TOPIC 5 Lab – B: Diagnostic Tools & Therapies – Blood & Lymphatic Disorders

Refer to chapter 17 and selected online sources. Refer to the front cover of Gould & Dyer for normal blood test values.

Complete and internet search for videos from reliable sources on blood donations and blood tests.

Topic 5 Lab - A: Blood and Lymphatic Disorders

You’ll need to refer to an anatomy & physiology textbook or lab manual to complete many of these objectives.

Blood Lab Materials
- Prepared slides of normal blood
- Prepared slides of specific blood pathologies
- Models of formed elements
- Plaque models of formed elements
- Blood typing model kits

Blood Lab Objectives – by the end of this lab, students should be able to:

1. Describe the physical characteristics of blood.

2. Differentiate between the plasma and serum.
3. Identify the formed elements on prepared slides, diagrams and models and state their main functions. You may wish to draw what you see in the space provided.

<table>
<thead>
<tr>
<th>Formed Element</th>
<th>Description / Function</th>
<th>Drawing</th>
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</thead>
<tbody>
<tr>
<td>Erythrocyte</td>
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<tr>
<td>Leukocytes</td>
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<td>Granulocytes</td>
<td>Neutrophil</td>
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<td></td>
<td>Eosinophils</td>
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<td>Basophils</td>
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<tr>
<td>Agranulocyte</td>
<td>Monocytes</td>
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<td></td>
<td>Lymphocytes</td>
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<tr>
<td>Thrombocytes</td>
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</table>

4. Define differential white blood cell count. State the major function and expected range (percentage) of each type of white blood cell in normal blood.

<table>
<thead>
<tr>
<th>WBC Type</th>
<th>Function</th>
<th>Expected %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
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<tr>
<td>Eosinophils</td>
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<tr>
<td>Basophils</td>
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<tr>
<td>Monocytes</td>
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<tr>
<td>Lymphocytes</td>
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</tbody>
</table>

5. Calculation of the differential count?

6. Define and use in proper context:

1. achlorhydria
2. acute leukemia
3. agnogenic myeloid metaplasia
4. aleukemic leukemia
5. amyloidosis
6. anemia
7. autosplenectomy
8. basophilic stippling
9. Bence Jones protein
10. Birbeck granule (HX body)
11. bronchus-associated lymphoid tissue (BALT)
12. chronic leukemia
13. circulating pool
14. coagulation
15. complete blood count (CBC)
16. cryoglobulinemia
17. direct antiglobulin (Coombs) test
18. dyserythropoiesis
19. dysmegakaryocytes
20. ecchymoses
21. erythropoiesis
22. erythropoietin
23. extramedullary hematopoiesis
24. extravascular hemolysis
25. ferritin
26. G6PD screen
27. granulocytopenia
28. granulopoiesis
29. Ham test
30. haptoglobin
31. hematocrit
32. hemolysis
33. hemoglobin electrophoresis
34. hemostasis
35. hyperviscosity syndrome
36. hypochromia
37. idiopathic thrombocytopenic purpura (ITP)
38. indirect antiglobulin (Coombs) test
39. ineffective hematopoiesis
40. intravascular hemolysis
41. intrinsic factor
42. left shift
43. leukemia
44. leukemoid reaction
45. leukocytosis
46. leukoerythroblastosis
47. leukopenia
48. lymphoma
49. macrocytosis
50. maturing pool
51. maturation/storage pool
52. mean cell hemoglobin (MCH)
53. mean cell hemoglobin concentration (MCHC)
54. mean cell volume (MCV)
55. microcytosis
56. mucosa-associated lymphoid tissue (MALT)
57. myelodysplastic syndrome
58. myelophthisic
59. myeloproliferative disorder
60. nuclear-cytoplasmic asynchrony
61. pancytopenia
62. petechiae
63. Philadelphia chromosome
64. Plummer-Vinson syndrome
65. poikilocytosis
66. polychromasia
67. proliferating pool
68. purpura
69. red cell distribution width (RDW)
70. reticulocyte count
71. Schilling test
72. sickle cell disease
73. sickle cell prep
74. sickle cell trait
75. stem cell
76. sugar water test
77. thalassemia
78. thrombocytopeny
79. thrombocytopenia
80. thrombocytopath
81. thrombocytosis
82. thrombopoiesis
83. thrombopoietin
84. thrombotic thrombocytopenic purpura (TTP)
85. total iron binding capacity (TIBC)
86. transferrin
87. von Willebrand factor

Define, state the significance of, and identify on a peripheral blood smear each of the following:

- erythrocyte (discocyte)
- reticulocyte
- acanthocyte (spur cell)
- echinocyte (burr cell)
- codocyte (leptocyte, target cell)

- stomatocyte
- schistocyte
- rouleaux
- ringed sideroblast
- Cabot ring
Howell-Jolly body  myeloblast
Pappenheimer body  Pelger-Huët cell
Heinz body  pseudo-Pelger-Huët cell
polymorphonuclear leukocyte (PMN)  Döhle body
neutrophil  basket (smudge) cell
band (stab) form  flame cell
basophil  grape cell (Mott cell, thesaurocyte)
eosinophil  Russell body
monocyte  Dutcher body
plasma cell  hairy cell
plasmacytoid lymphocyte  Sézary cell
atypical lymphocyte  platelet
lymphocyte  giant platelet
lymphoblast

88. Define, state the significance of, and identify on a bone marrow smear each of the following:
pronormoblast  myelocyte  eosinophil
normoblast  metamyelocyte  plasma cell
megaloblast  band (stab) form  lymphocyte
myeloblast  neutrophil  megakaryocyte
promyelocyte  basophil

89. Explain:
• the concept of reference (normal) range
• the theory of the automated cell counter
• the components of the complete blood count (CBC) and its application in patient evaluation

90. Compare and contrast the reporting of leukocyte differential counts as relative percentages vs. absolute numbers, in terms of the advantages and disadvantages of each system.

91. Discuss the stages of erythropoiesis in terms of:
• morphology of each stage
• stages in which hemoglobin is produced
• lifespan of reticulocytes and mature red blood cells
• mechanisms of degradation of senescent erythrocytes
• factors (vitamin, minerals and hormones) which influence erythropoiesis
7. Compare the appearance of acute and chronic granulocytic leukemia

8. State the normal ranges and discuss the clinical importance of each of the following:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Range</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total RBC count</td>
<td></td>
<td></td>
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<tr>
<td>Total WBC count</td>
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<tr>
<td>Hematocrit (Hct)</td>
<td></td>
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<tr>
<td>MCHC</td>
<td></td>
<td></td>
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<tr>
<td>MCV</td>
<td></td>
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<tr>
<td>MCH</td>
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<tr>
<td>RDW</td>
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</tbody>
</table>

- **Hemoglobin and Hematocrit Assay**

  The hematocrit describes the ratio of the volume of erythrocytes to the total blood volume (the SI unit is without dimension, e.g., 0.4).

  The automated hematology counter determines the mean corpuscular or cell volume (MCV, measured in femtoliters, fl) and the number of erythrocytes.

  It calculates the hematocrit (HCT) using the following formula:

  \[ \text{HCT} = \frac{\text{MCV} \text{ (fl)}}{\text{number of erythrocytes (106/\mu l)}} \]

- **Calculation of Erythrocyte Parameters**

  The quality of erythrocytes is characterized by their MCV, their mean cell hemoglobin content (MCH), and the mean cellular hemoglobin concentration (MCHC).

  - MCV is measured directly using an automated hemoglobin analyzer, or is calculated as follows:
    1. MCV
    2. Hematocrit (l/l)
    3. Number of erythrocytes (106/\mu l)
MCH (in picograms per erythrocyte) is calculated using the following formula:

1. MCH (pg) "
2. Hemoglobin (g/l)
3. Number of erythrocytes (10^6/μl)

\[
MCH (\text{pg}) = \frac{\text{Hemoglobin} \ (\text{g/l})}{\text{Number of erythrocytes} \ (10^6/\mu l)}
\]

MCHC is determined using this formula:

\[
MCHC \ (\text{g/dl}) = \frac{\text{Hemoglobin concentration} \ (\text{g/dl})}{\text{Hematocrit} \ (\text{l/l})}
\]

Red Cell Distribution Width (RDW)
Modern analyzers also record the red cell distribution width (cell volume distribution). In normal erythrocyte morphology, this correlates with the Price-Jones curve for the cell diameter distribution.

- **Anemia**
  - Define or describe the following disorders and terms associated with erythrocytes:
    - Anemia
      - Sickle cell anemia
      - Hemolytic anemia
      - Hemorrhagic anemia
      - Iron deficiency anemia
    - Polycythemia
      - Erythrocytosis
    - Microcytic
    - Macrocytic
    - Hyperchromic
Design a logarithm related to anemia, exploration and treatment.

- How to interpret red cell appearances
  - Microcytosis (reduced average cell size, MCV < 76 fL)
  - Macrocytosis (increased average cell size, MCV > 100 fL)
  - Target cells (central area of haemoglobinisation)
  - Spherocytes (dense cells, no area of central pallor)
  - Red cell fragments (intravascular haemolysis)
  - Nucleated red blood cells (normoblasts)
  - Howell-Jolly bodies (small round nuclear remnants)
  - Polychromasia (young red cells-reticulocytes present)
  - Basophilic stippling (abnormal ribosomes appear as blue dots)
<table>
<thead>
<tr>
<th>Erythrocytes bodies</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell-Jolly bodies (Wright stain)</td>
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<tr>
<td>Basophilic stippling</td>
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<td>Schistocytes</td>
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<tr>
<td>Reticulocytes (methylene blue stain)</td>
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<tr>
<td>Spherocytes</td>
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<tr>
<td>Target cell</td>
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<tr>
<td>Nucleated RBC</td>
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<tr>
<td>Teardrop cell</td>
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<tr>
<td>Acanthocyte</td>
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<tr>
<td>Agglutinated cell</td>
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<tr>
<td>Heinz body</td>
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<tr>
<td>Rouleaux</td>
<td></td>
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<tr>
<td>Dohle bodies</td>
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<tr>
<td>Pelger-Huet anomaly</td>
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</table>
1. Discuss the following classification of anemia in terms of rationale for its use, and specific examples in each category:
   - hypochromic-microcytic
   - normochromic-normocytic
   - macrocytic

2. Categorize and discuss laboratory test procedures used in the diagnosis of anemia, outlining the basic workup of a patient who presents with anemia.

3. Assess bone marrow function in the diagnosis of the anemic patient, on the basis of:
   - reticulocyte count (relative, absolute, and corrected)
   - serum bilirubin
   - urobilinogen concentration

4. Discuss the following types of anemia:
   - iron deficiency anemia
   - megaloblastic anemias
   - folate deficiency anemia
   - pernicious anemia
   - anemia of chronic disease
   - aplastic anemia

   in terms of:
   - incidence
   - associated risks
   - etiology and pathogenesis
   - marrow and peripheral blood morphology
   - laboratory diagnostic criteria
   - clinical features and course
5. Utilize peripheral blood and bone marrow smears to assess the deviations from normal marrow response which occur in:
   - hemolytic anemias
   - nuclear maturation defects
   - cytoplasmic maturation defects
   - hypoproliferative anemias

6. Compare and contrast anemia secondary to acute vs. chronic blood loss in terms of:
   - etiology
   - pathophysiologic changes
   - clinicopathologic diagnosis

7. Discuss the following types of anemia:
   - sickle cell anemia
   - the thalassemia disorders
   - hereditary spherocytosis
   - glucose-6-phosphate dehydrogenase (G6PD) deficiency
   - pyruvate kinase deficiency
   - paroxysmal nocturnal hemoglobinuria
   - mechanical hemolytic anemia
   - malaria
   
   in terms of:
   - genetics - molecular changes
   - incidence
   - etiology
   - pathogenesis
   - morphology
     - peripheral blood
     - bone marrow
     - liver
     - spleen
   - laboratory diagnosis
   - clinical features and course

8. Compare and contrast warm vs. cold antibody immunohemolytic anemias in terms of:
   - etiology
   - pathogenesis
   - associated risks-diseases
   - laboratory diagnosis
   - clinical features and course

9. Compare and contrast intravascular vs. extravascular hemolysis, in terms of:
   - etiology
   - pathogenesis
   - laboratory diagnosis
   - clinical findings and course
Define and causes of the following Leukocyte Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition and Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancytopenia</td>
<td></td>
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<tr>
<td>Leukocytosis</td>
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<tr>
<td>Lymphocytosis</td>
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<tr>
<td>Neutrophilia</td>
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<tr>
<td>Eosinophilia</td>
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<tr>
<td>Monocytosis</td>
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<tr>
<td>Polycythemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<td><em>Petechiae</em></td>
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<tr>
<td>Thrombocytosis</td>
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<tr>
<td>Splenomegaly</td>
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<tr>
<td>Plasmacytosis</td>
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</table>

9. Define the following:
   - Agglutinogen (surface antigen)
   - Agglutinin (antibody)
   - Cross-reaction
10. Use the blood typing models to make all the possible ABO / Rh combinations (e.g., A+, O-). Include the antibodies made by each. Use these combinations to review interactions between various blood types to determine which types may be given to each and from which types each may receive. Write + or – after the ABO letter to indicate Rh, e.g., O+ is O positive.

<table>
<thead>
<tr>
<th>ABO Blood Type</th>
<th>Antibodies present in serum</th>
<th>May receive blood from</th>
<th>May be donated safely to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh+</td>
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<tr>
<td>Rh-</td>
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1. Discuss basic qualifications of a potential blood donor including reasons for deferral and routine laboratory tests performed on donor blood.

2. Describe the methods by which whole blood is collected and processed into the following components:
   - packed red blood cells (RBCs)
   - additive solution packed RBCs
   - fresh-frozen plasma (FFP)
   - platelets
   - cryoprecipitate

3. Describe how ABO and Rh antigens are formed, including the genetic bases thereof

4. Describe the basic identification procedures, incidence, and inheritance of the ABO and Rh blood groups

5. Compare and contrast the precursor substance which forms the backbone of the Lewis antigens with the precursor of the ABH antigens

6. Discuss the following blood group systems:
   - Lewis
   - Duffy
   - Kidd
   - Kell

   in terms of:

   - importance of transfusion history
   - modes of acquisition of antibodies
   - clinical significance of antibodies
transfusion reactions
hemolytic disease of newborn (HDN)

34. Discuss thrombocytopenia in terms of:
   • differential diagnosis
   • clinical features
   • bone marrow morphology and
   • laboratory features

50. Discuss thrombocytosis in terms of diagnosis and differential diagnosis.

51. Outline the role of platelets in normal hemostasis.

52. Outline the process for stepwise evaluation of a patient with suspected platelet disorder

53. Compare and contrast the following disorders of platelets:
   Glanzmann thrombasthenia    gray platelet syndrome
   Chediak-Higashi syndrome     von Willebrand disease
   Bernard-Soulier disease      HIV-associated thrombocytopenia
   Hermansky-Pudlak syndrome   drug-induced thrombocytopenia

   in terms of:
   o definition
   o genetics
   o laboratory features including platelet aggregation patterns
   o clinical features

54. Categorize and discuss acquired disorders of platelet function in terms of etiology and pathogenesis.

55. Compare and contrast:
   • idiopathic thrombocytopenic purpura (ITP)
   • thrombotic thrombocytopenic purpura (TTP)
   • hemolytic-uremic syndrome (HUS)

   in terms of:
   o etiology
   o pathogenesis
   o clinical features
   o morphologic findings
   o clinicopathologic diagnosis

55. List and discuss the laboratory diagnostic procedures used to approach patients with:
   • bleeding disorders
   • thrombotic disorders

56. Discuss disseminated intravascular coagulopathy (DIC) in terms of:
   etiologies                     clinical presentation and course
   pathogenesis                   laboratory diagnosis
   morphologic features          complications and prognosis
Lymphatic System Materials

- Torso model
- Head plaques
- Heart with thymus model
- Lymphatic system plaque
- Lymph node histology slides
- Intestine model
- Ileum histology slides
- Spleen histology slides

Lymphatic System Objectives – by the end of this lab, students should be able to:

11. State the main functions of the lymphatic system and explain how it works together with the blood vascular system.

12. Identify the following lymphatic vessels and associated structures on diagrams and models and state the functions of each.
   Lymphatic collecting vessels
   - Cervical lymph nodes
   - Axillary lymph nodes
   - Right lymphatic duct
   - Thoracic duct
   - Cisterna chyli
   - Intestinal lymph nodes
   - Inguinal lymph nodes

13. Identify the following structures of a lymph node on diagrams and microscope slides* and state the function and/or description of each. Fig. 23.4 p. 434
   - Afferent lymphatic vessel
   - Capsule*
   - Cortex*
   - Germinal center
   - Medulla*
   - Efferent lymphatic vessel

14. Identify and state the function of the following lymphatic tissues and organs. Identify their histological features on diagrams and models and slides*, as appropriate.
Pharyngeal tonsil (adenoid)
Palatine tonsil*
  Crypt* (found in all types of tonsils)
  Follicle (found in all types of tonsils)
Lingual tonsil
Spleen *
  Capsule*
  Red pulp*
  White pulp*
Thymus
Peyer’s patches in ileum*
Appendix

Define the below:

Virchow lymph nodes
Sentinel lymph nodes

What are the secondary lymphoids organs?
MALT?
GALT?
BALT?

Discuss characteristics and treatment of common lymphatic disorders.

A. Tonsillitis
1. In childhood, tonsils become infected and enlarged
2. Difficulty swallowing
3. Tonsillectomy in extreme cases

B. Lymphadenitis (adenitis)
4. Swelling (enlargement) of lymph glands
5. Occurs when infection present and body making WBCs to fight infection

C. Hodgkin’s disease
1. Cancer of lymph nodes
2. Painless swelling of lymph node early symptom
3. Rx – chemotheraphy and radiation
D. Mononucleosis
1. Caused by virus
2. Young adults and children
3. Spread by oral contact (kissing)
4. Symptoms – lymphadenitis, fever, fatigue, leukocytes
5. Rx - bedrest

E. Hypersensitivity
1. Abnormal response to drug or allergen
2. Antibodies made in response to foreign material (allergen) irritate certain body cells
3. Allergen – antigen that causes allergic response (Examp. Ragweed, penicillin, bee stings, foods, etc.)

F. Anaphylaxis (Anaphylactic shock)
1. Severe or fatal allergic reaction
2. Antigen-antibody response stimulates massive secretion of histamine
3. Symptoms – breathing problems, headache, facial swelling, falling blood pressure, stomach cramps, vomiting
4. Rx – Adrenaline
5. Those prone should wear medic alert bracelet

AIDS and HIV
1. Acquired immunodeficiency syndrome
2. Cause – HIV virus
3. Three responses to HIV infection:
   a. AIDS – full disorder
   b. ARC – AIDS-related complex
   c. Asymptomatic infection
   4. Screening test for HIV available
   5. AIDS victim subject to opportunistic infections (cancer, infections) that a healthy person would fight off but AIDS victim has compromised immune response
   6. Incubation period – 1 month to 12 years
   7. Rx and prevention – advances being made
   8. ARC – AIDS-related complex – HIV but not AIDS – less severe symptoms
   9. Transmission
      a. Sex with someone HIV positive
      b. Sharing needles with infected drug users
      c. At birth from infected mother
   10. Cannot be spread by casual contact, coughing, sneezing, shaking hands and sharing eating utensils
   11. Prevention – avoid risky behaviors and observe standard precautions

10. Compare and contrast:
   - acute lymphoblastic leukemia (ALL)
   - acute myeloblastic leukemia (AML)
   - chronic lymphocytic leukemia (CLL)
   - chronic myeloid leukemia (CML)
   - hairy cell leukemia (HCL)

   in terms of:
11. Describe the FAB (French-American-British) classification of acute myeloblastic leukemias in terms of:
   - nomenclature
   - incidence of each type
   - general features of each type

12. List the major etiology and pathogenesis of the following:
   - leukopenia
   - leukemoid reaction
   - neutropenia (relative and absolute)
   - lymphocytosis (relative and absolute)
   - left shift
   - atypical lymphocytes
   - eosinophilia
   - monocytosis
   - basophilia
   - leukoerythroblastic reaction

13. Distinguish between leukemia and leukemoid reaction on the basis of:
   - etiology
   - pathogenesis
   - laboratory data

14. Morphologically differentiate a blast form from a monocyte and lymphocyte.

15. Discuss the following myelodysplastic syndromes:
   - refractory anemia
   - refractory anemia with ringed sideroblasts
   - refractory anemia with excess blasts (RAEB)
   - refractory anemia with excess blasts in transformation (RAEB-IT)
   - chronic myelomonocytic leukemia (CMML)

   in terms of:
   - clinical presentation
   - etiology
   - genetics
   - morphology of peripheral blood and bone marrow
   - laboratory diagnosis
   - clinical course
   - prognosis

16. Define and classify the myeloproliferative disorders.

17. Discuss the following myeloproliferative disorders:
   - chronic myeloid leukemia
   - polycythemia vera
   - myeloid metaplasia with myelofibrosis
   - essential thrombocythemia

   in terms of:
18. Compare and contrast:
   - polycythemia vera
   - relative polycythemia
   - secondary polycythemia

   in terms of:
   - etiology
   - diagnostic criteria
   - clinical course and complications

19. Describe the proper mode of submission of a lymph node biopsy to the surgical pathology laboratory for workup of a suspected lymphoproliferative disorder.

20. Define, state the significance of, and identify in a microscopic section of a lymph node or extranodal site of involvement each of the following:

   lymphocyte (normal)  Hodgkin cell
   small cleaved lymphocyte  Reed-Sternberg cell
   large lymphocyte  "popcorn" cell
   macrophage  lacunar cell

21. Compare and contrast:
   - follicular hyperplasia
   - follicular lymphoma

   on the basis of:
   - histologic criteria
   - clinical significance

22. Discuss general features of non-Hodgkin lymphomas in terms of:
   - incidence
   - immunophenotyping (T vs B cells)
   - morphologic patterns (diffuse vs. follicular)
   - principles of:
     - classification
     - grading
     - staging
   - laboratory methods of diagnosis
   - clinical features
   - prognosis
   - extralymphatic organs involved
   - likelihood of a leukemic phase
23. Compare and contrast:
   - small lymphocytic lymphoma
   - follicular lymphoma
   - diffuse large cell lymphoma

   in terms of:
   - incidence
   - associated conditions
   - age and sex distribution
   - morphology
   - immunophenotyping
   - clinical presentation
   - laboratory diagnosis
   - clinical features
   - prognosis

33. Compare and contrast:
   - lymphoblastic lymphoma
   - small noncleaved cell (Burkitt) lymphoma

   in terms of:
   - incidence
   - associated conditions
   - age/sex distribution
   - morphology
   - immunophenotyping
   - laboratory diagnosis
   - clinical features
   - prognosis

35. Discuss Hodgkin disease in terms of:
   - Classification, incidence of each type
   - etiology
   - pathogenesis
   - morphology of each types

36. Compare and contrast:
   - non-Hodgkin lymphomas
   - Hodgkin disease

   in terms of:
   - clinical features
   - methods of staging

37. Discuss:
   - mantle cell lymphoma
   - marginal zone lymphoma
   - peripheral T-cell lymphoma
   - adult T-cell lymphoma/leukemia
   - cutaneous T-cell lymphoma

   in terms of:
38. List benign and malignant etiologies of lymphoadenopathy and splenomegaly.

39. Categorize and discuss the different types of plasma cell dyscrasias in terms of definitions and clinical presentation.

40. Discuss multiple myeloma in terms of:
   - clinical presentation
   - etiology
   - clinicopathologic diagnosis
   - morphology and sites of lesions

41. Discuss Waldenström macroglobulinemia in terms of:
   - clinical presentation
   - etiology
   - morphology with immunophenotyping
   - associated conditions

42. Compare and contrast:
   - plasmacytoma
   - monoclonal gammopathy of uncertain significance (MGUS)
   - heavy chain disease
   in terms of:
     - incidence
     - clinical presentation
     - clinicopathologic diagnosis
     - clinical course
     - differentiation from multiple myeloma

43. Discuss the different laboratory procedures used in the clinicopathologic diagnosis of the different plasma cell dyscrasias.

44. List benign and malignant etiologies of monoclonal gammopathies.

45. Discuss Langerhans cell histiocytosis in terms of:
   - definition
   - classification
   - clinicopathologic diagnosis
   - morphology
   and for each type, discuss:
     - age of onset
     - distribution of lesions
     - clinical course/prognosis

46. Classify major causes of changes in size of spleen, in terms of both increase and decrease.

47. Enumerate the gross and microscopic characteristics of involvement of the spleen by:
   - infarcts
   - sickle cell disease
extramedullary hematopoiesis
passive congestion
amyloid
leukemia
lymphoma
rupture
48. List the major complications of splenomegaly.

49. Briefly describe the morphologic features and clinical findings in:
   - histiocytoses
   - Gaucher disease
   - Neimann-Pick disease
   - Tay-Sachs disease

**Laboratory Blood Tests** (1,2)

Blood tests examine chemical, physical and cellular parameters of blood.

1. Complete blood count (CBC)
   a. Red Blood Cells
      i. RBC count
      ii. Hematocrit (Hct)
      iii. Hemoglobin concentration (Hb)
         1. Mean corpuscular hemoglobin (MCH)
         2. Mean corpuscular hemoglobin concentration (MCHC)
      iv. Mean corpuscular volume (MCV)
      v. Reticulocyte count
   b. WBC
      i. WBC count
      ii. Differential WBC count
   c. Platelet count

2. Hemostasis tests
   a. Bleeding time
   b. International Normalized Ratio (INR)
      i. Tests extrinsic pathway
      ii. Patient on warfarin

---

c. Partial thromboplastin time (PTT)
   i. Tests intrinsic pathway
   ii. Patient on heparin

3. Bone marrow biopsy: where is it done? What is the structure of a normal red marrow? What stain is it used to show the iron amount?

4. Hemoglobin electrophoresis: What are the different types of hemoglobin and what are the pathological significance?

---

**Normal Hemoglobins:**

- **Hemoglobin A.** This is the designation for the normal hemoglobin that exists after birth. Hemoglobin A is a tetramer with two alpha chains and two beta chains (α₂β₂).

- **Hemoglobin A2.** This is a minor component of the hemoglobin found in red cells after birth and consists of two alpha chains and two delta chains (α₂δ₂). Hemoglobin A2 generally comprises less than 3% of the total red cell hemoglobin.

- **Hemoglobin F.** Hemoglobin F is the predominant hemoglobin during fetal development. The molecule is a tetramer of two alpha chains and two gamma chains (α₂γ₂).

**Clinically Significant Variant Hemoglobins:**

- **Hemoglobin S.** This is the predominant hemoglobin in people with sickle cell disease. The alpha chain is normal. The disease-producing mutation exists in the beta chain, giving the molecule the structure,
\[ \alpha_2^S \beta_2^C \]. People who have one sickle mutant gene and one normal beta gene have sickle cell trait which is benign.

- **Hemoglobin C.** Hemoglobin C results from a mutation in the beta globin gene and is the predominant hemoglobin found in people with hemoglobin C disease \((\alpha_2^S \beta_2^C)\). Hemoglobin C disease is relatively benign, producing a mild hemolytic anemia and splenomegaly. Hemoglobin C trait is benign.

- **Hemoglobin E.** This variant results from a mutation in the hemoglobin beta chain. People with hemoglobin E disease have a mild hemolytic anemia and mild splenomegaly. Hemoglobin E trait is benign. Hemoglobin E is extremely common in S.E. Asia and in some areas equals hemoglobin A in frequency.

- **Hemoglobin Constant Spring.** Hemoglobin Constant Spring is a variant in which a mutation in the alpha globin gene produces an alpha globin chain that is abnormally long. The result is a thalassemic phenotype. (The designation Constant Spring derives from the isolation of the hemoglobin variant in a family of ethnic Chinese background from the Constant Spring district of Jamaica.)

- **Hemoglobin H.** Hemoglobin H is a tetramer composed of four beta globin chains. Hemoglobin H occurs only with extreme limitation of alpha chain availability. Hemoglobin H forms in people with three-gene alpha thalassemia as well as in people with the combination of two-gene deletion alpha thalassemia and hemoglobin Constant Spring.

- **Hemoglobin Barts.** Hemoglobin Barts develops in foetuses with four-gene deletion alpha thalassemia. During normal embryonic development, the epsilon gene of the alpha globin gene locus combines with genes from the beta globin locus to form functional hemoglobin molecules. The epsilon gene turns off at about 12 weeks, and normally the alpha gene takes over. With four-gene deletion alpha thalassemia no alpha chain is produced. The gamma chains produced during foetal development combine to form gamma chain tetramers. These molecules transport oxygen poorly. Most individuals with four-gene deletion thalassemia and consequent hemoglobin Barts die in utero (hydrops fetalis). Compound Heterozygous Conditions

**Compound heterozygous:**

Occasionally someone inherits two different variant genes from the alpha globin gene cluster or two different variant genes from the beta globin gene cluster. This condition is called "compound heterozygous".

- **Hemoglobin SC disease.** Patients with hemoglobin SC disease inherit a gene for hemoglobin S from one parent, and a gene for hemoglobin C from the other. Hemoglobin C interacts with hemoglobin S to produce some of the abnormalities seen in patients with sickle cell disease. On average, patients with hemoglobin SC disease have milder symptoms than do those with sickle cell disease. This is only an average, however. Some people with hemoglobin SC disease have a condition equal in severity to that of any patient with sickle cell disease. A number other syndromes exist that involve a hemoglobin S compound heterozygous state. They are less common than hemoglobin SC disease, however. Ironically, hemoglobin SC disease is often a much more severe condition than is homozygous hemoglobin C disease. The expression of a single hemoglobin S gene normally produces no problem (i.e., sickle cell trait). The hemoglobin C molecule disturbs the red cell metabolism only slightly. However, the disturbance is enough to allow the deleterious
effects of the hemoglobin S to be manifested.

- **Sickle/beta-thalassemia.** In this condition, the patient has inherited a gene for hemoglobin S from one parent and a gene for beta-thalassemia from the other. The severity of the condition is determined to a large extent by the quantity of normal hemoglobin produced by the beta-thalassemia gene. (Thalassemia genes produce normal hemoglobin, but in variably reduced amounts). If the gene produces no normal hemoglobin, $\beta^0$-thalassemia, the condition is virtually identical to sickle cell disease. Some patients have a gene that produces a small amount of normal hemoglobin, called $\beta^+$-thalassemia. The severity of the condition is dampened when significant quantities of normal hemoglobin are produced by the $\beta^+$-thalassemia gene. Sickle/beta-thalassemia is the most common sickle syndrome seen in people of Mediterranean descent (Italian, Greek, Turkish). Beta-thalassemia is quite common in this region, and the sickle cell gene occurs in some sections of these countries. Hemoglobin electrophoresis of blood from a patient with sickle/$\beta^0$-thalassemia shows no hemoglobin A. Patients with sickle/$\beta^+$-thalassemia have an amount of hemoglobin A that depends on the level of function of the $\beta^+$-thalassemia gene.

- **Hemoglobin E/beta-thalassemia.** The combination of hemoglobin E and beta-thalassemia produces a condition more severe than is seen with either hemoglobin E trait or beta-thalassemia trait. The disorder manifests as a moderately severe thalassemia that falls into the category of thalassemia intermedia. Hemoglobin E/beta-thalassemia is most common in people of S.E. Asian background.

- **Alpha thalassemia/Hemoglobin Constant Spring.** This syndrome is a compound heterozygous state of the alpha globin gene cluster. The alpha globin gene cluster on one of the two chromosomes 16 has both alpha globin genes deleted. On the other chromosome 16, the alpha1 gene has the Constant Spring mutation. The compound heterozygous condition produces a severe shortage of alpha globin chains. The excess beta chains associate into tetramers to form hemoglobin H.


<table>
<thead>
<tr>
<th>Normal reference values can vary by laboratory, but are generally within the following ranges. Adults</th>
<th>Child (Hb F):</th>
</tr>
</thead>
</table>
| - Hgb A: 95-98%  
- Hgb A$_2$: 1.5-3.5%  
- Hgb F: 0.8-2.0%  
- Hgb S: 0%  
- Hgb C: 0%  | - 6 months: 8%  
- greater than 6 months: 1-2%  
- newborn (Hgb F): 50-80%  |

**Abnormal results**

Abnormal reference values can vary by laboratory, but when they appear within these ranges, results are usually associated with the conditions that follow in parentheses.

Hgb A$_2$:
- 4-5.8% (thalassemia minor)  
- under 2% (Hb H disease)
Hgb F:
- 2-5% (thalassemia minor)
- 10-90% (thalassemia major)
- 5-35% (Heterozygous hereditary persistence of fetal hemoglobin, or HPFH)
- 100% (Homozygous HPFH)
- 15% (Homozygous Hgb S)

Homozygous Hgb S:
- 70-98% (Sickle cell disease).

Homozygous Hgb C:
- 90-98% (Hgb C disease)

Platelet Function: Whole Blood Lumi-aggregometry

Platelet aggregation and ATP release are measured using thrombin, collagen, arachidonic acid, and ristocetin as stimulators. Requires at least 9 mL (three tubes) of whole blood with a minimum platelet count of 100 10^9/L. Specimen must be assayed within 3 hours of collection.

See the answers at the bottom with additional qmc

1. What is the function of platelet factor 3 (pf3)?
2. Which of the following coagulation factors does Antithrombin inhibit?
3. What is the defect in activated Protein C resistance?
4. Tissue Factor Pathway Inhibitor (TFPI) directly inhibits what clotting factors?
5. Which disorder will have an abnormal result with the ristocetin cofactor test?
6. The following coagulation test results were obtained on a patient:
   - APTT 29 seconds
   - PT INR = 1.6
   - Bleeding Time 4 minutes
   - Platelet count 190 x 10^9
   - D-dimer assay 0.5 mg/L

Which of the following conditions could cause the above results?
7. In which of the following situations would the platelet count be decreased?

8. What is the defect in Glanzmann's thrombasthenia?

9. Which of the following test results would most likely be seen in Hemophilia A?

10. Within what time frame must a PT test be done (at UAH)?

11. A positive D-dimer test would be seen in which situation?

12. When will platelet adhesion be abnormal?

13. Which of the following are found in platelet dense granules?

14. A deficiency of which clotting factors will lead to bleeding problems?

15. In the APTT test which substances can be used to activate the contact factors in vitro?

16. Which of the following occurs in primary fibrinolysis?

17. Which of the following are activators of plasminogen?

18. Which of the following occurs with DIC?

19. Which of the following could cause a prolonged template Bleeding Time?

20. Coumadin therapy will affect which clotting factors?

21. Which of the following should be considered when examining a plasma sample for coagulation testing? Samples should be examined for:

22. The Prothrombin Time (PT) can be used to detect or assess which of the following?

23. At UAH when would coagulation controls be run?

24. Describe how the fibrinolytic system removes clots. Include the roles of plasminogen, tPA, and alpha₂-antiplasmin in your discussion.
25. What is the purpose of thrombolytic therapy? Give an example of an agent which can be used in thrombolytic therapy.

Blood Disorder Therapies

5. Increasing volume and/or oxygen-carrying capacity*
   a. Whole blood*
   b. Plasma
   c. Artificial blood* - examples:
      i. Hemolink (human hemoglobin)
      ii. Hemopure (bovine hemoglobin)
      iii. Oxygent (artificial)
   d. Epoetin alfa (Procrit, Eprex)* – recombinant DNA
   e. Vitamin $\text{B}_{12}$ injections (for pernicious anemia)
   f. Hydroxyurea injections (for sickle cell anemia)

6. Bone marrow transplants / stem cell transplants
   a. when bone marrow is damaged or defective
   b. cancer treatment
   c. SCIDS (severe combined immunodeficiency syndrome)
     Read “Body Cure Thyself” in Discover (magazine):

7. Chemotherapy (bone marrow cancers: polycythemia vera, leukemias)

8. Clotting disorders therapies [SEE ANTICOAGULANTS]
   a. Aspirin – interferes with platelet aggregation
   b. Heparin – interferes with some reactions in the coagulation pathway
   c. Warfarin – interferes with vit. K use in the liver
   d. Streptokinase (Streptase) – increases breakdown of fibrin
   e. UROKINASE

Anticoagulant Therapy Monitoring
Warfarin (Coumadin)

- Prothrombin time (PT) & INR

Standard heparin

- Partial thromboplastin time (PTT)
- Chromogenic anti-Xa heparin assay

LMWH (Enoxaparin, Tinzaparin)

- Chromogenic anti-Xa heparin assay

Direct thrombin inhibitors: Argatroban, Lepirudin

- Partial thromboplastin time (PTT)

Complete List of Risk Factors for Venous Thrombosis

- Lupus anticoagulant
- Anti-cardiolipin antibody, IgG & IgM
- Activated protein C resistance (APCR)
  - Factor V Leiden mutation assay if APCR ratio low
- Prothrombin G20210A mutation
- Factor VIII activity
- Fasting homocysteine
- Protein C activity
  - Antigen assay if low
- Protein S activity
  - Antigen assay if low
- Antithrombin activity
  - Antigen assay if low

Partial List for Patients on Heparin or Warfarin, or for Acute Patients Who Have Had a Thrombotic Event in the Past Ten Days

- Lupus anticoagulant
- Anti-cardiolipin antibody, IgG & IgM
- Prothrombin G20210A mutation
- Fasting homocysteine
- Activated protein C resistance (APCR)
  - Factor V Leiden mutation assay if positive
Lymphatic System Therapies

9. Chemotherapy (myeloma)

10. Radiation therapy (Hodgkin’s disease)

11. ABDV therapy (Hodgkin’s disease; Chapter 5, p. 109)
   a. Adriamycin (doxorubicin), antitumor antibiotic
   b. Bleomycin, antitumor antibiotic
   c. Vinblastine, antimitotic drug
   d. Dacarbazine, “alkylating agent nonspecific drug”

---

**Hematology**

**Red blood cells**

These values (except Hemoglobin in plasma) are for total blood and not only blood plasma.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Hb)</td>
<td>male</td>
<td>2.0, 2.1</td>
<td>2.5, 2.7</td>
<td>mmol/L</td>
<td>Higher in neonates, lower in children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130,132, 135</td>
<td>162,170, 175</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>1.8, 1.9</td>
<td>2.3, 2.5</td>
<td>mmol/L</td>
<td>Sex difference negligible until adulthood.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>150, 152, 160</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin in plasma</td>
<td></td>
<td>0.16</td>
<td>0.62</td>
<td>μmol/L</td>
<td>Normally diminutive compared with inside red blood cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>4</td>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin (HbA1c)</td>
<td>&lt; 50 years</td>
<td>3.6</td>
<td>5.0</td>
<td>% of Hb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 50 years</td>
<td>3.9</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>&lt; 50 years</td>
<td>0.35</td>
<td>1.9</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 50 years</td>
<td>0.47</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (Hct)</td>
<td>male</td>
<td>0.39, 0.4, 0.41, 0.45</td>
<td>0.50, 0.52, 0.53, 0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Patient type</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td>Unit</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count (WBC.)</td>
<td>Adult</td>
<td>3.5, 3.9, 4.1, 4.5</td>
<td>9.0, 10.0, 10.9, 11</td>
<td>x10^9/L, x10^9/mm^3 or x10^9/μL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>9</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**White blood cells**

These values are for total blood and not only blood plasma.
<table>
<thead>
<tr>
<th></th>
<th>1 year old</th>
<th>6</th>
<th>18</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil granulocytes (A.K.A. grans, polys, PMNs, or segs)</td>
<td>Adult</td>
<td>1.3, 1.8, 2</td>
<td>5.4, 7, 8</td>
<td>$\times 10^9$/L</td>
<td>45-54</td>
<td>62, 74</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>6</td>
<td>26</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophilic band forms</td>
<td>Adult</td>
<td>0.7</td>
<td>$\times 10^9$/L</td>
<td>3</td>
<td>5</td>
<td>% of WBC</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Adult</td>
<td>0.7, 1.0</td>
<td>3.5, 3.9, 4.8</td>
<td>$\times 10^9$/L</td>
<td>16-25</td>
<td>33, 45</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>2</td>
<td>11</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>Adult</td>
<td>0.1, 0.2</td>
<td>0.8</td>
<td>$\times 10^9$/L</td>
<td>3, 4.0</td>
<td>7, 10</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>0.4</td>
<td>3.1</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mononuclear leukocytes (Lymphocytes + monocytes)</td>
<td>Adult</td>
<td>1.5</td>
<td>5</td>
<td>$\times 10^9$/L</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>CD4+ cells</td>
<td>Adult</td>
<td>0.4, 0.5</td>
<td>1.5, 1.8</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophil granulocytes</td>
<td>Adult</td>
<td>0.0, 0.04</td>
<td>0.44, 0.45, 0.5</td>
<td>$\times 10^9$/L</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>0.02</td>
<td>0.85</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophil granulocytes</td>
<td>Adult</td>
<td>40</td>
<td>100, 200, 900</td>
<td>$\times 10^9$/L</td>
<td>0.0</td>
<td>0.75, 2</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td></td>
<td>0.64</td>
<td>$\times 10^9$/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coagulation

Revised summer 2011
<table>
<thead>
<tr>
<th>Test</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocyte/Platelet count (Plt)</td>
<td>140, 150</td>
<td>350,400,450</td>
<td>x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Mean platelet volume (MPV)</td>
<td>7.4</td>
<td>10.4</td>
<td>fL</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>10, 11,12</td>
<td>13, 13.5,14,15</td>
<td>s</td>
<td>PT reference varies between laboratory kits - INR is standardised</td>
</tr>
<tr>
<td>INR</td>
<td>0.9</td>
<td>1.2</td>
<td></td>
<td>The INR is a corrected ratio of a patient's PT to normal</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT)</td>
<td>18, 30</td>
<td>28, 42,45</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td>Thrombin clotting time (TCT)</td>
<td>11</td>
<td>18</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.7, 2.0</td>
<td>3.6, 4.2</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>Antithrombin</td>
<td>0.80</td>
<td>1.2</td>
<td>kIU/L</td>
<td></td>
</tr>
<tr>
<td>Bleeding time</td>
<td>2</td>
<td>9</td>
<td>minutes</td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>1.5</td>
<td>1.72</td>
<td>cP</td>
<td></td>
</tr>
</tbody>
</table>

**Leukocyte Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancytopenia</td>
<td>Aplastic anemia Peripheral blood cytopenia with bone marrow aplasia</td>
</tr>
<tr>
<td></td>
<td>MDS Peripheral blood cytopenia with bone marrow dysplasia</td>
</tr>
<tr>
<td></td>
<td>Sepsis with DIC, SLE, or hypersplenism</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>CML Neutrophilia with left shift, Ph chromosome, basophilia, LAP score,</td>
</tr>
<tr>
<td></td>
<td>splenomegaly, smudge cells; heterogeneous</td>
</tr>
<tr>
<td></td>
<td>Leukemoid rxn LAP score, normal cytogenetics; variety of granulocyte</td>
</tr>
<tr>
<td></td>
<td>precursors</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>CLL Sea of lymphocytes in marrow (usually B cells); elderly pt with</td>
</tr>
<tr>
<td></td>
<td>lymphocytosis; blood—lymphocytes smaller, clumped nuclei</td>
</tr>
<tr>
<td></td>
<td>Viral infection Often EB</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>Chronic stimulation: cytokine release, CML, metastatic infiltration Acute</td>
</tr>
<tr>
<td></td>
<td>shift: steroid treatment, bacterial infection</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>NAACP (neoplasm, allergies, asthma, collagen vascular disease, parasites)</td>
</tr>
<tr>
<td>Monocytosis</td>
<td>Chronic infection (TB, malaria) or chronic inflammation (SLE, rheumatoid</td>
</tr>
<tr>
<td></td>
<td>arthritis)</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>PCV Splenomegaly, Hb, Hct; LAP score, B12, EPO</td>
</tr>
<tr>
<td></td>
<td>EPO-dependent Elevated EPO: normal or pathogenic response</td>
</tr>
</tbody>
</table>

Revised summer 2011
## Platelet biochemistry

- Made by megakaryocytes in bone marrow. Lifespan 8-10 days. 2-3 m in size. No nucleus, but do have mitochondria and mRNA.
- At any given time, 80% in circulation and 20% localized in spleen.

### Three types of functional granules

- **Dense granules**: ATP, ADP, serotonin, calcium; *Promote further platelet aggregation*
- **Alpha granules** (clear under electron microscope)
  - Platelet specific proteins: Platelet factor 4, beta-thromboglobulin, PDGF; *Mitogens and growth factors*
  - Large molecular weight proteins
  - Coagulation proteins: Thrombospondin, vWF, fibrinogen, HK
  - Plasma protease inhibitors: Alpha-2 macroglobulin, antithrombin-3, C1 inhibitor, PAI-1 (SERPINS)
- **Lysosomal granules**: Beta-glucuronidase, acetylglicosaminidase, etc.

### Function

#### Hemostasis

- **Adhesion**: Initiation of platelet plug. vWF helps platelet GPIba, factor V, and factor IX stick to the injured subendothelium.
- **Activation**: Internal phosphorylation, calcium mobilization, and release of granule contents (ADP, serotonin) that recruit more platelets
- **Aggregation**: Fibrinogen binds to glycoprotein IIb/IIIa and links to other platelets

#### Procoagulation: Platelet surface becomes site for tenase (FX) and prothrombin (FII) elaboration

### Platelet functional assays

<table>
<thead>
<tr>
<th>Test name</th>
<th>How it works</th>
<th>What results mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral smear</td>
<td>Examine presence, size, and granularity of the platelets</td>
<td>- Appearance of platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Number of platelets</td>
</tr>
</tbody>
</table>

Revised summer 2011
Platelet counts
Quantitative assay
· Normal 150000-400000/ml

Bleeding time
Rough estimate of platelet function and number
· Prolonged as count decreases below 100000/ml
· Prolonged with normal numbers and qualitative defect

Platelet aggregation
With agonist addition (ADP, epi, collagen, thrombin), normal platelets aggregate and fall out of solution
· Qualitative assay --detect stimulus-coupling defect
· Not specific

Quantitative Platelet Defects: Thromocytopenia and Thrombocytosis

<table>
<thead>
<tr>
<th>Mechanism (Disorder)</th>
<th>Clinical Syndromes</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased production (Thrombocytopenia)</td>
<td>-Bone marrow failure, invasion, or injury</td>
<td></td>
</tr>
<tr>
<td>Increased destruction (Thrombocytopenia) *</td>
<td>-Idiopathic, connective tissue disease (SLE), medications -Post-transfusion purpura -Heparin induced thrombocytopenia (HIT) -Mild thrombocytopenia (rarely &lt;100000) -Direct heparin-platelet interaction (cleared by spleen) -Heparin induced thrombocytopenia and thrombosis syndrome (HITTS) -Heparin-platelet factor 4 complex induces Ab formation -Heparin-PF4-Aβ complex binds platelet FcgII receptor -Activation, aggregation, degranulation occurs -See increasingly severe thrombocytopenia in presence of heparin -Auto-immune thrombocytopenia (Immune thrombocytopenia, ITP) -Ig coats platelets; cleared by splenic macrophages with Fc receptors -New platelets in circulation (count of 50,000 may give normal bleeding time) -Acute (self-limited, in children) vs chronic (adults, diagnosis by exclusion)</td>
<td>-ITP -PT normal -APTT normal -Plt count decreased -Schistocytes: NONE</td>
</tr>
<tr>
<td>Increased destruction (Thrombocytopenia) * Non-immune mediated</td>
<td>-DIC (w/ concurrent decrease in clotting factors) -Thrombotic thrombocytopenia purpura (TTP) and Hemolytic uremic syndrome (HUS) -fever -mental status changes -renal insufficiency -microangiopathic hemolytic anemia (MAHA) -thrombocytopenia --&gt; thought to result from damage to endothelium leading to abnormal release of ultra-high MW vWF causing platelet aggregation</td>
<td>-DIC -PT increased -APTT increased -Plt count decreased -Schistocytes: occasionally present -TTP -PT normal -APTT normal -Plt count decreased -Schistocytes present (also fibrinogen normal, Hg decreased)</td>
</tr>
<tr>
<td>Sequestration (Thrombocytopenia)</td>
<td>-Disorders of spleen (ex. splenomegaly)</td>
<td></td>
</tr>
<tr>
<td>Primary (autonomous) Thrombocytosis</td>
<td>-Myeloproliferative disorders</td>
<td></td>
</tr>
</tbody>
</table>
Secondary (reactive) Thrombocytosis
- Reactive bone marrow response
- Iron deficiency
- Malignancy
- Post-splenectomy
- Inflammatory disease

Qualitative (Functional) Platelet Disorders: Congenital and Acquired

Disorder | Clinical Syndromes
--- | ---
**Acquired platelet dysfunction** - More common
- Uremia (renal failure)
- Myeloproliferative disorders
- Myelodysplastic disorders and acute leukemias (inability to release granules or abnormal secretion and aggregation patterns)
- Cardiopulmonary bypass (tubing causes platelet activation)
- Antiplatelet antibodies (Usually against GP IIb/IIIa receptor, see bleeding at higher platelet counts than expected)
- Drugs: Penicillins, Cephalosporins (Dysfunction of platelet membrane or functional pathway)
- Also, Liver disease & DIC

**Congenital platelet disorders** - Classified by stage
- Adhesion disorders: Defect of GPIb receptor pathway; Defect NOT seen in aggregation assays
- Von Willebrand disease -- plasma factor (defect in vWF); No response to ristocetin
- Bernard Soulier syndrome -- receptor factor (defect in presence or expression of receptor)
- Aggregation disorders
- Afibrinogenemia: No fibrinogen; Can’t link IIb/IIIa receptors
- Glanzmann’s thrombasthenia: Defect of IIb/IIIa; Can’t make effective plug; Won’t respond to agonists in aggregation assays;

**Will respond to ristocetin**
- Activation/Secretion disorders
- Storage pool deficiency: Absent dense granules
- Primary secretion defects: Abnormal platelet secretion apparatus

**Treatment of platelet disorders**
- **Thrombocytopenia**: Platelet transfusion
- **Thrombocytosis**: Modulate platelet function (by blocking activation); May use more than one class of meds for the high-risk patient
- **Cyclooxygenase inhibitors** (Aspirin gold standard): Irreversibly inhibits thromboxane A2 pathway of aggregation; Think cardiology
- **ADP receptor inhibitors** (Ticlopidine, clopidogrel): Inhibit binding of ADP to receptor and block ADP-dependent aggregation
- **GPIIb/IIIa receptor antagonists** (Abciximab [monoclonal Ab], peptide inhibitors like Eptifibatide [competitive fibrin pieces]): Block ability to make large platelet plugs
### Enzymes and proteins

<table>
<thead>
<tr>
<th>Test</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>50</td>
<td>150</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>1.7</td>
<td>μmol/L</td>
<td></td>
</tr>
<tr>
<td>LDH (enzyme activity)</td>
<td>1.8</td>
<td>3.4</td>
<td>μkat/L</td>
<td>&lt; 70 years old</td>
</tr>
<tr>
<td>Amylase</td>
<td>25, 30, 53</td>
<td>110, 120, 123, 125, 190</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>1.1</td>
<td>μkat/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>240</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>D-dimer</td>
<td>n/a</td>
<td>500</td>
<td>mg/dL</td>
<td>Higher in pregnant women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>mg/L</td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>7, 10, 23</td>
<td>60, 150, 208</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme (ACE)</td>
<td>23</td>
<td>57</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>3.0</td>
<td></td>
<td>ng/mL</td>
<td></td>
</tr>
<tr>
<td>Eosinophil cationic protein (ECP)</td>
<td>2.3</td>
<td>16</td>
<td>μg/L</td>
<td></td>
</tr>
</tbody>
</table>

Answers refer also to the lecture slides

- **Howell-Jolly bodies (Wright stain)**: Asplenia: splenectomy, functional asplenia (Sickle Cell disease)
- **Basophilic stippling**: Dysfuntional Hb synthesis: **lead poisoning**, hypochromic microcytic anemias (sideroblastic anemia, sometimes Fe deficiency anemia, thalessemia)
- **Schistocytes**: MAHA, homozygous b-thal
- **Reticulocytes (methylene blue stain)**: Appear polychromatophilic on Wright stain
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherocytes</td>
<td>Hereditary spherocytosis&lt;br&gt;Autoimmune hemolytic anemia&lt;br&gt;Heinz body hemolytic anemia (G6PD)</td>
</tr>
<tr>
<td>Target cell</td>
<td><strong>Hb disorders</strong> (thalassemia, HbS, HbC); liver disease, abetalipoproteinemia, post-splenectomy</td>
</tr>
<tr>
<td>Nucleated RBC</td>
<td>Hemolytic anemia, stem cell disorder (pancytopenia), acute blood loss, bone marrow infiltration/fibrosis</td>
</tr>
<tr>
<td>Teardrop cell</td>
<td>Bone marrow infiltration or fibrosis (leukoerythroblastosis)</td>
</tr>
<tr>
<td>Acanthocyte</td>
<td>Severe liver disease (spur cell anemia); abetalipoproteinemia (abnormal membrane fluidity, Rx splenectomy)</td>
</tr>
<tr>
<td>Agglutinated cell</td>
<td>Cold agglutinin disease (IgM)</td>
</tr>
<tr>
<td>Heinz body (special stain required)</td>
<td>G6PD deficiency, unstable Hb; evidenced as bite cells</td>
</tr>
<tr>
<td>Rouleaux</td>
<td>Hypergammaglobulinemic states (Multiple myeloma)</td>
</tr>
<tr>
<td>Dohle bodies</td>
<td>Aggregated RER in PMNs during serious chronic infection</td>
</tr>
<tr>
<td>Pelger-Huet anomaly</td>
<td>Two-lobed PMN in chronic or acute leukemia</td>
</tr>
</tbody>
</table>
### Differential Diagnosis of Anemia Based upon the Three General Mechanisms

<table>
<thead>
<tr>
<th>General Mechanism of Anemia Cause</th>
<th>General Cause</th>
<th>Specific Cause</th>
<th>Specific Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>Acute blood loss</td>
<td>Trauma</td>
<td>GI malignancy, menstruation</td>
</tr>
<tr>
<td>Chronic blood loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased production</td>
<td>Defect of stem cells</td>
<td>Aplastic anemia, pure red cell aplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defective heme production</td>
<td>Iron deficiency anemia, thalassemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defective DNA production</td>
<td>Vitamin B12 and folate deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Destruction of bone marrow</td>
<td>Metastatic tumor</td>
<td></td>
</tr>
<tr>
<td>Increased destruction</td>
<td>External factors: Isohemagglutinin</td>
<td>Transfusion reactions, erythroblastosis fetalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>antibody mediated</td>
<td>Autoimmune</td>
<td>Warm and cold autoimmune</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>External factors:</td>
<td>Trauma</td>
<td>Infections Sequestration</td>
</tr>
<tr>
<td></td>
<td>non–antibody-mediated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hereditary internal factors</td>
<td>Defect in cytoskeleton</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal hemoglobin</td>
<td>Sickle cell anemia, HbC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzyme deficiency</td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Acquired internal factors</td>
<td>PNH</td>
<td></td>
</tr>
</tbody>
</table>

GI, gastrointestinal; Hb, hemoglobin; G6PD, glucose-6-phosphate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria.

### Bleeding Disorders

#### Intrinsic pathway assay
- Partial thromboplastin time (PTT)

#### Extrinsic pathway assay
- Prothrombin time (PT) & INR

#### Common pathway assays
- Fibrinogen activity

### Coagulation Factor Inhibitors

#### Follow-up to Abnormal PT and/or PTT
- PTT mixing studies
- PT mixing studies

#### Inhibitors
- Lupus anticoagulant
- Factor VIII inhibitor (Bethesda)
- Factor IX inhibitor (Bethesda)
- Inhibitors to all other factors

Revised summer 2011
- Thrombin clotting time (TCT)
- Reptilase time (not prolonged by heparin)

### Factor assays
- Fibrinogen activity
- Prothrombin (II), V, VII, or X activity
  - VIII, IX, XI, or XII activity
- Factor XIII activity by urea solubility

### Fibrinolysis Assays
- Fibrinogen activity
- Thrombin time (TCT)
- Reptilase time
- Euglobulin clot lysis time (ECLT)
- Plasminogen activator inhibitor-1 (PAI-1, performed in outside laboratory)

### Von Willebrand Disease

#### Initial profile
- Factor VIII activity
- von Willebrand factor activity (AKA ristocetin cofactor)
- von Willebrand factor antigen

#### Follow-up tests (when indicated)
- Ristocetin response curve
- von Willebrand factor multimers (performed in outside laboratory)

### Disseminated Intravascular Coagulation

- Partial thromboplastin time (PTT)
- Prothrombin time (PT)
- Fibrinogen activity
- Quantitative D-dimer

### Lupus Anticoagulant (LA) with Follow-Up Assays

#### Two LA screens are used
- LA sensitive PTT (PTT-LA)
- Dilute Russell viper venom time (dRVVT)

#### Follow-up assays when the LA screen is positive
- Thrombin time to R/O heparin
- PTT-LA mixing study
- StaClot-LA: PTT confirmatory test using hexagonal phase phospholipid
<table>
<thead>
<tr>
<th>neutralization procedure (PNP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dRVVT mixing study</td>
</tr>
<tr>
<td>dRVVT confirmatory test (dRVVT ratio reported)</td>
</tr>
</tbody>
</table>

### How to interpret red cell appearances

**Microcytosis** (reduced average cell size, MCV < 76 fL)

- Iron deficiency
- Thalassaemia
- Sideroblastic anaemia

**Macrocytosis** (increased average cell size, MCV > 100 fL)

- Vitamin B₁₂ or folate deficiency
- Liver disease, alcohol
- Hypothyroidism
- Drugs (e.g. zidovudine)

**Target cells** (central area of haemoglobinisation)

- Liver disease
- Thalassaemia
- Post-splenectomy
- Hemoglobin C disease

**Spherocytes** (dense cells, no area of central pallor)

- Autoimmune hemolysis
- Post-splenectomy
- Hereditary spherocytosis

**Red cell fragments** (intravascular hemolysis)

- Disseminated intravascular coagulation (DIC)
• Hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP)

**Nucleated red blood cells (normoblasts)**

• Marrow infiltration  
• Severe hemolysis  
• Myelofibrosis  
• Acute hemorrhage

**Howell-Jolly bodies (small round nuclear remnants)**

• Hyposplenism  
• Post-splenectomy  
• Dyshematopoiesis

**Polychromasia (young red cells-reticulocytes present)**

• Hemolysis, acute hemorrhage  
• Increased red cell turnover

**Basophilic stippling (abnormal ribosomes appear as blue dots)**

• Dyshematopoiesis  
• Lead poisoning

<table>
<thead>
<tr>
<th>Qmc of the open above exercises</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choose the most correct answer.</strong></td>
<td><strong>Answers</strong></td>
</tr>
</tbody>
</table>
| **1. What is the function of platelet factor 3 (pf3)?** | 1. b  
2. c  
3. d  
4. b  
5. a  
6. c  
7. a  
8. c |
| a) it is necessary for the activation of factor VIII | |
| b) it provides a catalytic surface for the formation of coagulation complexes | |
c) it acts as a bridge between Ca++ and vitamin K-dependent factors

d) it is necessary for the activation of factor XIII

2. Which of the following coagulation factors does Antithrombin inhibit?

a) factor V
b) factor VIII
c) factor IX
d) factor XIII

3. What is the defect in activated Protein C resistance?

a) a defective Protein S molecule
b) defective activation of Protein C
c) a defective factor VIII molecule
d) a defective factor V molecule

4. Tissue Factor Pathway Inhibitor (TFPI) directly inhibits what clotting factors?

a) factor V and factor II
b) factor VIIa and factor Xa
c) factor VIII and factor IXa
d) factor Xla and factor XIIa

5. Which disorder will have an abnormal result with the ristocetin cofactor test?

a) von Willebrand's disease
b) Bernard Soulier disease
c) Glanzman's thrombasthenia
d) Storage pool disease

24. After the blood vessel has healed, and the hemostatic plug is no longer needed, the fibrinolytic system removes the clot so that the blood flow can be restored. During the clotting process a small amount of plasma plasminogen binds to fibrin and becomes incorporated throughout the clot. Tissue plasminogen activator (tPA) which is released by damaged endothelial cells, works its way into the clot and activates this plasminogen. The plasmin thus formed then slowly breaks down the fibrin clot to form fibrin degradation products.

Some alpha2-antiplasmin will also bind to the clot and will prevent premature clot dissolution. Any plasmin that happens to dissociate from the clot and go off into the circulation will be quickly neutralized by alpha2-antiplasmin close by.

26. Thrombolytic therapy is used to remove clots that have formed in the patient's circulation.

An example of an agent which can be used in thrombolytic therapy is recombinant tissue plasminogen activator.
obtained on a patient:

- APTT 29 seconds
- PT INR = 1.6
- Bleeding Time 4 minutes
- Platelet count 190 x 10^9
- D-dimer assay 0.5 mg/L

Which of the following conditions could cause the above results?

- a) a factor X deficiency
- b) afibrinogenemia
- c) a factor VII deficiency
- d) problems with pf₃ availability

7. In which of the following situations would the platelet count be decreased?

- a) in hemolytic uremic syndrome
- b) in Essential Thrombocythemia
- c) post splenectomy
- d) in polycythemia rubra vera

8. What is the defect in Glanzmann's thrombasthenia?

- a) giant platelets
- b) a lack of glycoprotein Ib
- c) a lack of glycoprotein IIb/IIa
- d) deficiency of stored ADP in the platelet granules

9. Which of the following test results would most likely be seen in Hemophilia A?

- a) an abnormal PT
b) an abnormal Bleeding Time  
c) abnormal von Willebrand factor levels  
d) an abnormal APTT

10. Within what time frame must a PT test be done (at UAH)?
   
a) within 1 hour of collection  
b) within 2 hours of collection  
c) within 12 hours of collection  
d) within 24 hours of collection

11. A positive D-dimer test would be seen in which situation?
   
a) in DIC  
b) in primary fibrinolysis  
c) with heparin therapy  
d) with coumadin therapy

Each question in this section is followed by four suggested answers, one or more being the correct one. Place a check mark in front of each correct answer. All correct answers must be chosen in order to receive marks for the question.

12. When will platelet adhesion be abnormal?
   ___1) when platelets are missing GPIIb/IIIa  
   ___2) when platelets are missing GP Ib  
   ___3) when calcium levels in the platelet are decreased by prostacyclin  
   ___4) when von Willebrand factor levels are decreased
<table>
<thead>
<tr>
<th>13. Which of the following are found in platelet dense granules?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___1) ADP</td>
</tr>
<tr>
<td>___2) platelet derived growth factor</td>
</tr>
<tr>
<td>___3) serotonin</td>
</tr>
<tr>
<td>___4) von Willebrand's factor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>14. A deficiency of which clotting factors will lead to bleeding problems?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___1) factor I</td>
</tr>
<tr>
<td>___2) prekallikrein</td>
</tr>
<tr>
<td>___3) factor XI</td>
</tr>
<tr>
<td>___4) factor XII</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15. In the APTT test which substances can be used to activate the contact factors in vitro?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___1) micronized silica</td>
</tr>
<tr>
<td>___2) asbestos</td>
</tr>
<tr>
<td>___3) ellagic acid</td>
</tr>
<tr>
<td>___4) glass</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16. Which of the following occurs in primary fibrinolysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___1) increased formation of plasmin</td>
</tr>
<tr>
<td>___2) decreased levels of some coagulation factors</td>
</tr>
<tr>
<td>___3) increased destruction of fibrinogen</td>
</tr>
<tr>
<td>___4) a thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>17. Which of the following are activators of plasminogen?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___1) urokinase</td>
</tr>
<tr>
<td>___2) recombinant tPA</td>
</tr>
</tbody>
</table>
18. Which of the following occurs with DIC?
___1) activation of the fibrinolytic system
___2) thrombocytopenia
___3) increased production of FDP's
___4) consumption of coagulation factors

19. Which of the following could cause a prolonged template Bleeding Time?
___1) abnormal vascular function
___2) afibrinogenemia
___3) Glanzman's thrombasthenia
___4) a factor IX deficiency

20. Coumadin therapy will affect which clotting factors?
___1) factor XI
___2) factor IX
___3) factor X
___4) factor XII

21. Which of the following should be considered when examining a plasma sample for coagulation testing? Samples should be examined for:
___1) correct volume in the tube
___2) presence of lipemia
___3) presence of hemolysis
___4) correct anticoagulant tube used

22. The Prothrombin Time (PT) can be used to detect or assess which of the following?
___1) a contact factor deficiency
___2) a circulating inhibitor against factor X
___3) a pi deficiency
___4) coumadin therapy (therapeutic range)

23. At UAH when would coagulation controls be run?
___1) at the beginning of each shift
___2) once a day
___3) when a reagent change is made
___4) once an hour

Short Answer Questions:

24. Describe how the fibrinolytic system removes clots. Include the roles of plasminogen, tPA, and alpha2-antiplasmin in your discussion.

25. What is the purpose of thrombolytic therapy? Give an example of an agent which can be used in thrombolytic therapy.

Exercises

Role play the following situations:

- A new student has enrolled in your school, and the rumor mill has it that the new student has AIDS. You become friends with this new student, and decide to ask your friend if the rumors are true.
- A young woman complains of swelling in her right arm after a right radical mastectomy. Explain to the woman the likely cause of the swelling, and answer her questions.
- Your friend comes to you complaining about her “swollen glands” in her neck. What questions would you ask, and how would you explain this condition to your friend?
- A friend of yours comes to school one day, depressed because her cousin has been diagnosed with Hodgkin’s disease. How would you explain this diagnosis to your friend?
- A friend tells you he is allergic to bee stings, but now his crazy doctor and mother are insisting he wear an ID bracelet “telling the world.” Your friend assures you he is not a wimp and is not going to wear the stupid bracelet. How would you respond?