SUMMARY

PATHOLOGY OF ANEMIA

Causes

- Blood loss (hemorrhage)
- Increased red cell destruction (hemolysis)
- Decreased red cell production

Morphology

- Microcytic (iron deficiency, thalassemia)
- Macrocytic (folate or vitamin B_{12} deficiency)
- Normocytic but with abnormal shapes (hereditary spherocytosis, sickle cell disease)

Clinical Manifestations

- **Acute:** shortness of breath, organ failure, shock
- **Chronic**
  - Pallor, fatigue, lassitude
  - With hemolysis: jaundice and gallstones
  - With ineffective erythropoiesis: iron overload, heart and endocrine failure
  - If severe and congenital: growth retardation, bone deformities due to reactive marrow hyperplasia

SUMMARY

ANEMIA OF DIMINISHED ERYTHROPOIESIS

Iron Deficiency Anemia

- Caused by chronic bleeding or inadequate iron intake; results in insufficient hemoglobin synthesis and hypochromic, microcytic red cells

Anemia of Chronic Inflammation

- Caused by inflammatory cytokines, which increase hepcidin levels and thereby sequester iron in macrophages, and also suppress erythropoietin production

Megaloblastic Anemia

- Caused by deficiencies of folate or vitamin B_{12} that lead to inadequate synthesis of thymidine and defective DNA replication
- Results in enlarged abnormal hematopoietic precursors (megaloblasts), ineffective hematopoiesis, macrocytic anemia, and (in most cases) pancytopenia

Aplastic Anemia

- Caused by bone marrow failure (hypocellularity) resulting from diverse causes, including exposures to toxins and radiation, idiosyncratic reactions to drugs and viruses, and inherited defects in telomerase and DNA repair

Myelophthisic Anemia

- Caused by replacement of the bone marrow by infiltrative processes such as metastatic carcinoma and granulomatous disease
- Leads to the appearance of early erythroid and granulocytic precursors (leukoerythroblastosis) and teardrop-shaped red cells in the peripheral blood

SUMMARY

HEMOLYTIC ANEMIA

Hereditary Spherocytosis

- Autosomal dominant disorder caused by mutations that affect the red cell membrane skeleton, leading to loss of membrane and eventual conversion of red cells to spherocytes, which are phagocytosed and removed in the spleen
- Manifested by anemia, splenomegaly

Sickle Cell Anemia

- Autosomal recessive disorder resulting from a mutation in β-globin that causes deoxygenated hemoglobin to self-associate into long polymers that distort the red cell
- Blockage of vessels by sickled cells causes pain crises and tissue infarction, particularly of the marrow and spleen
- Red cell membrane damage caused by repeated bouts of sickling results in a moderate to severe hemolytic anemia
- Patients are at high risk for bacterial infections and stroke

Thalassemia

- Autosomal codominant disorders caused by mutations in α- or β-globin that reduce hemoglobin synthesis, resulting in a microcytic, hypochromic anemia. In β-thalassemia, unpaired α-globin chains form aggregates that damage red cell precursors and further impair erythropoiesis.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- X-linked disorder caused by mutations that destabilize G6PD, making red cells susceptible to oxidant damage

Immunohemolytic Anemia

- Caused by antibodies against either normal red cell constituents or antigens modified by haptens (such as drugs)
- Antibody binding results in either red cell opsonization and extravascular hemolysis or (uncommonly) complement fixation and intravascular hemolysis

Malaria

- Intracellular red cell parasite that causes chronic hemolysis of variable severity
- Falciparum malaria may be fatal because of the propensity of infected red cells to adhere to small vessels in the brain (cerebral malaria)

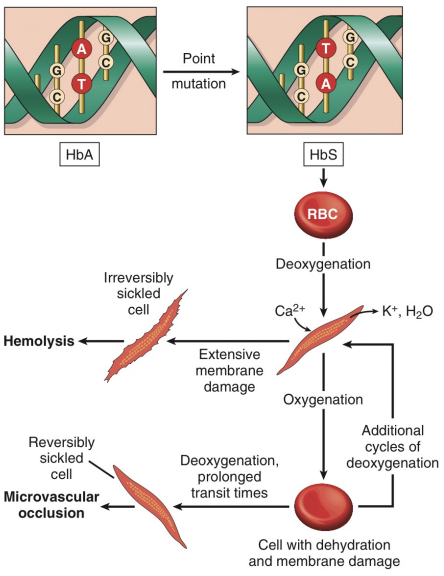

Fig. 12.4 Pathophysiology of sickle cell disease.

SUMMARY

BLEEDING DISORDERS

Disseminated Intravascular Coagulation

- Syndrome in which systemic activation of the coagulation leads to consumption of coagulation factors and platelets
- Can be dominated by bleeding, vascular occlusion and tissue hypoxemia, or both
- Common triggers: sepsis, major trauma, certain cancers, obstetric complications

Immune Thrombocytopenic Purpura

- Caused by autoantibodies against platelet antigens
- May be triggered by drugs, infections, or lymphomas, or may be idiopathic

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

- Both manifest with thrombocytopenia, microangiopathic hemolytic anemia, and renal failure; fever and CNS involvement are more typical of TTP.
- *TTP:* Caused by acquired or inherited deficiencies of ADAMTS 13, a plasma metalloprotease that cleaves very-high-molecular-weight multimers of vWF. Deficiency of ADAMTS 13 results in abnormally large vWF multimers that activate platelets.
- *Hemolytic uremic syndrome:* Caused by deficiencies of complement regulatory proteins or agents that damage endothelial cells, such as a Shiga-like toxin elaborated by *E. coli* strain O157:H7. The endothelial injury initiates platelet activation, platelet aggregation, and microvascular thrombosis.

von Willebrand Disease

- Autosomal dominant disorder caused by mutations in vWF, a large protein that promotes the adhesion of platelets to subendothelial collagen.
- Typically causes a mild to moderate bleeding disorder resembling that associated with thrombocytopenia.

Hemophilia

- *Hemophilia A:* X-linked disorder caused by mutations in factor VIII. Affected males typically present with severe bleeding into soft tissues and joints and have a PTT.
- *Hemophilia B:* X-linked disorder caused by mutations in coagulation factor IX. It is clinically identical to hemophilia A.

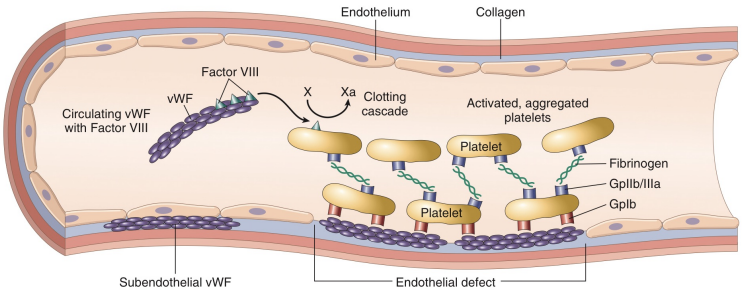

Fig. 12.31 Structure and function of factor VIII–von Willebrand factor (vWF) complex. Factor VIII and vWF circulate as a complex. vWF also is present in the subendothelial matrix of normal blood vessels. Factor VIII takes part in the coagulation cascade by activating factor X by means of factor IX *(not shown)*. vWF causes adhesion of platelets to subendothelial collagen, primarily through the glycoprotein Ib (GpIb) platelet receptor.

Table 12.5 Pathophysiologic Classification of Polycythemia

Relative
Reduced plasma volume (hemoconcentration)
Absolute
Primary
Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera); inherited activating mutations in the erythropoietin receptor (rare)
Secondary
Increased erythropoietin levels *Adaptive:* Lung disease, high-altitude living, cyanotic heart disease *Paraneoplastic:* Erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatomacellular carcinoma, cerebellar hemangioblastoma) *Surreptitious:* Endurance athletes

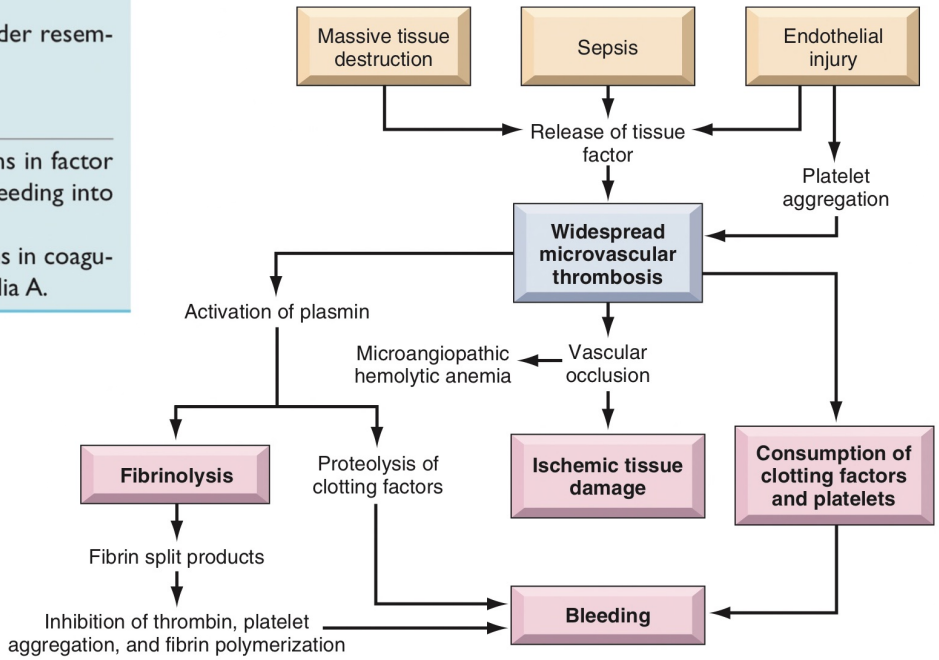

Fig. 12.30 Pathophysiology of disseminated intravascular coagulation.