leukemia and myelodysplastic syndromes (Chapter 13), which can have identical clinical manifestations. In aplastic anemia, the marrow is hypocellular (and usually markedly so), whereas myeloid neoplasms are associated with hypercellular marrows filled with neoplastic progenitors.

The prognosis is variable. Bone marrow transplantation is the treatment of choice in those with a suitable donor and provides a 5-year survival of more than 75%. Older patients or those without suitable donors often respond well to immunosuppressive therapy.

Pure Red Cell Aplasia

Pure red cell aplasia is a primary marrow disorder in which only erythroid progenitors are suppressed. In severe cases, red cell progenitors are completely absent from the marrow. It may occur in association with neoplasms, particularly thymoma and large granular lymphocytic leukemia (Chapter 13), drug exposures, autoimmune disorders, and parvovirus infection (see later). With the exception of those with parvovirus infection, it is likely that most cases have an autoimmune basis. When a thymoma is present, resection leads to hematologic improvement in about half of the patients. In patients without thymoma, immunosuppressive therapy is often beneficial. Plasmapheresis may also be helpful in unusual patients with pathogenic autoantibodies, such as neutralizing antibodies to erythropoietin that appear de novo or following the administration of recombinant erythropoietin.

A special form of red cell aplasia occurs in individuals infected with parvovirus B19, which preferentially infects and destroys red cell progenitors. Normal individuals clear parvovirus infections within 1 to 2 weeks; as a result, the aplasia is transient and clinically unimportant. However, in persons with moderate to severe hemolytic anemias, even a brief cessation of erythropoiesis results in rapid worsening of the anemia, producing an aplastic crisis. In those who are severely immunosuppressed (e.g., persons with advanced HIV infection), an ineffective immune response sometimes permits the infection to persist, leading to chronic red cell aplasia and a moderate to severe anemia.

Other Forms of Marrow Failure

Myelophthisic anemia **describes a form of marrow failure in which space-occupying lesions replace normal marrow elements.** The commonest cause is metastatic cancer, most often carcinomas arising in the breast, lung, and prostate. However, any infiltrative process (e.g., granulomatous disease) involving the marrow can produce identical findings. Myelophthisic anemia is also a feature of the spent phase of myeloproliferative disorders (Chapter 13). All of the responsible diseases cause marrow distortion and fibrosis, which act to displace normal marrow elements and disturb mechanisms that regulate the egress of red cells and granulocytes from the marrow. The latter effect causes the abnormal release of nucleated erythroid precursors and immature granulocytic forms *(leukoerythroblastosis)* into peripheral smears, and the appearance of *teardrop-shaped red cells*, which are believed to be deformed during their tortuous escape from the fibrotic marrow.

Chronic renal failure**, whatever its cause, is almost invariably associated with an anemia that tends to be roughly proportional to the severity of the uremia.** The basis of anemia in renal failure is multifactorial, but the dominant cause is the diminished synthesis of erythropoietin by the damaged kidneys, which leads to inadequate red cell production. Other contributors are an extracorpuscular defect that reduces red cell life span, and iron deficiency due to platelet dysfunction and increased bleeding, which is often encountered in uremia. Administration of recombinant erythropoietin results in a significant improvement of the anemia, although an optimal response may require concomitant iron replacement therapy.

Hepatocellular liver disease, whether toxic, infectious, or cirrhotic, is associated with anemia attributed to decreased marrow function. Folate and iron deficiencies caused by poor nutrition and excessive bleeding often exacerbate anemia in this setting. Erythroid progenitors are preferentially affected; depression of the white cell count and platelets is less common but also occurs. The anemia is often slightly macrocytic due to lipid abnormalities associated with liver failure, which cause red cell membranes to acquire phospholipid and cholesterol as they circulate in the peripheral blood.

Endocrine disorders, particularly hypothyroidism, may also be associated with a mild normochromic, normocytic anemia.

KEY CONCEPTS

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
- B_{12} deficiency also associated with neurologic damage, particularly in the posterior and lateral tracts of the spinal cord

Iron Deficiency Anemia

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

Anemia of Chronic Disease

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

Aplastic Anemia

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

Pure Red Cell Aplasia

- Acute: Parvovirus B19 infection (may persist in immunosuppressed patients)
- Chronic: Associated with thymoma, large granular lymphocytic leukemia, presence of neutralizing antibodies against erythropoietin, and other autoimmune phenomenon

Other Causes of Underproduction Anemias

- Marrow replacement (tumors, granulomatous disease; so-called myelophthisic anemias), renal failure, endocrine disorders, liver failure