What might be the reason for iron sequestration in the setting of inflammation? The best guess is that it enhances the body's ability to fend off certain types of infection, particularly those caused by bacteria (e.g., *H. influenzae*) that require iron for pathogenicity. In this regard it is interesting to consider that hepcidin is structurally related to defensins, a family of peptides that have intrinsic antibacterial activity. This connection further highlights the poorly understood but intriguing relationship between inflammation, innate immunity, and iron metabolism.

The anemia is usually mild, and the dominant symptoms are those of the underlying disease. The red cells can be normocytic and normochromic, or hypochromic and microcytic, as in anemia of iron deficiency. The presence of increased storage iron in marrow macrophages, a high serum ferritin level, and a reduced total iron-binding capacity readily rule out iron deficiency as the cause of anemia. Only successful treatment of the underlying condition reliably corrects the anemia. However, some patients, particularly those with cancer, benefit from administration of erythropoietin.

Aplastic Anemia

Aplastic anemia refers to a syndrome of chronic primary hematopoietic failure and attendant *pancytopenia* (anemia, neutropenia, and thrombocytopenia). In the majority of patients autoimmune mechanisms are suspected, but inherited or acquired abnormalities of hematopoietic stem cells also seem to contribute in at least a subset of patients.

Etiology. The most common circumstances associated with aplastic anemia are listed in Table 14-7. Most cases of "known" etiology follow exposure to chemicals and drugs. Certain drugs and agents (including many cancer chemotherapy drugs and the organic solvent benzene) cause marrow suppression that is dose related and reversible. In other instances, aplastic anemia arises in an unpredictable, idiosyncratic fashion following exposure to drugs that normally cause little or no marrow suppression. The implicated drugs include chloramphenicol and gold salts.

Persistent marrow aplasia can also appear after a variety of *viral infections,* most commonly viral hepatitis of the non-A, non-B, non-C, non-G type, which is associated with 5% to 10% of cases. Why aplastic anemia develops in certain individuals is not understood.

Whole-body *irradiation* can destroy hematopoietic stem cells in a dose-dependent fashion. Persons who receive therapeutic irradiation or are exposed to radiation in nuclear accidents (e.g., Chernobyl) are at risk for marrow aplasia.

Specific abnormalities underlie some cases of aplastic aplasia.

- *Fanconi anemia* is a rare autosomal recessive disorder caused by defects in a multiprotein complex that is required for DNA repair (Chapter 7). Marrow hypofunction becomes evident early in life and is often accompanied by multiple congenital anomalies, such as hypoplasia of the kidney and spleen and bone anomalies, which most commonly involve the thumbs or radii.
- Inherited defects in *telomerase* are found in 5% to 10% of adult-onset aplastic anemia. Telomerase is required for cellular immortality and limitless replication (Chapters 1 and 7). It might be anticipated, therefore, that partial deficits in telomerase activity could result in premature hematopoietic stem cell exhaustion and marrow aplasia.
- Even more common than telomerase mutations are abnormally short telomeres, which are found in the marrow cells of as many as half of those affected with aplastic anemia. It is unknown whether this shortening is due to other unappreciated telomerase defects or is a consequence of excessive stem cell replication.

Table 14-7 Major Causes of Aplastic Anemia

Acquired
Idiopathic
Acquired stem cell defects
Immune mediated
Chemical Agents
Dose related
Alkylating agents
Antimetabolites
Benzene
Chloramphenicol
Inorganic arsenicals
Idiosyncratic
Chloramphenicol
Phenylbutazone
Organic arsenicals
Methylphenylethylhydantoin
Carbamazepine
Penicillamine
Gold salts
Physical Agents
Whole-body irradiation
Viral Infections
Hepatitis (unknown virus)
Cytomegalovirus infections
Epstein-Barr virus infections
Herpes zoster (varicella zoster)
Inherited
Fanconi anemia
Telomerase defects

In most instances, however, no initiating factor can be identified; about 65% of cases fall into this *idiopathic* category.

Pathogenesis. The pathogenesis of aplastic anemia is not fully understood. Indeed, it is unlikely that a single mechanism underlies all cases. However, **two major etiologies have been invoked: an extrinsic, immune-mediated suppression of marrow progenitors, and an intrinsic abnormality of stem cells** (Fig. 14-24).

Experimental studies have focused on a model in which activated T cells suppress hematopoietic stem cells. Stem cells may first be antigenically altered by exposure to drugs, infectious agents, or other unidentified environmental insults. This provokes a cellular immune response, during which activated T_H1 cells produce cytokines such as interferon-γ (IFN-γ) and TNF that suppress and kill hematopoietic progenitors. This scenario is supported by several observations.

- Analysis of the few remaining marrow stem cells from aplastic anemia marrows has revealed that genes