11 A 32-year-old woman from Hanoi, Vietnam, gives birth at 34 weeks' gestation to a markedly hydropic stillborn male infant. Autopsy findings include hepatosplenomegaly and cardiomegaly, serous effusions in all body cavities, and generalized hydrops. No congenital anomalies are noted. There is marked extramedullary hematopoiesis in visceral organs. Which of the following hemoglobins is most likely predominant on hemoglobin electrophoresis of the fetal RBCs?

A Hemoglobin A_1
B Hemoglobin A_2
C Hemoglobin Bart's
D Hemoglobin E
E Hemoglobin F
F Hemoglobin H

9 A 3-year-old boy from Sicily has a poor appetite and is underweight for his age and height. Physical examination shows hepatosplenomegaly. The hemoglobin concentration is 6 g/dL, and the peripheral blood smear shows severely hypochromic and microcytic RBCs. The total serum iron level is normal, and the reticulocyte count is 10%. A radiograph of the skull shows maxillofacial deformities and expanded marrow spaces. Which of the following is the most likely cause of this child's illness?

A Imbalance in α-globin and β-globin chain production
B Increased fragility of erythrocyte membranes
C Reduced synthesis of hemoglobin F
D Relative deficiency of vitamin B_{12}
E Sequestration of iron in reticuloendothelial cells

12 A 17-year-old girl has had a history of fatigue and weakness for her entire life. She has not undergone puberty. On physical examination, secondary sex characteristics are not well developed. She has hepatosplenomegaly. CBC shows hemoglobin of 9.1 g/dL, hematocrit of 26.7%, MCV of 66 μm^3, platelet count of 89,000/mm^3, and WBC count of 3670/mm^3. The appearance of the peripheral blood smear is shown in the figure. Additional laboratory findings include serum glucose of 144 mg/dL, TSH of 6.2 mU/mL, and ferritin of 679 ng/mL. A mutation in a gene encoding for which of the following is most likely to be present in this girl?

A Ankyrin
B β-Globin
C G6PD
D HFE
E NADPH oxidase

31 A clinical study is performed using adult patients diagnosed with peptic ulcer disease, chronic blood loss, and hypochromic microcytic anemia. Their serum ferritin levels average 5 to 7 ng/mL. The rate of duodenal iron absorption in this study group is found to be much higher than in a normal control group. After treatment with omeprazole and clarithromycin, study group patients have hematocrits of 40% to 42%, MCV of 82 to 85 μm^3, and serum ferritin of 30 to 35 ng/mL. Measured rates of iron absorption in the study group after therapy are now decreased to the range of the normal controls. Which of the following substances derived from liver is most likely to have been decreased in the study group patients before therapy, and returned to normal after therapy?

A Divalent metal transporter-1 (DMT-1)
B Hemosiderin
C Hepcidin
D HLA-like transmembrane protein
E Transferrin

5 A 28-year-old woman has had a constant feeling of lethargy since childhood. On physical examination, she is afebrile and has a pulse of 80/min, respirations of 15/min, and blood pressure of 110/70 mm Hg. The spleen tip is palpable, but there is no abdominal pain or tenderness. Laboratory studies show hemoglobin of 11.7 g/dL, platelet count of 159,000/mm^3, and WBC count of 5390/mm^3. The peripheral blood smear shows small round erythrocytes that lack a zone of central pallor. An inherited abnormality in which of the following RBC components best accounts for these findings?

A α-Globin chain
B β-Globin chain
C Carbonic anhydrase
D Glucose-6-phosphate dehydrogenase
E Heme with porphyrin ring
F Spectrin cytoskeletal protein

8 A clinical study of patients who inherit mutations that reduce the level of ankyrin, the principal binding site for spectrin, in the RBC membrane cytoskeleton shows an increased prevalence of chronic anemia with splenomegaly. For many patients, it is observed that splenectomy reduces the severity of anemia. This beneficial effect of splenectomy is most likely related to which of the following processes?

A Decrease in opsonization of RBCs and lysis in spleen
B Decrease in production of reactive oxygen species by splenic macrophages
C Decrease in splenic RBC sequestration and lysis
D Increase in deformability of RBCs within splenic sinusoids
E Increase in splenic storage of iron

- Being functionally asplenic → susceptible to infections caused by encapsulated bacteria (e.g; pneumococci)

10 A 10-year-old child has experienced multiple episodes of pneumonia and meningitis with septicemia since infancy. Causative organisms include *Streptococcus pneumoniae* and *Haemophilus influenzae*. On physical examination, the child has no organomegaly and no deformities. Laboratory studies show hemoglobin of 9.2 g/dL, hematocrit of 27.8%, platelet count of 372,000/mm^3, and WBC count of 10,300/mm^3. A hemoglobin electrophoresis shows 1% hemoglobin A_2, 7% hemoglobin F, and 92% hemoglobin S. Which of the following is the most likely cause of the repeated infections in this child?

A Absent endothelial cell expression of adhesion molecules
B Diminished hepatic synthesis of complement proteins
C Impaired neutrophil production
D Loss of normal splenic function
E Reduced synthesis of immunoglobulins

14 A 25-year-old woman has a 3-year history of arthralgias. Physical examination shows no joint deformity, but she appears pale. Laboratory studies show total RBC count of 4.7 million/mm^3, hemoglobin of 12.5 g/dL, hematocrit of 37.1%, platelet count of 217,000/mm^3, and WBC count of 5890/mm^3. The peripheral blood smear shows hypochromic and microcytic RBCs. Total serum iron and ferritin levels are normal. Hemoglobin electrophoresis shows 93% hemoglobin A_1 with elevated hemoglobin A_2 level of 5.8% and hemoglobin F level of 1.2%. What is the most likely diagnosis?

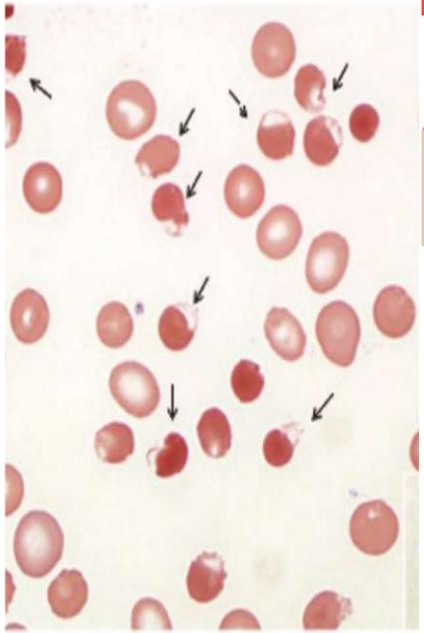
A Anemia of chronic disease
B Autoimmune hemolytic anemia
C β-Thalassemia minor
D Infection with *Plasmodium vivax*
E Iron deficiency anemia

15 A 23-year-old African-American man passes dark reddish brown urine 3 days after taking an anti-inflammatory medication that includes phenacetin. He is surprised, because he has been healthy all his life and has had no major illnesses. On physical examination, he is afebrile, and there are no remarkable findings. CBC shows a mild normocytic anemia, but the peripheral blood smear shows precipitates of denatured globin (Heinz bodies) with supravital staining and scattered "bite cells" in the population of RBCs. Which of the following is the most likely diagnosis?

A α-Thalassemia minor
B β-Thalassemia minor
C Glucose-6-phosphate dehydrogenase deficiency
D Sickle cell trait
E Abnormal ankyrin in RBC cytoskeletal membrane
F Warm antibody autoimmune hemolytic anemia

G6PD deficiency

- Oxidized hemoglobin denatures→ precipitates intracellular inclusions called **Heinz bodies.**
- → damage the RBC membrane → intravascular hemolysis
- Lesser damaged cells lose their deformability and splenic phagocytes attempt to "pluck out" the Heinz bodies, creating **bite cells.**
- → trapped on recirculation to the spleen & destroyed by phagocytes (extravascular hemolysis)



16 Since childhood, a 30-year-old man has been easily fatigued with minimal exercise. Laboratory studies show hypochromic microcytic anemia. Hemoglobin electrophoresis reveals decreased Hgb A_1 with increased Hgb A_2 and Hgb F. His serum ferritin is markedly increased. Which of the following mutations is most likely to be present in the β-globin gene of this man?

A New stop codon
B Single base insertion, with frameshift
C Splice site
D Three-base deletion
E Trinucleotide repeat

- Two β genes are present on chromosome 11.
- **Mutations** associated with β-thalassemia fall into two categories:

(1) β0, no β-globin chains are produced
(2) β+, reduced (but detectable) β-globin synthesis.

- Mutations are usually involving RNA splicing, β-globin gene promoter or coding regions.

18 A 30-year-old, previously healthy man from Lagos, Nigeria, passes dark brown urine 2 days after starting the prophylactic antimalarial drug primaquine. On physical examination, he appears pale and is afebrile. There is no organomegaly. Laboratory studies show that his serum haptoglobin level is decreased. Which of the following is the most likely explanation of these findings?

A Antibody-mediated hemolysis
B Impaired DNA synthesis
C Impaired globin chain synthesis
D Increased susceptibility to complement-induced lysis
E Mechanical fragmentation of RBCs as a result of vascular narrowing
F Oxidative injury to hemoglobin
G Reduced deformability of RBC membrane

- **Patients are asymptomatic and have transient episodes of intravascular hemolysis caused by exposure to an environmental that produces oxidant stress.**
  1. Drugs: include antimalarials (e.g., primaquine), sulfonamides, nitrofurantoin, phenacetin, aspirin (in large doses), and vitamin K derivatives.
  2. Infection (more common) → induce phagocytes to generate oxidants as part of the host response.
  3. Favism
- Hemolysis typically 2-3 days after exposure with variable severity
- Regeneration of GSH is impaired in G6PD-def.cells → oxidants are free to "attack" other red cell components including globin chains.

19 A 34-year-old woman reports becoming increasingly tired for the past 5 months. On physical examination, she is afebrile and has mild splenomegaly. Laboratory studies show a hemoglobin concentration of 10.7 g/dL and hematocrit of 32.3%. The peripheral blood smear shows spherocytes and rare nucleated RBCs. Direct and indirect Coombs test results are positive at 37° C, although not at 4° C. Which of the following underlying diseases is most likely to be diagnosed in this patient?

A *Escherichia coli* septicemia
B Hereditary spherocytosis
C Infectious mononucleosis
D *Mycoplasma pneumoniae* infection
E Systemic lupus erythematosus

Warm Antibody Immunohemolytic Anemia

- **Binding of high-affinity autoantibodies to red cells → removed from the circulation by phagocytes in the spleen and elsewhere.**
- **PB:** Erythrophagocytosis, spherocytes (incomplete consumption (nibbling) of antibody-coated RBCs by macrophages)
- Caused by immunoglobulin G (IgG) or (rarely)IgA →active at 37°C.
  - 60% idiopathic (primary)
  - 25% secondary to an immunologic disorder (e.g., systemic lupus erythematosus), B cells neoplasms, or drugs.
- Patients have chronic mild anemia and moderate splenomegaly and require no treatment.

20 A 22-year-old woman has experienced malaise and a sore throat for 2 weeks. Her fingers turn white on exposure to cold. On physical examination, she has a temperature of 37.8° C, and the pharynx is erythematous. Laboratory findings include a positive monospot (heterophile antibody) test result. Direct and indirect Coombs test results are positive at 4° C, although not at 37° C. Which of the following molecules bound on the surfaces of the RBCs most likely accounts for these findings?

A α_2-Macroglobulin
B Complement C3b
C Fibronectin
D Histamine
E IgE

Cold Antibody Immunohemolytic Anemia

- **Binding by low-affinity IgM antibodies to red cell membranes only at temperatures below 30°C.**
- **Occur in distal parts of the body (e.g., ears, hands, and toes) in cold weather.**
- IgM fixes complement → latter steps of the complement cascade occur

inefficiently due to lower temp. (< 37°C) → most cells are not lysed intravascularly.

- But cells are phagocytosed by macrophages mainly in the spleen and liver→ **extravascular**.
- IgM also crosslinks red cells and causes them to clump (*agglutinate*)→ Sludging of blood in capillaries because of agglutination → *Raynaud phenomenon* in the extremities of affected individuals.

27 A 33-year-old previously healthy man with persistent fever and heart murmur is diagnosed with infective endocarditis. He receives a high dosage of a cephalosporin antibiotic during the next 10 days. He now has increasing fatigue. On physical examination he has tachycardia and scleral icterus. Laboratory studies show a hemoglobin level of 7.5 g/dL, platelet count of 261,000/mm^3, and total WBC count of 8300/mm^3. The direct Coombs test is positive. The peripheral blood smear shows reticulocytosis. Which of the following is the most likely cause for his anemia?

A Dietary nutrient deficiency
B Disseminated intravascular coagulopathy
C Immune-mediated hemolysis
D Infection with parvovirus
E Inherited hemoglobinopathy
F RBC cytoskeletal protein disorder

29 A 54-year-old, previously healthy man has experienced minor fatigue on exertion for the past 9 months. On physical examination, there are no remarkable findings. Laboratory studies show hemoglobin of 11.7 g/dL, hematocrit of 34.8%, MCV of 73 μm^3, platelet count of 315,000/mm^3, and WBC count of 8035/mm^3. Which of the following is the most sensitive and cost-effective test that the physician should order to help to determine the cause of these findings?

A Bone marrow biopsy
B Hemoglobin electrophoresis
C Serum ferritin
D Serum haptoglobin
E Serum iron
F Serum transferrin

Microcytic anemia

- Small, often hypochromic, red blood cells in a peripheral blood smear and is usually characterized by a low MCV (< 80 fl).
- Iron deficiency is the most common cause of microcytic anemia.
- Other causes include anemia of chronic disease, sideroblastic anemia, and thalassemia.

32 A 39-year-old man has experienced chronic fatigue and weight loss for the past 3 months. There are no remarkable findings on physical examination. Laboratory studies show hemoglobin, 10.0 g/dL; hematocrit, 30.3%; MCV, 91 μm^3; platelet count, 240,000/mm^3; WBC count, 7550/mm^3; serum iron 80 µg/dL; total iron-binding capacity, 145 µg/dL; and serum ferritin, 565 ng/mL. Serum erythropoetin levels are low for the level of Hb and hepcidin levels are elevated. Which of the following is the most likely diagnosis?

A Anemia of chronic disease
B Aplastic anemia

Anemia of chronic inflammation

- The most common form of anemia in hospitalized patients.
- Arises from the suppression of erythropoiesis by systemic inflammation

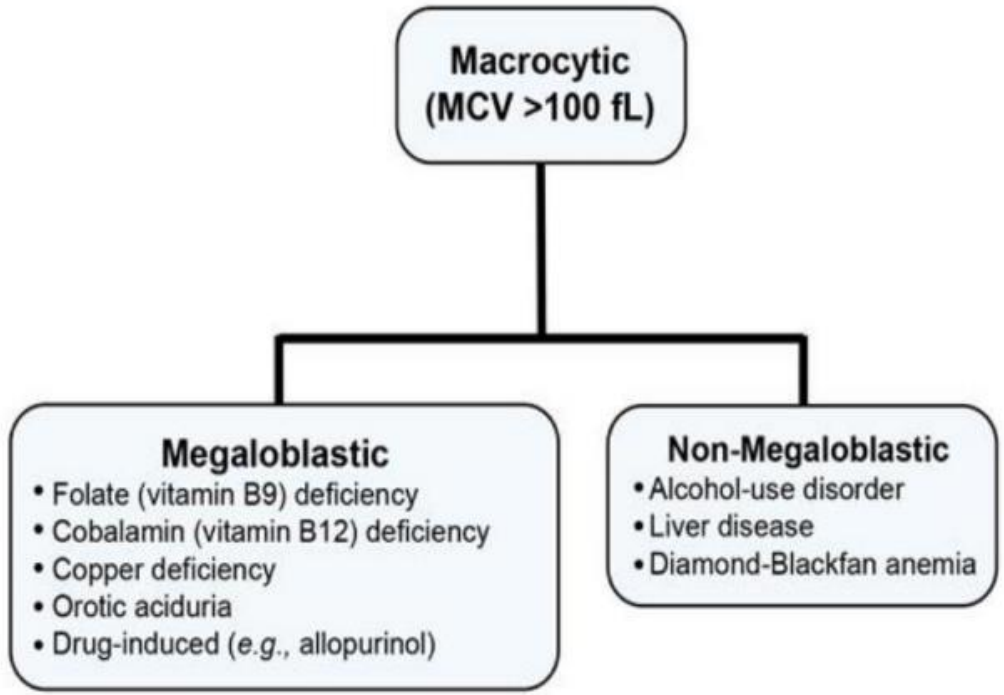
1. Chronic microbial infection (osteomyelitis, endocarditis).
2. Chronic immune disorders (RA).
3. Neoplasms (Carcinoma or lymphoma)

- Anemia of chronic inflammation stems from:

1- high levels of plasma hepcidin, which blocks the transfer of iron to erythroid precursors by downregulating ferroportin in macrophages and duodenum.
The elevated hepcidin levels are caused by proinflammatory cytokines such as IL-6 (increase hepatic hepcidin synthesis)
2-Chronic inflammation blunts erythropoietin synthesis by the kidney

37 A 37-year-old woman has experienced abdominal pain and intermittent low-volume diarrhea for the past 3 months. On physical examination, she is afebrile. A stool sample is positive for occult blood. A colonoscopy is performed, and biopsy specimens from the terminal ileum and colon show microscopic findings consistent with Crohn disease. She does not respond to medical therapy, and part of the colon and terminal ileum are removed. She is transfused with 2 U of packed RBCs during surgery. Three weeks later, she appears healthy, but complains of easy fatigability. On investigation, CBC findings show hemoglobin of 10.6 g/dL, hematocrit of 31.6%, RBC count of 2.69 million/μL, MCV of 118 μm^3, platelet count of 378,000/mm^3, and WBC count of 9800/mm^3. The reticulocyte count is 0.3%. Which of the following is most likely to produce these hematologic findings?

A Anemia of chronic disease
B Chronic blood loss
C Hemolytic anemia
D Myelophthisic anemia
E Vitamin B_{12} deficiency



50 A 56-year-old woman suffers the sudden onset of headache and photophobia, and her condition worsens for the next 2 days. On physical examination, she has a temperature of 38° C and is disoriented. CBC shows hemoglobin of 11.2 g/dL, hematocrit of 33.7%, MCV of 94 μm^3, platelet count of 32,000/mm^3, and WBC count of 9900/mm^3. The peripheral blood smear shows schistocytes. The serum urea nitrogen level is 38 mg/dL, and the creatinine level is 3.9 mg/dL. Which of the following is the most likely diagnosis?

A Autoimmune hemolytic anemia
B β-Thalassemia major
C Disseminated intravascular coagulation
D Idiopathic thrombocytopenic purpura
E Paroxysmal nocturnal hemoglobinuria
F Thrombotic thrombocytopenic purpura

- TTP is associated with the **pentad**: fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, & renal failure

54 A clinical study is performed involving adult patients diagnosed with microangiopathic hemolytic anemia. A subgroup of patients who had fever or diarrhea preceding the initial diagnosis of anemia were excluded. The patients had schistocytes present on peripheral blood smears. Some of these patients were found to have a deficiency of a metalloproteinase known as ADAMTS13. Which of the following conditions were the patients with this deficiency most likely to have?

- **A** Disseminated intravascular coagulation (DIC)
- **B** Hemolytic-uremic syndrome (HUS)
- **C** Heparin-induced thrombocytopenia (HIT)
- **D** Idiopathic thrombocytopenic purpura (ITP)
- **E** Thrombotic thrombocytopenic purpura (TTP)

Thrombotic Microangiopathies: TTP and HUS

- TTP usually affects adult, pathogenic mechanism:
  1. Inherited: Deficiency of metalloprotease (ADAMTS 13) needed for cleaving very HMW_vWF (multimers).

53 A 42-year-old woman has had nosebleeds, easy bruising, and increased bleeding with her menstrual periods for the past 4 months. On physical examination, her temperature is 37° C, pulse is 88/min, and blood pressure is 90/60 mm Hg. She has scattered petechiae over the distal extremities. There is no organomegaly. Laboratory studies show hemoglobin of 12.3 g/dL, hematocrit of 37%, platelet count of 21,500/mm^3, and WBC count of 7370/mm^3. A bone marrow biopsy specimen shows a marked increase in megakaryocytes. The prothrombin and partial thromboplastin times are within the reference range. What is the most likely diagnosis?

A Disseminated intravascular coagulation
B Hemophilia B
C Immune thrombocytopenic purpura
D Metastatic breast carcinoma
E Thrombotic thrombocytopenic purpura
F Vitamin K deficiency
G Von Willebrand disease

Immune Thrombocytopenic Purpura

- The onset of chronic ITP is insidious.
- Common findings: petechiae, easy bruising, epistaxis, gum bleeding, and hemorrhages after minor trauma.

Immune Thrombocytopenic Purpura (ITP)

- includes two clinical subtypes:
1. *Chronic ITP*: A relatively common disorder, affect women 20-40 years.
2. *Acute ITP*: A self-limited form, seen mostly in children after viral infections.
- **Pathogenesis: Antibodies against platelet membrane glycoproteins IIb/IIIa or Ib/IX complexes (detected in ~ 80% of cases of chronic ITP)**
- Splenectomy→ normalizes the platelet count & induces a complete remission in more than two-thirds of patients.
  - Splenomegaly is not a feature of uncomplicated ITP
  - But the spleen is an important site of anti-platelet antibody production
  - the spleen is major site of the premature destruction of the IgG-coated platelets.
- BM contains increased numbers of megakaryocytes (common to all forms of thrombocytopenia due to accelerated platelet destruction)

55 A 45-year-old woman has had episodes of blurred vision and headaches for the past 6 months. She has had worsening confusion with paresthesias over the past 3 days. On physical examination, she has a temperature of 39.6° C, pulse of 100/min, respiratory rate of 20/min, and blood pressure of 80/50 mm Hg. Petechial hemorrhages are noted over her trunk and extremities. Laboratory findings include hemoglobin, 10.9 g/dL; hematocrit, 34%; MCV, 96 μm^3; platelet count, 28,000/mm^3; and WBC count, 8500/mm^3. Fragmented RBCs are noted on her peripheral blood smear. Blood urea nitrogen is 40 mg/dL, and serum creatinine is 3.1 mg/dL. Which of the following is the most likely underlying cause for her findings?

A Circulating toxin that injures capillary endothelium
B Decreased factor VIII activity
C Defective ADP-induced platelet aggregation
D Formation of autoantibodies to platelet glycoproteins IIb/IIIa and Ib-IX
E Inappropriate release of thromboplastic substances into blood
F Presence of antibodies against ADAMTS13 metalloproteinase

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