BLOOD

- BLOOD = Plasma + Formed Elements

- PLASMA = 91% Water + 7-8% Proteins + 1-2% small molecules
  By definition, if you spin out plasma, you get serum - blood without clotting factors.

- SERUM = Plasma – Clotting Factors
PLASMA PROTEINS

Together, the plasma proteins regulate osmotic pressure in the intravascular space, a property called colloidal osmotic pressure.

The major protein that regulates osmotic pressure is albumin.

Sodium also has a significant role in the regulation of osmotic pressure, but it is “non-colloidal.” More later.
PLASMA PROTEINS

- **ALBUMIN**: 54%. Regulates Osmotic Pressure in the vascular space, Acts as a buffer, Carries stuff.

- **GLOBULINS**: 38%. ALPHA- Transports hormones & bilirubin. BETA- Transports Iron & Copper. Gamma- The antibodies.

- **FIBRINOGEN**: 7%. Clotting Factor I. Converts to Fibrin (clotting factor Ia).

- **1-2%**: Hormones, Enzymes, Complement, Carriers for Lipids.
THE FORMED ELEMENTS

- RBC’S
- WBC’S
- PLATELETS
RBC’S

Originate in the bone marrow.

Biconcave disks.

Contains Hemoglobin (Hb)- Transports Oxygen.

No Nucleus- 110-120 day lifespan. Can not reproduce.

Removed by the spleen.

Prematurely released RBC’s WITH a nucleus are called reticulocytes.

Hemolytic anemia - RBCs destroyed by immune system.

Hemoglobin binds to oxygen, transports throughout the body. Have no nucleus, last a long time, but cannot reproduce.

Removed by the spleen.

When RBC’s broken down bilirubin is a byproduct.

All jaundice is caused by too much bilirubin. Lots of reasons, however - usually rsvp to a systemic poison of some kind.

Early newborn blood cell - similar to the band form of neutrophils

See a lot of reticulocytes in a CBC = blood loss, low O2 level, etc.

EPO (erythropoietin) causes blood cell production so O2 goes up. About the only thing causing this hormone to go up is blood loss. Also, might have enough RBC's, but they aren't doing their job and thus more are created.
WBC’S

- Originate in the Bone Marrow.
- Circulate thru lymphoid tissues.
- Role: The Inflammatory Process and The Immune Process.

- GRANULOCYTES. aka myeloid cells
- AGRANULOCYTES.
GRANULOCYTES

- 1) NEUTROPHILS
- 2) EOSINOIPHILS
- 3) BASOPHILS

- Phagocytic Cells.
- Cytoplasmic Granules.
- Multi-Lobar Nuclei.
NEUTROPHILS

- The “poly’s”, “segs”, or “PMN’s”.
- 55-65% of total WBC’s.
- Involved in acute inflammation.
- Defend against foreign invaders: bacteria, fungi, other debris, substances.
- Engulf and destroy invaders by releasing contents of cytoplasmic granules.
- 1st to arrive and respond to tissue damage, foreign substances.
EOSINOPHILS

- 1-3% of total WBC’s.
- Increased in allergies and parasitic infections.
BASOPHILS

- 0.3-0.5% of total WBC’s.

- Granules contain Heparin and Histamine.

- Involved in allergies.
AGRANULOCYTES

- LYMPHOCYTES.
- MONOCYTES.
LYMPHOCYTES

- 20-30% of total WBC’s.
- Originate in the Bone Marrow.
- Move between the blood and the lymphatics.
- Defend against micro-organisms.
- B-Cells- Humoral Immunity, antibodies.
- T-Cells- Cell-Mediated Immunity, Activate other cells of the Immune System.
MONOCYTES

- 3-8% of total WBC’s.
- Involved in chronic inflammation.
- Called macrophages when they enter tissues.
- Engulf larger particles than do neutrophils.
- Involved in granuloma formation- wall-off material that can’t be digested.
- Called Histiocytes in loose connective tissue, Kupffer Cells in the liver, and Microglial Cells in the brain.
THROMBOCYTES

- PLATELETS - fragments of Megakaryocytes.
- Form a platelet plug, initiating the clotting process.
- Granules release mediators of hemostasis.
- Last 8-9 days, removed by the spleen.
THE CBC

- The Complete Blood Count.
- Hb/Hct- Hemoglobin/Hematocrit. The “H and H”
- THE RBC INDICES- MCV, MCH, MCHC.
- WBC COUNT- total #, with “diff” (differential) the absolute # and % of individual WBC’s.
- PLATELET COUNT.
- PERIPHERAL SMEAR- A visual exam of morphology, size/shape/color.
HEMOSTASIS

Stasis = stop/slow. Non-moving, non-changing
THE 5 STAGES

1) VESSEL SPASM.
2) FORMATION OF PLATELET PLUG.
3) FORMATION OF FIBRIN CLOT.
4) CLOT RETRACTION.
5) CLOT DISSOLUTION.
1) VESSEL SPASM

- Initiated by endothelial injury.
- Local and humoral mechanisms.
- Constricts blood vessels, decreased flow.
- Platelets → Thromboxane A2 → vasoconstriction.
- Lasts < 1 minute.
2) PLATELET PLUG

- Platelets $\rightarrow$ Enzymes $\rightarrow$ Prostaglandins $\rightarrow$ Thromboxane A2.
- Granules- $\alpha$ and $\delta$ - see text.
- Requires the von Willebrand Factor, carrier protein for factor VIII.
- ADHESION- To the subendothelial layer, exposed collagen at site of injury.
- AGGLUTINATION- Occurs next, mediated by the contents of the granules.
3) BLOOD COAGULATION

- The “Coagulation Cascade”- see text.
- Fibrinogen (I) → Fibrin (Ia) – The “Mesh”
- Cements platelets and other components.
- Extrinsic and Intrinsic Pathways.
- Result of both is activation of Factor X and conversion of Prothrombin (II) to Thrombin (IIa).
- Thrombin converts Fibrinogen (I) to Fibrin (Ia).
CLOTTING FACTORS

- Synthesized in the liver.
- Factors VII, IX, X, II (Prothrombin) and Protein C require Vitamin K.
- Calcium (Factor IV) required in all but the 1st two steps.
ANTICOAGULANTS

- Naturally-occurring, regulate clotting.
- **ANTI-THROMBIN III** - Inactivates coagulation factors, and neutralizes thrombin.
  - Inhibits clot formation.
- **PROTEIN C** - Inactivates Factors V and VIII.
- **PROTEIN S** - Accelerates action of Protein C.
- **HEPARIN** - Naturally-occurring, released by Basophils, accelerates action of Anti-thrombin III

Body produced heparin in the lungs and a number of other places. When administered artificially and too fast actually increases rate of platelet formation and eventually bleeding disorders. Doesn’t work well chronically -- use cumidin or warfarin which decreases prothrombin and alters availability of Vita K. Since Vita K is a cofactor for so many coag factors, this slows coagulation.

See top pg 290. Once factor 10 is triggered....this untriggers it.
4) CLOT RETRACTION

- Squeezes serum from the clot.
- Joins the edges of the broken vessel.
- Occurs 20-60 min. after clot formation.
- Requires lots of platelets, can not occur w/ decreased platelet count.
5) CLOT DISSOLUTION

- AKA Fibrinolysis.

- Plasminogen converted to Plasmin by "Plasminogen activators": TPA, Urokinase-type plasminogen activator.

- Plasmin digests Fibrin, and clotting factors.
HYPERCOAGUABILITY

- 1) INCREASED PLATELET FUNCTION.
- 2) ACCELERATED CLOTTING ACTIVITY.
1) INCREASED PLATELET FUNCTION

- Results in platelet adhesion, formation of platelet plugs, and decreased flow.

- Caused by: disturbance of flow; endothelial damage; increased sensitivity of platelets to factors causing adhesion and agglutination.

- Found in: atherosclerosis; diabetes; smoking; elevated lipids, inc. platelet count.
2) ACCELERATED CLOTTING ACTIVITY

- **ACQUIRED**: pregnancy and the puerperium, OCP’s, post-op, immobility, CHF, malignancy, obesity.

- **INHERITED**: 1) Mutations in the genes for Factor V (the Leiden mutation) and Prothrombin. Mutant Factor V is not inactivated by Protein C because it is not recognized—anti-coagulant activity is lost. 2) Deficiencies of anti-coagulants: Protein C, Anti-thrombin III, Protein S.
THROMBOCYTOPENIA

- Count < 100,000. bruising and bleeding, less than 25K and you're in trouble.

- Caused by:
  1) Decreased production.
  2) Increased removal / destruction.
  3) Sequestration in the spleen.
1) DECREASED PRODUCTION

- APLASTIC ANEMIA.

- MARROW REPLACED BY MALIGNANCY.

- HIV- SUPPRESSED PRODUCTION OF MEGAKARYOCYTES.

- RADIATION, CHEMO.
2) INCREASED DESTRUCTION

- ANTI-PLATELET ANTIBODIES- I.T.P. / A.I.T.P.

- MECHANICAL- Prosthetic heart valves, malignancy, hypertension.

- CONSUMPTION- D.I.C., T.T.P- see text.
3) SEQUESTRATION IN THE SPLEEN

- Hypersplenism, as in portal hypertension in cirrhosis.
- Splenomegaly- as from mononucleosis.
- Lymphoma.
MANIFESTATIONS OF THROMBOCYTOPENIA

- Clinically significant bleeding does not typically occur until platelets < 50,000.
- Easy bruising.
- Nose bleeds (epistaxis).
- Bleeding from the gums.
- Heavy menses.
COAGULOPATHIES

1) IMPAIRED SYNTHESIS OF CLOTTING FACTORS.

2) HEREDITARY DISORDERS.

3) VON WILLEBRAND’S DISEASE.
1) IMPAIRED SYNTHESIS OF CLOTTING FACTORS

- Liver disease.

- Vitamin K deficiency.  
  
  *this happens when liver failing.*
2) HEREDITARY DISORDERS

- Hemophilia B - defective production of Factor IX.
- Soft-tissue bleeding.
- Hemarthroses.
- See text.
3) VON WILLEBRAND’S DISEASE

- Most common hereditary bleeding disorder.
- Autosomal dominant with “variable penetrance”
- Deficiency or defect of von Willebrand Factor—the carrier protein for Factor VIII.
- Decreased platelet adhesion, decreased levels of Factor VIII.
- Easy bruising, nosebleeds, etc.
- Often not diagnosed until surgery or dental work.
MANIFESTATIONS OF ANEMIA:

1) Impaired oxygen transport, and compensatory mechanisms: fatigue, weakness, dyspnea, headache, faintness, pallor, tachycardia, palpitations.

2) Reduction in Hb and RBC Indices.

3) Signs/Sx’s of the process causing the anemia.
TYPES OF ANEMIA

1) BLOOD LOSS.

2) HEMOLYTIC.

3) DECREASED RED CELL PRODUCTION.

lack of bone marrow activity too.
1) BLOOD LOSS

- **ACUTE-** Decreased blood volume, shock. In acute blood loss, RBC’s are normal size and shape. Hb/Hct fall due to hemodilution.

2) HEMOLYTIC ANEMIAS

- Premature destruction of RBC’s.
- Normochromic, normocytic, unless it is chronic and iron stores become depleted, then the RBC’s become hypochromic, microcytic.

- 2 Categories:
  - 1) Intrinsic to the RBC.
  - 2) Extrinsic to the RBC.
INTRINSIC CAUSES OF HEMOLYTIC ANEMIA

- **DEFECTS OF THE RBC MEMBRANE** - hereditary spherocytosis.
- **HEMOGLOBINOPATHIES** -
  - Sickle cell disease
  - The Thalassemias
- **Enzyme defects** - G-6-PD
HEREDITARY SPHEROCYTOSIS

- Autosomal dominant.
- Defect of red cell membrane proteins.
- Spherical shape $\rightarrow$ gobbled up by the spleen
SICKLE CELL DISEASE

- Autosomal recessive.
- 10% of African-Americans carry the gene (heterozygous).
- Single amino acid substitution in the beta chain of Hb.
- Cells sickle w/ decreased oxygen tension.
- Gobbled up by the spleen and hemolyzed.
- Cells adhere to the endothelium \(\rightarrow\) endothelial activation \(\rightarrow\) activator substances \(\rightarrow\) platelet activation \(\rightarrow\) thrombosis
SICKLE CELL DISEASES

- Thrombosis $\rightarrow$ Sickle cell crisis.
- Tissue infarction- bone, spleen, lung.
- Chronic pain, susceptibility to infection, pulmonary compromise.
- Dx: Hb electrophoresis.
THE THALASSEMIA

- Autosomal recessive- homozygous (thalassemia major): severe disease; heterozygous (thalassemia minor): milder disease.
- Absent or defective production of $\alpha$ or $\beta$ chain of Hb.
- Anemia is from: 1) Reduced Hb synthesis, or 2) imbalance in globin chain production.
- Hypochromic / microcytic- can mimic Fe deficiency.
ENZYME DEFECTS

- G-6-PD Deficiency. RBC’s are more vulnerable to oxidants → hemolysis in the spleen.
EXTRINSIC CAUSES OF HEMOLYTIC ANEMIA

- Cause hemolysis by direct membrane destruction, or by antibody-mediated lysis.
- Causes: drugs, toxins, chemicals, infection, antibodies.
- Antibodies: auto-immune; lupus, ulcerative colitis, drug-induced, idiopathic.
ANEMIAS OF DEFICIENT RED CELL PRODUCTION

1) **IRON DEFICIENCY** - decreased prod. of Hb. Microcytic, hypochromic.

2) **MEGALOBLASTIC** - macrocytic, hypochromic. B12 (cobalamin), Folic Acid - required for nucleic acid synthesis.

3) **APLASTIC ANEMIA** - decreased prod. of red cells in the marrow; also dec. WBC’s, platelets; radiation, chemo., drugs, toxins, idiopathic.

4) **ANEMIA OF CHRONIC DISEASE** - microcytic, hypochromic; cancer, infection, HTN, renal failure, inflammation.

bone marrow just stops producing RBCs in response to the sickness.
POLYCYTHEMIA

- Increased red cell mass, **HCT > 50%**.
- PRIMARY VS. SECONDARY.

Increased RBC production. Excessive bone marrow prod of RBC. Blood sluggish, easy to clot.
PRIMARY POLYCYTHEMIA

POLYCYTHEMIA VERA - A Myeloproliferative Disorder.

- Increased RBC’s, WBC’s, Platelets. ^--all 3 go up.
- Sx’s related to ↑ red cell mass: ↑ viscosity, ↓ C.O., HTN, plethora, headaches, itching fingers and toes
- Thromboembolism - death 10-40%.
- Treatment - periodic phlebotomy, bone marrow irradiation for severe cases.

More systemic and more gradual onset than sickle cell, but there are similarities.
SECONDARY POLYCYTHEMIA

- ↑ RBC’s only.
- A compensatory response to hypoxia.
- High altitude, smoking, chronic heart / lung disease.

Happens slowly over time. Pt rarely feels pain or discomfort from it.
DISORDERS OF WBC’s AND LYMPHOID TISSUE

- NEUTROPENIA-

  - ↓ in neutrophils, <1500 / µl

  - If < 200 = severe neutropenia = agranulocytosis

- ACQUIRED.

- CONGENITAL.
ACQUIRED NEUTROPENIA

- Manifestations: malaise, fever, chills, fatigue, susceptibility to infection: bacterial, fungal, respiratory,
- Impaired bone marrow production- aplastic anemia, chemo, XRT, leukemia, lymphoma, bacterial / viral infection (neutrophils are “used up”).
- Most cases are drug-related- cause antibodies to be produced against neutrophils.
MONONUCLEOSIS

- Self-limiting lymphoproliferative disorder.
- Caused by Epstein Barr Virus (EBV).
- Signs / Sx’s:
  1) Prodrome- malaise, anorexia, chills, pharyngitis, lymphadenopathy (generalized).
  2) Rubella-like skin rash.
  3) Hepatitis- nausea, jaundice, ↑ LFT’s.
  4) Splenomegaly.
  5) Sx’s 2-3 weeks, fatigue 2-3 months.
LYMPHOMAS

1) Hodgkins Lymphoma.
   Cureable - seen in very young or over 50, single node.

2) Non-Hodgkins Lymphoma.
   Not so much, multiple nodes.

Derived from neoplastic lymphoid tissue cells:
  lymphocytes, histiocytes.
HODGKINS DISEASE

- Characterized by the Reed-Sternberg Cell.

- Bimodal age distribution- early 20’s, both sexes; after 50, primarily males.

- Signs / Sx’s: painless lymphadenopathy, fever, chills, night sweats, weight loss, susceptibility to infection: viral, fungal, protozoal- impaired cellular immunity.
NON-HODGKINS LYMPHOMA

- 3X more frequent than Hodgkins.
- Divided into 3 groups: low-grade, intermediate-grade, high-grade.
- Most are of B-Cell origin.
- Signs / Sx’s- painless lymphadenopathy, susceptibility to infection: bacterial, viral, fungal- impaired humoral immunity.

same sx, more frequent than hodgkins
THE LEUKEMIAS

- Acute and Chronic.

- **Lymphocytic** (lymphocytes)- involve immature lymphocytes, originate in the bone marrow but infiltrate the spleen, nodes, CNS.

  - 2 types

- **Myelogenous** (granulocytes, monocytes)- involve the pluripotent stem cell, interferes w/ all cell lines- RBC’s, WBC’s, platelets.

  - more common in kids, 85% cureable
  - adults, don't rsvp well to tx.
ACUTE LEUKEMIAS

- Sudden onset.
- Signs / Sx’s related to deficient bone marrow function.
- A.M.L.- Adults.
- Manifestations- fatigue, pallor, weight loss, fever, chills, night sweats, infection, easy bruising, epistaxis.
- Lymphadenopathy, Splenomegaly, Hepatomegaly, CNS involvement.