothelial cells, smooth muscle fibers, & fibroblasts to accelerate repair process
*endothelial cell membranes become “sticky” & in small capillaries, endothelial cells on opposite sides of vessel may stick together & close off passageway
*platelet phase:
*platelets now begin to attach to sticky endothelial surfaces, to basement membrane, & to exposed collagen fibers
*platelet adhesion: attachment of platelets to exposed surfaces
*platelet aggregation: platelets sticky to each other
*process forms platelet plug that may close break in vascular lining (within 30 seconds)
*as they arrive, platelets become activated
*first sign is that platelets change shape, becoming more spherical & developing cytoplasmic processes that extend toward adjacent platelets
*at this time, they begin synthesizing & releasing wide variety of compounds, including:
*ADP: primary stimulus for platelet aggregation, shape changes, & platelet secretion
*released by endothelial cells at injury site during vascular phase
*causes platelet aggregation by binding to aggregin, receptor protein on platelet membrane → activates adenylate cyclase, & camp then activates variety of cytoplasmic enzymes that lead to changes in cell shape & to synthesis & secretion of ADP & other compounds

*Thromboxane A₂: paracrine factor related to prostaglandins
*released by activated platelets
*causes (1) platelet aggregation & stimulation of secretory activities by individual platelets, & (2) smooth muscle contractions in vessel walls, enhancing vascular spasms
*Sertotonin: released by activated platelets & by mast cells in surrounding connective tissue assists thromboxane A₂ in stimulating local vasoconstriction
*Platelet factors: include proteins called procoagulants, which play role in blood coagulation, & platelet-derived growth factor (PDGF), peptide that promotes vessel repair by stimulating division of endothelial cells, smooth muscle cells, & fibroblasts
*Ca²⁺ ions released by activated platelets supplement local plasma supply of Ca²⁺
*required for platelet aggregation
*regulation of platelet phase
*this phase proceeds rapidly because each arriving platelet releases ADP, thromboxane, & Ca²⁺ ions that stimulate further aggregation
*factors that limit growth of platelet plug:
  *prostacyclin: prostaglandin that inhibits platelet aggregation & is released by endothelial cells
  *inhibitory compounds released by WBC entering area
  *circulating plasma enzymes that break down ADP near plug
  *compounds that, when abundant, inhibit plug formation
  *development of blood clot, which reinforces platelet plug but separates it from general circulation
*coagulation phase: blood clotting
*starts 30 sec or more after vessel has been damaged
*involves complex sequence of steps leading to conversion of circulating fibrinogen into insoluble protein fibrin
*as fibrin network grows, it covers surface of platelet plug
*blood clot: effectively seals off damaged portion of vessel
*coagulation factors
*normal coagulation cannot occur unless plasma contains necessary clotting factors – procoagulants: include Ca²⁺ & 11 different proteins
*proenzymes: when converted to active enzymes they direct essential reactions in clotting response
*during coagulation phase, enzymes & proenzymes interact
  *activation of one proenzyme commonly creates enzyme that activates second proenzyme – cascade
*extrinsic pathway – begins outside bloodstream
  *begins with release of tissue factor (TF) (phospholipid) by damaged endothelial cells or peripheral tissues;
  *TF then combines with Ca²⁺ & another procoagulant to form enzyme called tissue thromboplastin
*intrinsic pathway – begins inside bloodstream
  *begins with activation of proenzymes exposed to collagen fibers at injury site
  *proceeds with assistance of platelet factor (PF-3) (phospholipid) released by aggregating platelets
  *after series of linked reactions, several activated proenzymes, Ca²⁺, & PF-3 combine to form complex called platelet thromboplastin
*extrinsic & intrinsic pathways converge at common pathways
*begins when thromboplastin from either intrinsic or extrinsic pathway appears in plasma
*first step involves activation of enzyme prothrombinase – activated Factor X; converts proenzyme prothrombin into enzyme thrombin
*thrombin then completes coagulation process by converting fibrinogen, plasma protein, to insoluble strands of fibrin – which then weaves way across hole & lumin of vessel – stick to platelets

*interactions among pathways
*clotting usual begins within about 15 sec of blood vessel damage
*extrinsic pathway – shorter & faster than intrinsic, & it initiates clotting process
*produces small amount of thrombin very quickly
*quick patch is reinforced by intrinsic pathway, which produces greater amounts of thrombin, but somewhat later

*feedback control of coagulation
*thrombin generated in common pathway stimulates process of coagulation by (1) stimulating formation of tissue thromboplastin, & (2) stimulating release of PF-3 by platelets
*coagulation process is restricted by factors that either inactivate or remove proagulants & other stimulatory agents from blood; examples:
*normal plasma contains several anticoagulants, enzymes that inhibit coagulation
*heparin: compound released by basophils & mast cells; cofactor that accelerates activation of antithrombin-III
*thrombomodulin: released by endothelial cells; protein binds to thrombin & converts it to enzyme that activates protein C: plasma protein that inactivates several clotting factors & stimulates formation of plasmin, enzyme that breaks down fibrin strands
*prostacyclin released during platelet phase inhibits platelet aggregation & opposes stimulatory action of thrombin, ADP, & other factors

*Ca\(^{2+}\) ions, vitamin K, & blood coagulation
*Ca\(^{2+}\) ions & vitamin K affect almost every aspect of clotting process
*adequate amounts of vitamin K must be present for liver to be able to synthesize 4 clotting factors, including prothrombin
*fat-soluble vitamin that is absorbed with dietary lipid

*clot retraction: syneresis
*stabilize margin of cut
*pull threads together – tightly pack threads & platelets
*platelets contract
*pulls torn edges of vessel closer together, reducing residual bleeding & stabilizing injury site
*reduces size of damaged area, making it easier for fibroblasts, smooth muscle cells, & endothelial cells to complete repairs

*fibrinolysis: process of dissolving clot
*begins with activation of proenzyme plasminogen by 2 enzymes: thrombin, produced by common pathway, & tissue plasminogen activator (t-PA), released by damaged tissue at injury site
*activation of plasminogen by thrombin or t-PA produces enzyme plasmin, which begins digesting fibrin strands & eroding foundation of clot