

**TABLE 19-14**  
**COMMON INDICATIONS FOR SPLENECTOMY<sup>a</sup>**

<b>Medical (hematologic) indications</b>	
Congenital hemolytic anemias	
Hereditary spherocytosis; other severe congenital hemolytic diseases	
Sequestration crisis of sickle cell anemia	
Acquired immunohematologic diseases	
Chronic idiopathic thrombocytopenic purpura; autoimmune hemolytic anemia	
Hypersplenic syndromes:	
Gaucher disease, thalassemia major and intermedia; congestive splenomegaly	
<b>Surgical indications</b>	
Cysts, tumors	
Exposure, shunting for portal hypertension	
Relief of mechanical symptoms because of size	
Trauma	

<sup>a</sup> These indications are not absolute and must be individualized for each specific patient.

indications include congenital hemolytic anemias (see Sec. 19.5). In storage diseases such as Gaucher disease the spleen enlarges and may be a mechanical burden. Partial splenectomy is feasible, but its effectiveness in the management of these diseases is controversial.

Surgical splenectomy is obviously associated with a total loss of splenic function. The risk of postsplenectomy sepsis is related to the patient's age at the time of surgery and to the underlying condition. The young child, especially <5 years of age, has a high risk of postsplenectomy sepsis, but any age group may be affected. Patients who have undergone splenectomy for trauma and for benign hematologic conditions such as ITP and hereditary spherocytosis are at less risk than patients with malignancies, thalassemia, or those with Wiskott-Aldrich syndrome.

### 19.8.5 Splenic Injury

Laceration and rupture of the normal spleen may occur with blunt trauma to the abdomen or follow relatively minor trauma in children with splenomegaly, especially the acute enlargement that occurs in infectious mononucleosis. Massive internal hemorrhage may result in hypovolemic shock. Physical findings include persistent and increasing abdominal pain and peritoneal signs including rebound tenderness and abdominal muscle spasm. Diaphragmatic pain may be referred to the left shoulder. Blunt splenic trauma can be diagnosed by <sup>99m</sup>Tc scan, CT scan, or ultrasound, which may show a wide range of injuries from subcapsular hemorrhage to total fracture and maceration of the spleen. Almost all children with blunt splenic trauma can be managed conservatively with inpatient observation, bed rest, and transfusions as necessary to maintain circulatory stability. A small number of children with blunt splenic trauma who cannot be clinically stabilized and those with multiple organ injury require surgery. In some circumstances, splenic repair or partial splenectomy may be possible. Long-term follow-up of children treated nonoperatively for blunt splenic trauma have not revealed significant numbers of late complications. A significant proportion of children whose spleens are removed for trauma develop splenosis.

Enlarged spleens that are not protected by the rib cage are at increased risk of splenic trauma. Children with splenomegaly should avoid contact sports and other physical activities associated with significant risk of abdominal trauma.

### 19.8.6 Management of Children with Asplenia and Hyposplenia

Prophylactic therapy with penicillin or an equivalent antibiotic is strongly recommended for infants or young children who have hyposplenia or asplenia. In a prospective double-blind trial of sickle cell anemia children less than 5 years old with functional hyposplenia, oral penicillin prophylaxis was shown to reduce the incidence of bacteremia by 84%. A second controlled study showed no significant benefit of penicillin prophylaxis after 5 years of age. The emergence of penicillin-resistant pneumococci may reduce the effectiveness of penicillin prophylaxis.

Children with asplenia or splenic dysfunction should be immunized with vaccines against *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*. The 23-valent pneumococcal polysaccharide vaccine is inconstantly effective in children <5 years of age, but the seven-valent conjugate polysaccharide vaccine is immunogenic in infants. The conjugate *H. influenzae* vaccine has virtually eliminated severe disease caused by this pathogen. If a child requires an elective splenectomy, these immunizations should be given in advance of surgery but are also effective when given after splenectomy.

Parents of children with splenic dysfunction must be educated to regard significant febrile illnesses (>102°F) as signaling a potentially life-threatening situation and mandates prompt evaluation by a physician. After a blood culture has been obtained, parenteral broad-spectrum antibiotics, currently third-generation cephalosporins, should be administered. Although the risk of postsplenectomy sepsis is greatest in young children in the first few years after splenectomy, severe infections have occurred decades after splenectomy. A syndrome of severe and frequently fatal infection by *Capnocytophaga canimorsus* acquired from a sometimes trivial dog bite has been reported, and asplenic patients should be treated empirically with amoxicillin/clavulanic acid after dog bites. Asplenic patients also appear to be at increased risk of serious infections with *Bartonella bacilliformis*.

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## 19.9 BONE MARROW FAILURE SYNDROMES

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### NORMAL HEMATOPOIESIS

The development of in vivo and in vitro clonal assays for pluripotent and committed hematopoietic progenitors and the character-

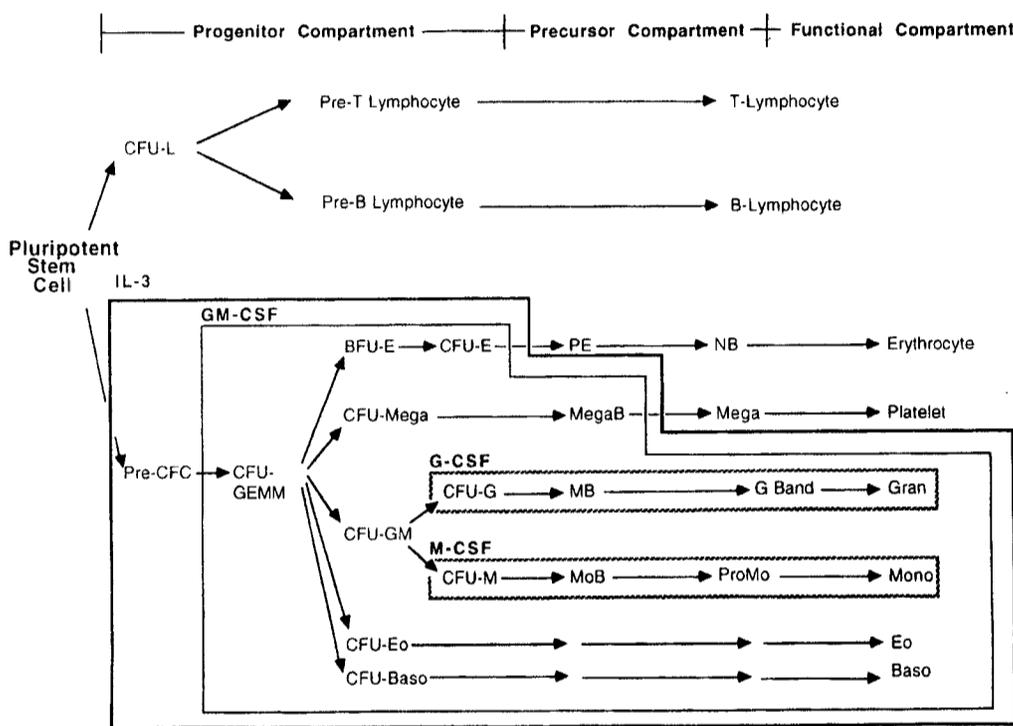
ization of hematopoietic cell surface antigens by flow cytometry have resulted in the developmental model of hematopoiesis (see Fig. 19-10). This model describes the proliferation and differentiation of pluripotent hematopoietic stem cells that can populate the entire marrow with nucleated RBC, WBC, and platelet precursors. The immediate offspring of the stem cells are the committed progenitors of the lymphocyte (CFU-L, colony-forming unit-lymphocyte) and the multipotent hematopoietic or myeloid progenitor, the CFU-GEMM, that gives rise to committed progenitors of the granulocyte, erythrocyte, monocyte/macrophage, and megakaryocyte as well as eosinophil and basophil populations. These progenitors appear as immature, undifferentiated mononuclear cells and are present in small numbers in the bone marrow. In addition to the hematopoietic components of the system, a complex array of growth factors in addition to support elements or stroma and accessory lymphocytes, macrophages, fibroblasts, endothelial cells, and adipocytes create a regulatory milieu that interacts with differentiating hematopoietic cells. Hematopoietic cell differentiation is controlled by intrinsic transcriptional regulators within niches in the

bone marrow. Specific receptor-ligand relationships within the microenvironment support the proliferation and differentiation of specific cell types and provide a scaffold on which blood-forming cells, accessory cells, and growth factors may interact at close range.

Cell culture and recombinant DNA technology have led to the identification and ultimate cloning of the genes for many specific hematopoietic growth factors or cytokines as well as EPO. In some circumstances these factors may also influence the function of the terminally differentiated cell. In addition, an array of growth antagonists provide feedback inhibition.

The hematopoietic bone marrow has been compared to a garden. Stem cell "seeds" are anchored by receptor-ligand "roots" nurtured in stromal "soil" by growth factor and nutrient "fertilizers" to give rise to a beautiful and complex hematopoietic garden. Thus, a number of mechanisms can lead to bone marrow failure, which could result from faulty stem/progenitor cells (seeds), defective stroma and accessory cells (soil), or immunologic weeds. The hematopoietic garden concept provides a model for under-

The Progenitor Basis of Hematopoiesis



**FIGURE 19-10** The progenitor basis of hematopoiesis. Schematic diagram as defined by clonal assays and flow cytometric analysis in the human and murine systems and studies in diseases of clonal proliferation. Enclosed areas define the effect of the colony stimulating factors IL-3 (interleukin-3). GM-CSF (granulocyte, macrophage-colony stimulating factor), G-CSF (granulocyte-colony stimulating factor), and M-CSF (macrophage-colony stimulating factor). The hierarchy of hematopoietic cell differentiation proceeds from the pluripotent stem cell through the progenitor compartment, cells that are not morphologically identifiable but have undergone commitment to the morphologically identifiable precursor compartment. CFU-L, colony forming unit-lymphocyte; pre-CFC, pre-colony forming cell; CFU-GEMM, colony forming unit-granulocyte, erythrocyte, megakaryocyte, macrophage; BFU-E, burst forming unit-erythroid; CFU-E, colony forming unit erythroid; PE, proerythroblast; NB, normoblast; CFU-Mega, colony forming unit-megakaryocyte, Mega B, megakaryoblast; Mega, megakaryocyte; CFU-GM, colony forming unit-granulocyte, macrophage; CFU-G, colony forming unit-granulocyte; MB, myeloblast; G Band, granulocytic band; Gran, Granulocyte; CFU-M, colony forming unit-macrophage; MoB, monoblast; ProMo, promonocyte; Mono, monocyte; Eo, eosinophil; Baso, basophil.

standing the pathophysiology of aplastic anemia and the other bone marrow failure syndromes observed in children.

### 19.9.1 Aplastic Anemia

The term *aplastic anemia* describes pancytopenia, not just anemia. Onset is often insidious, with complaints of fatigue, pallor, thrombocytopenic bleeding, bruising, and epistaxis. Infections are usually a late complication. Acquired aplastic anemia has an annual incidence of about two to six per  $10^6$  population, one-10th the incidence of leukemia. There is no racial or gender propensity and no peak age in childhood.

Some exposures such as radiation, cytotoxic drugs, and organic solvents regularly induce aplasia in a dose-related manner, whereas others, such as certain antibiotics and other drugs and chemicals, do so only sporadically and idiosyncratically. The antibiotic chloramphenicol, which is associated with both dose-related and idiosyncratic aplasia, warrants special mention because it may cause severe aplasia. Viruses and specific immune diseases may be implicated in some cases. Drug or viral exposures may have occurred weeks or months before the clinical presentation. Genetic propensity for a specific environmental factor and inherited familial predispositions have been described. Nonetheless, more than half of all cases remain "idiopathic."

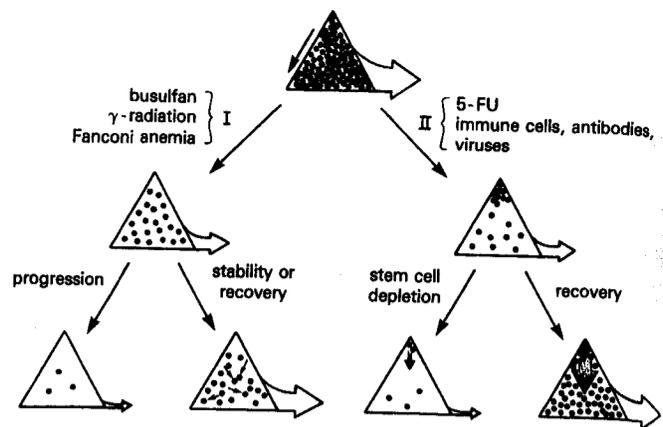
The diagnosis requires reduction in three cell lines—anemia, thrombocytopenia, and neutropenia—as well as a hypocellular bone marrow. Physical examination may show pallor and bruising, but hepatosplenomegaly or lymphadenopathy is not present.

The diagnosis of aplastic anemia requires a complete blood count and assessment of the bone marrow for morphology and cellularity. Most patients have anemia and thrombocytopenia before granulocytopenia. The differential diagnosis includes malignant marrow infiltrations by leukemia, lymphoma, metastatic tumor, or granulomas and ineffective hematopoiesis, as in myelodysplasia.

Acquired aplastic anemia is further classified as moderate or severe. In severe aplastic anemia, the patient is pancytopenic: platelets  $<20 \times 10^9/L$ ; neutrophils  $<0.5 \times 10^9/L$ ; and absolute reticulocytopenia  $<40 \times 10^9/L$ . "Stress" erythropoiesis may be reflected by macrocytosis (MCV  $>100$  fL), increased fetal hemoglobin, and fetal i antigen on RBC membranes. The bone marrow is hypocellular with increased fat, and more than 70% of the marrow cells are nonhematopoietic: lymphocytes, reticulum cells, mast cells, and plasma cells. Megakaryocytes are markedly reduced in number. Patients with moderate aplastic anemia do not meet these criteria for severe disease but have pancytopenia and hypocellular bone marrow. Categorization of the patient has prognostic implications because the "severe" group does poorly.

### PATHOPHYSIOLOGY

Hematopoietic progenitors in blood and marrow are very low in number and respond poorly to hematopoietic stimuli, suggesting that the most primitive stem cells are absent. As primitive cells mature, the potential for self-renewal is lost, and entry into a pathway for terminal differentiation is likely. Two mechanisms of hematopoietic cell damage giving rise to aplastic anemia have been postulated (Fig. 19-11). The most primitive stem cells are mitotically quiescent. Type I damage is random, striking both immature and mature cells but most notably affecting the immature and perhaps nonmitotic cells that require many mitoses for maturation. The



**FIGURE 19-11** Mechanisms of stem cell compartment damage. SOURCE: Young NS, Alter BP: *Aplastic Anemias: Acquired and Inherited*. Philadelphia, Saunders, 1994:37.

mechanism may involve direct injury to DNA by irradiation or alkylating agents (busulfan). A permanent effect might be depletion of stem cell number and self-renewal capacity. Type II damage occurs in the more mitotically and metabolically active compartment of differentiating cells, which have distinct antigenic phenotypes. Cell cycle-specific chemotherapeutic agents, viral infection, or immune mechanisms may be involved, and stem cell depletion occurs as cells differentiate and are vulnerable to damage. Response of some patients to immune therapy (immunomodulation) with antithymocyte globulin or cyclosporine suggests that type II damage is relevant. With either type of damage, recovery of hematopoiesis may occur from a very small number of stem cells and thus be "clonal."

### TREATMENT AND OUTCOME

Definitive treatment of the aplastic anemia is required because patients receiving only supportive care have a 50% mortality within the first 6 months and a long-term survival rate of  $<25\%$ .

The optimal and curative treatment for severe aplastic anemia is stem cell transplantation (BMT) (see Sec. 20.4). About 80% of patients will have a complete or partial response to immunosuppressive therapy, most commonly antilymphocyte globulin (ATG or ALG) and cyclosporine. Corticosteroids, to prevent serum sickness from ATG or ALG, and growth factors G- or GM-CSF to increase the neutrophil count are usually included. Sustained neutrophil responses may appear within 1 month, and RBC and platelet responses by 2 to 3 months. Immunomodulatory therapy is indicated for patients with severe aplastic anemia without an HLA-matched sibling donor but may not be a long-term success because of a substantial risk of developing a clonal hematopoietic disorder such as paroxysmal nocturnal hemoglobinuria, myelodysplasia, or acute myelocytic leukemia. Even patients who recover spontaneously develop clonal disease because of intrinsic problems in immune surveillance or in the stem cell itself.

Androgen treatment may have a role in the management of moderate but not severe aplastic anemia. Supportive management is critical. Bleeding can be prevented or treated with platelet transfusions, which may be required long term in unresponsive patients. The development of alloantibodies, usually to HLA-A or -B antigens, may limit effectiveness (Sec. 19.11). The platelet count should be maintained above  $5 \times 10^9/L$ , although higher counts

may be necessary to prevent serious hemorrhage. Practical measures include good dental hygiene, avoidance of trauma, and suppression of menses. An antifibrinolytic agent such as ε-aminocaproic acid may be helpful during acute oral bleeding episodes.

Neutropenia is associated with a risk of bacterial and fungal infections. Local sites such as catheter insertions require meticulous care. Febrile episodes should be treated empirically with broad-spectrum parenteral antibiotics. Prophylactic antibiotics predispose to resistant bacteria or fungi and are not recommended.

Anemia is readily treated with transfusions of packed RBC to maintain a hemoglobin >70 g/L. Development of alloantibodies may be avoided by the use of phenotypically matched blood. Iron overload will occur after a large number of transfusions. Because all patients with aplastic anemia are considered to be potential candidates for BMT, family members should not be used as donors of blood products.

Blood products should be leukocyte-depleted to reduce sensitization to leukocyte antigens and reduce the number of lymphocytes that may contain cytomegalovirus. Blood products should be irradiated to prevent graft-versus-host disease (see Sec. 19.11).

**19.9.2 Inherited Bone Marrow Failure Syndromes**

What appears to be “acquired” aplastic anemia may occur in individuals who are heterozygous, hemizygous, or homozygous for genes associated with marrow failure. The precise incidences of the inherited syndromes (Table 19-15) are not known. In large series, 25 to 30% of children with marrow aplasia may have an inherited disorder, resulting in 300 to 1000 new cases annually in the United States. Because of the familial association, as well as the frequency of congenital anomalies in some of the syndromes, patients may be diagnosed before the development of marrow failure, and prenatal testing is available for some conditions. Most of the diagnoses are based on clinical findings (Table 19-15) and not on specific laboratory tests. Absence of anomalies does not exclude a diagnosis, but the presence of characteristic findings suggests an inherited syndrome. Specific diagnoses have prognostic and therapeutic impli-

cations, and these patients may be at increased risk for developing malignancies (see Chapter 10 and Sec. 19.2).

**FANCONI ANEMIA**

Fanconi in 1927 described several siblings who had congenital anomalies, short stature, and aplastic anemia. Fanconi anemia (FA) is an autosomal recessive disorder in which about 75% of patients have major or minor congenital anomalies. More than 90% develop aplastic anemia at a mean age of 8 to 9 years, ranging from birth to 48 years. About 3% of cases are diagnosed in the first year of life, and 10% after age 16 years. The “classical” phenotype includes short stature, absent or abnormal thumbs and abnormal radii, microcephaly, café-au-lait and hypopigmented spots, dark pigmentation, and renal anomalies. The sex ratio is equal, and all ethnic groups are affected.

At least eight FA mutations have been identified. The genes for two of these have been cloned: *FANCA* and *FANCC*, which account for more than 75% of cases. The usual diagnostic test for FA involves the identification of DNA repair abnormalities in cultured peripheral blood lymphocytes, including a high proportion of metaphases with breaks, gaps, rearrangements, exchanges, endoreduplication, and triradials. These abnormalities are increased when cells are cultured with a DNA-damaging agent such as diepoxybutane (DEB) or mitomycin C (MMC). Chromosome breakage analyses have been used for prenatal diagnosis of FA.

**PRESENTATION AND CLINICAL COURSE** Single cytopenias, particularly thrombocytopenia, may precede the development of pancytopenia. Macrocytic erythrocytes with increased fetal hemoglobin are often present before anemia develops. When pancytopenia develops, the bone marrow is usually hypocellular and fatty, but occasionally dyserythropoiesis and dysmyelopoiesis are found. Marrow examination, including chromosome analyses, should be performed periodically to detect malignant transformation. Cultures of marrow and blood demonstrate decreased numbers of stem cell progenitors, which correlates with hematologic abnormalities. Mean survival in FA is now in the mid-30s, with most deaths re-

**TABLE 19-15**  
**PHYSICAL ABNORMALITIES IN INHERITED BONE MARROW FAILURE SYNDROMES**

FANCONI ANEMIA	DIAMOND-BLACKFAN ANEMIA	DYSKERATOSIS CONGENITA	KOSTMANN SYNDROME	SHWACHMAN-DIAMOND SYNDROME	THROMBO-CYTOPENIA ABSENT RADII	AMEGAKARYOCYTIC THROMBO-CYTOPENIA
Skin-pigmented, café-au-lait	Facies characteristic	Skin—reticular pigmentation	Short Retardation	Short Malabsorption Retardation	Radii absent, thumbs present	Normal or CNS anomalies
Short radii and/or thumb anomalies	Thumb anomalies	Nail dystrophy			Humeri short	Retardation
Hypogonads	Eyes—glaucoma, other	Leukoplakia			Fingers abnormal	Congenital heart disease
Microcephaly	Renal anomalies	Eyes—epiphora			Leg anomalies	
Eyes—small, strabismus	Hypogonads	Teeth bad			Skeletal anomalies	
Renal anomalies	Neck—web, short	Retardation				
Low birth weight	Skeletal anomalies	Skeletal anomalies				
Retardation	Congenital heart disease	Short				
Deafness	Retardation	Hyperhidrosis				
Hyperreflexia		Hair loss				
Skeletal anomalies		Urethral stenosis				
		Esophageal anomalies				

sulting from infections and hemorrhage. Supportive care is important.

**TREATMENT** Unlike acquired aplastic anemia, a favorable response to androgens occurs in more than 50% of patients with FA. Most responders require continued treatment, and eventually most become unresponsive. Synthetic androgens may cause peliosis hepatis and liver tumors, and patients should be monitored regularly by ultrasonography.

Stem cell transplant is the only cure for the aplasia, but patient preparation must be modified because immunosuppression regimens that include cyclophosphamide and radiation are very toxic to nonmarrow dividing cells, which cannot repair DNA damage. The short-term survival following transplant from HLA-matched related donors is >75%. Stem cells obtained from placental blood have been used successfully to reconstitute FA patients. Ten to fifteen percent of FA patients develop acute myelogenous leukemia, and some did not have preceding aplastic anemia. Because of the DNA repair defect, most patients tolerate chemotherapy poorly, and bone marrow transplantation conditioning must use special, less myeloablative protocols. Several patients have been described with pancytopenia and myelodysplasia, with abnormal bone marrow dysplastic changes despite normal or increased cellularity. A clonal cytogenetic abnormality, possibly preleukemic, has been seen in some of these patients. FA patients are at increased risk of hepatic malignancy, which is enhanced by androgen treatment. About 5% of FA patients have developed other malignancies.

### DYSKERATOSIS CONGENITA

More than 200 cases of dyskeratosis congenita (DC) have been reported, representing all racial and ethnic groups. About 80% of cases have X-linked recessive inheritance; the rest are autosomal recessive or dominant. The X-linked condition has been linked to Xq28, and the gene *DKC1* encodes the protein dyskerin, which makes prenatal diagnosis possible. The diagnostic triad of DC includes (1) dystrophic finger- and toenails, (2) reticulated mottled hyperpigmentation of the skin, and (3) mucous membrane leukoplakia. Less frequent physical findings include blocked lacrimal ducts, dentition problems, hyperhidrosis, and keratosis (Table 19-15). Approximately half the patients develop aplastic anemia with pancytopenia, macrocytosis, and increased HbF. Bone marrows are usually hypocellular. The median survival age is in the mid-30s, with most deaths resulting from complications of pancytopenia or malignancies. The average age for the development of aplasia is 15 years, and for malignancies 30 years.

**TREATMENT** Pancytopenia responds to androgen therapy in about 50% of patients. Supportive care is important. BMT has cured about 25% of a small number of patients, but procedure-related deaths are not infrequent because of the increased tissue sensitivity to chemotherapy. GM-CSF or G-CSF therapy may have a therapeutic role. Myelodysplasia and acute myelogenous leukemia have been reported in patients with DC.

### 19.9.3 Single Cytopenias

#### ACQUIRED RED CELL APLASIA

The differential diagnosis of acquired pure red cell aplasia (PRCA) is shown on Table 19-16. Acquired PRCA of the adult type may

**TABLE 19-16**  
**CLASSIFICATION OF SINGLE-LINEAGE**  
**CYTOPENIAS**

ACQUIRED	INHERITED
<b>Pure red cell aplasia (PRCA)</b>	
Idiopathic	Diamond-Blackfan anemia
Drugs and chemicals	
Immune	
Thymoma	
B19 parvovirus	
Transient erythroblastopenia of childhood (TEC)	
<b>Neutropenia</b>	
Drugs, toxins	Kostmann syndrome
Idiopathic	Shwachman-Diamond syndrome
T $\gamma$ lymphoproliferative disease	Reticular dysgenesis
<b>Thrombocytopenia</b>	
Idiopathic amegakaryocytic thrombocytopenia	Thrombocytopenia with absent radii
Drugs, toxins	
Immune	

SOURCE: Young NS, Alter BP: *Aplastic Anemia: Acquired and Inherited*. Philadelphia, WB Saunders, 1994:9.

be idiopathic or related to drugs, particularly phenytoin and chloramphenicol. Immune-mediated PRCA occurs in many idiopathic cases as well as those with thymoma, systemic lupus erythematosus, and chronic lymphocytic leukemia. In vitro erythroid colony assays may reveal the presence of serum lymphocyte inhibitors of erythropoiesis, and about two-thirds will respond to immunosuppression or cytotoxic agents. RBC transfusions are the primary treatment.

*B19 parvovirus* infects erythroid progenitors and causes transient or chronic RBC aplasia. The chronic type occurs because of persistence of parvovirus in immunodeficient patients who cannot produce neutralizing antibody. The patients have severe transfusion-dependent anemia, and bone marrows show reduced erythroid precursors. The few RBC precursors are giant pronormoblasts. Diagnosis requires demonstration of parvovirus genome (DNA) in serum, blood, or bone marrow cells. Treatment with intravenous  $\gamma$ -globulin (IVIgG) is usually effective.

*Transient aplastic crisis (TAC)* caused by parvovirus occurs only once in patients with underlying hemolytic anemias (see Sec. 19.5). Occasionally, neutrophils and platelets will also be decreased. Diagnostic levels of IgM antibody appear in the first week after infection. In utero infection with parvovirus results in up to 10% fetal death during the first and second trimesters, and neonatal hydrops fetalis occurs occasionally.

*Transient erythroblastopenia of childhood (TEC)* is an acquired condition in previously hematologically normal children and usually involves only anemia, reticulocytopenia, and marrow erythroblastopenia. The mean age of diagnosis is 26 months, with the majority between 1 and 3 years of age. Although many patients have had an antecedent viral illness, no specific virus has been implicated, and parvovirus has usually been excluded. Pallor and tachycardia are the only relevant findings. The anemia may require one or two transfusions, but patients usually recover spontaneously within 1 to 2 months. Bone marrow shows erythroid hypoplasia, and cultures show decreased colony-forming units-erythroid (CFU-E). Serum or cellular inhibitors of erythropoiesis are often identified. TEC has an excellent prognosis, and later hematologic complications have not been reported. TEC can be distinguished from Diamond-

Blackfan anemia because TEC patients are usually older than 1 year and have normocytic red cells, levels of HbF normal for age, no excess membrane antigen, and no congenital anomalies.

*Diamond-Blackfan anemia* (DBA; *congenital hypoplastic anemia*) is characterized by macrocytic anemia and reticulocytopenia (pure red cell anemia). The bone marrow is normocellular, but erythroid precursors are markedly reduced or absent. Ninety percent of patients are diagnosed under 1 year of age, although a few cases with later onset have been described. Most of the more than 500 reported cases are white, but blacks and Asians have been affected. Three-quarters of cases are sporadic, but both dominant and recessive pedigrees have been described. One DBA gene has been cloned and mapped on chromosome 19, and at least two additional DBA genes may exist.

Approximately one-third of patients have abnormal physical findings (see Table 19-15). An increase in RBC adenosine deaminase (ADA) activity is present in 90% of cases, and chromosome breakage is not increased.

Approximately 80% of patients improve on corticosteroid therapy, maintain normal hemoglobin levels without transfusions, and can be managed on small alternate-day doses, but some require prohibitively toxic levels, and some respond initially and then become refractory, resulting in an overall response rate of only about 50%. Spontaneous remissions occur in about 25% of cases independent of steroid responsiveness (steroid responders and nonresponders). Bone marrow transplantation was curative in 25 of 35 reported cases. Non-steroid responsive patients require chronic transfusion therapy and inevitably develop iron overload that requires chelation (Sec. 19.4.7).

The current median survival is about 40 to 45 years because of improved transfusion and chelation therapy. A few patients have developed aplastic anemia (see Table 19-15), and about 5% have developed leukemia or myelodysplasias. Thus, DBA may be a myeloid premalignant condition.

Inherited single neutropenias—*Kostmann syndrome* (KS), *infantile genetic agranulocytosis*, *Schwachman syndrome*, and *cartilage hair syndrome*—are discussed in Sec. 19.6. Inherited thrombocytopenia, the TAR syndrome, and amegakaryocytic thrombocytopenia are discussed in Sec. 19.7.

*Pearson syndrome* is characterized by refractory macrocytic sideroblastic anemia with vacuolization of bone marrow myeloid and erythroid precursors, exocrine pancreatic deficiency with malabsorption, and metabolic acidosis. Ringed sideroblasts, which are iron-laden mitochondria, are present, and there are decreased numbers of progenitors. Patients have evidence of mitochondrial cytopathies, including metabolic acidosis and abnormalities of oxidative phosphorylation. Large deletions of mitochondrial DNA can be demonstrated. The inheritance of mitochondrial diseases is maternal because only ova and not sperm have mitochondria, and all of the approximately 50 reported cases have been sporadic. Most patients die in infancy. In children who survive, there is hematologic improvement, but they may develop the neurologic abnormalities of Kayne-Sayres disease (see Chapter 25).

#### 19.9.4 Myelophthistic Anemia

Peripheral cytopenias caused by marrow replacement by disorders not intrinsic to the marrow lead to *leukoerythroblastosis* (anemia with nucleated RBC and immature white cells), which must be distinguished from *leukemoid reactions*, in which there is a reactive leukocytosis with an orderly progression of immature through ma-

ture cells, and a *leukemic hiatus*, in which there are both immature and mature cells but a gap with a lack of intermediate cells.

The major causes of myelophthistic disease in children are marrow invasion by metastatic tumor, granulomas, myelofibrosis, or osteopetrosis. *Osteopetrosis*, or marble bone disease, can be a benign autosomal dominant or severe autosomal recessive disease characterized by dense fragile bones caused by abnormal osteoclasts that do not resorb bone normally. The patients have craniomegaly and hepatosplenomegaly because of extramedullary hematopoiesis, blindness, deafness, cranial nerve palsies, and fractures. Macrocytic leukoerythroblastic anemia occurs, and bone marrow biopsies show small constricted medullary cavities, hypocellularity, and fibrosis. Cytopenias result from decreased production and increased splenic pooling. BMT can be curative, because osteoclasts are derived from marrow stem cells.  $\alpha$ -Interferon may stimulate bone resorption, and M-CSF may augment osteoclast activity. Prenatal ultrasonography can detect increased bone density and fractures.

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## 19.10 HEMOSTASIS

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Hemostasis is a complex physiological process that functions to stop hemorrhage and repair vascular injury without compromising blood flow. Hemostasis involves interactions among elements of the blood vessel wall and subendothelial supporting structures, circulating blood platelets, and plasma coagulation proteins. Although, *in vivo*, all components of this system interact in a dynamic, coordinated fashion, the initiating event in hemostasis is platelet-vessel interaction followed by formation of the fibrin clot. Clot propagation is regulated and cleared by physiological fibrinolysis.

### PLATELET-VESSEL INTERACTION

A series of reactions involved in the formation of a hemostatic plug is the primary means by which bleeding is arrested at the level of small blood vessels. Vascular injury exposes subendothelial collagen fibrils and provides a site for adhesion of platelets. Platelet adhesion requires the interaction of platelet membrane with the damaged endothelium via the von Willebrand protein, which binds both to subendothelial collagen and to glycoprotein Ib of activated platelets. Aggregation of additional platelets is facilitated by agonists in the area of vascular injury including thrombin, epinephrine, collagen, and ADP, which are released from other platelets. Stimulation of the platelet membrane causes activation of phospholipids, which