megaloblastic changes in the intestinal tract, may decrease the macrocytosis. Patients frequently have pancytopenia.

A peripheral smear demonstrates large, oval cells (macro-ovalocytes), hypersegmented neutrophils, and large platelets. The bone marrow is hypercellular, with megaloblastic changes and abnormally large precursors. In addition, intramedullary destruction of erythrocytes (ineffective hematopoiesis) causes elevated concentrations of bilirubin and lactate dehydrogenase.

Cobalamin deficiency is associated with neurologic abnormalities that are not seen with other causes of megaloblastic anemia. The neurologic signs may range widely, from a subtle loss of vibratory sensation and position sense caused by demyelination of the dorsal columns to frank dementia and neuropsychiatric disease. The neurologic changes may be present without anemia, especially if a patient with cobalamin deficiency is treated with folate, which may correct the hematologic manifestations of megaloblastic anemia but does not treat the neurologic abnormalities. The neurologic manifestations of cobalamin deficiency are thought to be secondary to loss of function of the mitochondrial enzyme methylmalonyl-CoA mutase. One proposed explanation is that the failure to metabolize odd-chain fatty acids, which results in their improper incorporation into myelin, causes the neurologic dysfunction. This explains why these findings are uniquely seen in patients with cobalamin deficiency and are not seen in those with the megaloblastic anemias caused by abnormalities in the folate pathway.

Serum levels of both cobalamin and folate should be measured in patients with megaloblastic anemia because megaloblastic changes in the gut mucosa can cause concomitant malabsorption of folate in the presence of cobalamin deficiency and vice versa. RBC folate levels better reflect the body folate stores and should be measured if a deficiency is clinically suggested but the serum folate levels are normal. Recent studies have shown, however, that many patients with pernicious anemia may have normal serum cobalamin levels. Homocysteine levels are elevated in cobalamin and folate deficiency, and methylmalonic acid levels are elevated in cobalamin deficiency. These levels should be measured if cobalamin deficiency is suggested but serum cobalamin levels are in the normal range. Anti-IF and anti–parietal cell antibodies may help determine the cause of cobalamin deficiency.

### Treatment of Megaloblastic Anemia

For patients with cobalamin deficiency, both high-dose oral and parenteral cobalamin administration have been shown to be effective. The oral dose should be at least 1000 μg daily. Patients with neurologic abnormalities or medication noncompliance and those who have not responded to oral therapy should receive parenteral therapy with 1000 μg subcutaneously or intramuscularly several times per week for four to eight doses. Maintenance therapy should then be instituted with 1000 μg parenterally monthly. Therapy with cobalamin should be accompanied by folate therapy because concomitant secondary folate deficiency may develop when RBC production increases with the availability of cobalamin. Treatment of pernicious anemia should be continued for life.

Patients with folate deficiency should receive replacement with 1 to 5 mg per day of oral folate. As previously stated, it is critical to be certain that patients are not cobalamin deficient: Replacement of folate may correct the hematologic parameters in patients with cobalamin deficiency, but it will not improve the neurologic sequelae.

After treatment of megaloblastic anemia, a rapid response usually occurs. Reticulocytosis is seen as early as 2 days after therapy and peaks within 7 to 10 days. Despite rapid resolution of neutropenia, hypersegmentation of neutrophils may persist for several days. During this period, rapid cellular proliferation and turnover occur, which may precipitate hypokalemia, hyperuricemia, or hypophosphatemia. Patients should also be monitored for the development of iron deficiency, which may occur in the face of increased hematopoiesis. Anemia and other cytopenias should respond completely within 1 to 2 months, but the neurologic manifestations of cobalamin deficiency improve slowly and may be irreversible.

## Normocytic Anemias

The differential diagnosis of a normocytic hypoproductive anemia is extensive. Most nutritional anemias that cause microcytosis or macrocytosis begin as a normocytic anemia. Patients with combined nutritional deficiencies may also have a normal MCV. The measurement of EPO levels may be helpful in the diagnosis of anemia resulting from renal failure, and many of the anemias associated with chronic inflammation and endocrinopathies exhibit a depressed EPO level. However, interpretation of EPO levels can be difficult in patients with mild anemia because the levels do not usually rise above the normal range until the hematocrit is depressed below 30%. Even with a hematocrit level of 30%, the EPO level is often in the normal range, but such levels are inappropriately low in the setting of anemia. An elevated EPO level suggests an inadequate marrow response to anemia and increases the likelihood of myelophthisis or primary bone marrow failure. In patients for whom the diagnosis is not clear after routine nutritional and endocrine studies, a bone marrow examination is indicated to rule out primary pathologic conditions of the marrow.

### Anemia of Chronic Inflammation

The anemia of chronic inflammation (previously called anemia of chronic disease) occurs in patients with chronic inflammatory, infectious, malignant, or autoimmune disorders. Patients have low-serum iron levels, but in contrast to the iron indices in iron deficiency anemia, the iron-binding capacity is also reduced, and the transferrin saturation is usually greater than 10%. Ferritin levels are often elevated, both as an acute phase reactant and as a reflection of decreased iron incorporation. These patients have inappropriately high levels of hepcidin, an acute phase reactant that facilitates the metabolism of ferroportin and reduces both intestinal iron absorption and iron mobilization from macrophages. Cytokines, including tumor necrosis factor, the interleukins, and interferon, also play a role in the anemia of chronic inflammation, both by inducing hepcidin and by directly increasing EPO resistance in erythroid progenitors. Patients have an absolute or relative EPO deficiency, poor iron incorporation into developing erythrocytes, and shortened erythrocyte survival time. The prevalence of anemia of inflammation increases with age; most likely, this is related to age-related comorbidities and