target cells, basophilic stippling, and nucleated red blood cells. Little or no hemoglobin A is present. Variable amounts of hemoglobin A2 are seen, and the major hemoglobin present is hemoglobin F.

Differential Diagnosis

Mild forms of thalassemia must be differentiated from iron deficiency. Compared to iron deficiency anemia, patients with thalassemia have a lower MCV, a more normal red blood count, and a more abnormal peripheral blood smear at modest levels of anemia. Iron studies are normal. Severe forms of thalassemia may be confused with other hemoglobinopathies. The diagnosis is made by hemoglobin electrophoresis.

Treatment

Patients with mild thalassemia (α-thalassemia trait or β-thalassemia minor) require no treatment and should be identified so that they will not be subjected to repeated evaluations and treatment for iron deficiency. Patients with hemoglobin H disease should take folate supplementation and avoid medicinal iron and oxidative drugs such as sulfonamides. Patients with severe thalassemia are maintained on a regular transfusion schedule and receive folate supplementation. Splenectomy is performed if hypersplenism causes a marked increase in the transfusion requirement. Deferoxamine is routinely given as an iron-chelating agent to avoid or postpone hemosiderosis. Deferasirox is a new oral iron chelator that has been approved for clinical use.

Allogeneic bone marrow transplantation is the treatment of choice for β-thalassemia major. Children who have not yet experienced iron overload and chronic organ toxicity do well, with long-term survival in more than 80% of cases.

VITAMIN B₁₂ DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia.
- Macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear.
- Serum vitamin B₁₂ level less than 100 pg/mL.

General Considerations

Vitamin B₁₂ belongs to the family of cobalamins and serves as a cofactor for two important reactions in humans. As methylcobalamin, it is a cofactor for methionine synthetase in the conversion of homocysteine to methionine, and as adenosylcobalamin for the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. All vitamin B₁₂ comes from the diet and is present in all foods of animal origin. The daily absorption of vitamin B₁₂ is 5 mcg.

After being ingested, vitamin B₁₂ is bound to intrinsic factor, a protein secreted by gastric parietal cells. Other cobalamin-binding proteins (called R factors) compete with intrinsic factor for vitamin B₁₂. Vitamin B₁₂ bound to R factors cannot be absorbed. The vitamin B₁₂–intrinsic factor complex travels through the intestine and is absorbed in the terminal ileum by cells with specific

SIDEROBLASTIC ANEMIA

The sideroblastic anemias are a heterogeneous group of disorders in which hemoglobin synthesis is reduced because of failure to incorporate heme into protoporphyrin to form hemoglobin. Iron accumulates, particularly in the mitochondria. A Prussian blue stain of the bone marrow will reveal ringed sideroblasts, cells with iron deposits encircling the red cell nucleus. The disorder is usually acquired. Sometimes it represents a stage in evolution of a generalized bone marrow disorder (myelodysplasia) that may ultimately terminate in acute leukemia. Other causes include chronic alcoholism and lead poisoning.

Patients have no specific clinical features other than those related to anemia. The anemia is usually moderate, with hematocrits of 20–30%, but transfusions may occasionally be required. Although the MCV is usually normal or slightly increased, it may occasionally be low, leading to confusion with iron deficiency. The peripheral blood smear characteristically shows a dimorphic population of red blood cells, one normal and one hypochromic. In cases of lead poisoning, coarse basophilic stippling of the red cells is seen.

The diagnosis is made by examination of the bone marrow. Characteristically, there is marked erythroid hyperplasia, a sign of ineffective erythropoiesis (expansion of the erythroid compartment of the bone marrow that does not result in the production of reticulocytes in the peripheral blood). The iron stain of the bone marrow shows a generalized increase in iron stores and the presence of ringed sideroblasts. Other characteristic laboratory features include a high serum iron and a high transferrin saturation. In lead poisoning, serum lead levels will be elevated.

Occasionally, the anemia is so severe that support with transfusion is required. These patients usually do not respond to erythropoietin therapy.


receptors for the complex. It is then transported through plasma and stored in the liver. Three plasma transport proteins have been identified. Transcobalmins I and III (differing only in carbohydrate structure) are secreted by white blood cells. Although approximately 90% of plasma vitamin B₁₂ circulates bind to these proteins, only transcobalamin II is capable of transporting vitamin B₁₂ into cells. The liver contains 2000–5000 mcg of stored vitamin B₁₂. Since daily losses are 3–5 mcg/d, the body usually has sufficient stores of vitamin B₁₂ so that vitamin B₁₂ deficiency develops more than 3 years after vitamin B₁₂ absorption ceases.

Since vitamin B₁₂ is present in all foods of animal origin, dietary vitamin B₁₂ deficiency is extremely rare and is seen only in vegans—strict vegetarians who avoid all dairy products as well as meat and fish (Table 13–6). Abdominal surgery may lead to vitamin B₁₂ deficiency in several ways. Gastrectomy will eliminate that site of intrinsic factor production; blind loop syndrome will cause competition for vitamin B₁₂ by bacterial overgrowth in the lumen of the intestine; and surgical resection of the ileum will eliminate the site of vitamin B₁₂ absorption. Rare causes of vitamin B₁₂ deficiency include fish tapeworm (Diphyllobothrium latum) infection, in which the parasite uses luminal vitamin B₁₂, pancreatic insufficiency (with failure to inactivate competing cobalamin-binding proteins), and severe Crohn’s disease, causing sufficient destruction of the ileum to impair vitamin B₁₂ absorption.

The most common cause of vitamin B₁₂ deficiency is associated with pernicious anemia. Although the disease is hereditary, it is rare clinically before age 55 years. Pernicious anemia produces a number of clinical findings in addition to anemia. Atrophic gastritis is invariably present and results in histamine-fast achlorhydria. These patients may also have a number of other autoimmune diseases, including immunoglobulin (Ig) A deficiency, as well as polyglanudular endocrine insufficiency. The atrophic gastritis is associated with an increased risk of gastric carcinoma.

### Clinical Findings

#### A. Symptoms and Signs

The hallmark of symptomatic vitamin B₁₂ deficiency is megaloblastic anemia. However, subclinical cobalamin deficiency is an increasingly recognized condition, especially in those with predisposing conditions such as ileal disease or gastric surgery. In advanced cases, the anemia may be severe, with hematocrits as low as 10–15%, and may be accompanied by leukopenia and thrombocytopenia. The megaloblastic state also produces changes in mucosal cells, leading to glossitis, as well as other vague gastrointestinal disturbances such as anorexia and diarrhea. Vitamin B₁₂ deficiency also leads to a complex neurologic syndrome. Peripheral nerves are usually affected first, and patients complain initially of paresthesias. The posterior columns next become impaired, and patients complain of difficulty with balance. In more advanced cases, cerebral function may be altered as well, and on occasion demetia and other neuropsychiatric changes may precede hematologic changes.

Patients are usually pale and may be mildly icteric. Neurologic examination may reveal decreased vibration and position sense but is more commonly normal in early stages of the disease.

#### B. Laboratory Findings

The megaloblastic state produces an anemia of variable severity that on occasion may be very severe. The MCV is usually strikingly elevated, between 110 and 140 fl. However, it is possible to have vitamin B₁₂ deficiency with a normal MCV. Occasionally, the normal MCV may be explained by coexistent thalassemia or iron deficiency, but in other cases the reason is obscure. Patients with neurologic symptoms and signs that suggest possible vitamin B₁₂ deficiency should be evaluated for that deficiency despite a normal MCV and the absence of anemia. The peripheral blood smear is usually strikingly abnormal, with anisocytosis and poikilocytosis. A characteristic finding is the macroovalocyte, but numerous other abnormal shapes are usually seen. The neutrophils are hypersegmented. Typical features include a mean lobe count greater than four or the finding of six-lobed neutrophils. The reticulocyte count is reduced. Because vitamin B₁₂ deficiency affects all hematopoietic cell lines, in severe cases the white blood cell count and the platelet count are reduced, and pancytopenia is present.

Bone marrow morphology is characteristically abnormal. Marked erythroid hyperplasia is present as a response to defective red blood cell production (ineffective erythropoiesis). Megaloblastic changes in the erythroid series include abnormally large cell size and asynchronous maturation of the nucleus and cytoplasm—ie, cytoplasmic maturation continues while impaired DNA synthesis causes retarded nuclear development. In the myeloid series, giant metamyelocytes are characteristically seen.

Other laboratory abnormalities include elevated serum lactate dehydrogenase (LDH) and a modest increase in indirect bilirubin. These two findings are a reflection of intramedullary destruction of developing abnormal erythroid cells and are similar to those observed in peripheral hemolytic anemias.

The diagnosis of vitamin B₁₂ deficiency is made by finding an abnormally low vitamin B₁₂ (cobalamin) serum level. Whereas the normal vitamin B₁₂ level is > 240 pg/mL, most patients with overt vitamin B₁₂ deficiency will have
serum levels < 170 pg/mL, with symptomatic patients usually having levels < 100 pg/mL. A level of 170–240 pg/mL is borderline. When the serum level of vitamin B₁₂ is borderline, the diagnosis is best confirmed by finding an elevated level of serum methylmalonic acid (>1000 nmol/L). However, elevated levels of serum methylmalonic acid can be due to renal insufficiency. The Schilling test is now rarely used.

**Differential Diagnosis**

Vitamin B₁₂ deficiency should be differentiated from folic acid deficiency, the other common cause of megaloblastic anemia, in which red blood cell folate is low while vitamin B₁₂ levels are normal. The distinction between vitamin B₁₂ deficiency and myelodysplasia (the other common cause of macrocytic anemia with abnormal morphology) is based on the characteristic morphology and the low vitamin B₁₂ level.

**Treatment**

Patients with pernicious anemia have historically been treated with parenteral therapy. Intramuscular injections of 100 mcg of vitamin B₁₂ are adequate for each dose. Replacement is usually given daily for the first week, weekly for the first month, and then monthly for life. It is a lifelong disorder, and if patients discontinue their monthly therapy the vitamin deficiency will recur. Oral cobalamin may be used instead of parenteral therapy and can provide equivalent results. The dose is 1000 mcg/d and must be continued indefinitely. Patients respond to therapy with an immediate improvement in their sense of well-being. Hypokalemia may complicate the first several days of therapy, particularly if the anemia is severe. A brisk reticulocytosis occurs in 5–7 days, and the hematologic picture normalizes in 2 months. Central nervous system symptoms and signs are reversible if they are of relatively short duration (less than 6 months) but become permanent if treatment is not initiated promptly.


**FOLIC ACID DEFICIENCY**

**ESSENTIALS OF DIAGNOSIS**

- Macrocystic anemia.
- Macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear.
- Normal serum vitamin B₁₂ levels.
- Reduced folate levels in red blood cells or serum.

**General Considerations**

Folic acid is the term commonly used for pteroylmonoglutamic acid. Folic acid is present in most fruits and vegetables (especially citrus fruits and green leafy vegetables) and daily requirements of 50–100 mcg/d are usually met in the diet. Total body stores of folate are approximately 5000 mcg, enough to supply requirements for 2–3 months.

By far the most common cause of folate deficiency is inadequate dietary intake (Table 13–7). Alcoholics, anorectic patients, persons who do not eat fresh fruits and vegetables, and those who overcook their food are candidates for folate deficiency. Reduced folate absorption is rarely seen, since absorption occurs from the entire gastrointestinal tract. However, drugs such as phenytoin, trimethoprim-sulfamethoxazole, or sulfasalazine may interfere with folate absorption. Folic acid requirements are increased in pregnancy, hemolytic anemia, and exfoliative skin disease, and in these cases the increased requirements (five to ten times normal) may not be met by a normal diet. Patients with increased folate requirements should receive supplementation with 1 mg/d of folic acid.

**Differential Diagnosis**

The megaloblastic anemia of folate deficiency should be differentiated from vitamin B₁₂ deficiency by the finding of a normal vitamin B₁₂ level and a reduced red blood cell folate or serum folate level. Alcoholics, who often have folate deficiency, may also have anemia of liver disease. This latter macrocytic anemia does not cause megaloblastic anemia.

**FOLIC ACID DEFICIENCY**

**ESSENTIALS OF DIAGNOSIS**

- Macrocystic anemia.
- Macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear.
- Normal serum vitamin B₁₂ levels.
- Reduced folate levels in red blood cells or serum.

**Clinical Findings**

**A. Symptoms and Signs**

The features are similar to those of vitamin B₁₂ deficiency, with megaloblastic anemia and megaloblastic changes in mucosa. However, there are none of the neurologic abnormalities associated with vitamin B₁₂ deficiency.

**B. Laboratory Findings**

Megaloblastic anemia is identical to anemia resulting from vitamin B₁₂ deficiency (see above). However, the serum vitamin B₁₂ level is normal. A red blood cell folate level of less than 150 ng/mL is diagnostic of folate deficiency.

**Differential Diagnosis**

The megaloblastic anemia of folate deficiency should be differentiated from vitamin B₁₂ deficiency by the finding of a normal vitamin B₁₂ level and a reduced red blood cell folate or serum folate level. Alcoholics, who often have folate deficiency, may also have anemia of liver disease. This latter macrocytic anemia does not cause megaloblastic anemia.

**Table 13–7. Causes of folate deficiency.**

<table>
<thead>
<tr>
<th>Dietary deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased absorption</td>
</tr>
<tr>
<td>Tropical sprue</td>
</tr>
<tr>
<td>Drugs: phenytoin, sulfasalazine, trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Increased requirement</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Exfoliative skin disease</td>
</tr>
<tr>
<td>Loss: dialysis</td>
</tr>
<tr>
<td>Inhibition of reduction to active form</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
</tbody>
</table>
morphologic changes but rather produces target cells in
the peripheral blood. Hypothyroidism is associated with
mild macrocytosis but also with pernicious anemia.

### Treatment

Folic acid deficiency is treated with folic acid, 1 mg/d
orally. The response is similar to that seen in the treatment
of vitamin B12 deficiency, with rapid improvement and a
sense of well-being, reticulocytosis in 5–7 days, and total
correction of hematologic abnormalities within 2 months.
Large doses of folic acid may produce hematologic
responses in cases of vitamin B12 deficiency but will allow
neurologic damage to progress.

Clarke R et al. Vitamin B12 and folate deficiency in later life. Age

### Pure Red Cell Aplasia

Adult acquired pure red cell aplasia is rare. It appears to be
an autoimmune disease mediated either by T lymphocytes or
(rarely) by an IgG antibody against erythroid precursors.
In adults, the disease is usually idiopathic. However,
cases have been seen in association with systemic lupus
erthematous, chronic lymphocytic leukemia, lymphomas,
or thymoma. Some drugs (phenytoin, chloramphenicol)
may cause red cell aplasia. Transient episodes of red
cell aplasia are probably common in response to viral
infections, especially parvovirus infections. However, these
cases will go unrecognized unless the patient has
a chronic hemolytic disorder, in which case the hematocrit
may fall precipitously.

The only signs are those of anemia unless the patient has
an associated autoimmune or lymphoproliferative dis-
order. The anemia is often severe and normochromic, with
low or absent reticulocytes. Red blood cell morphology is
normal, and the myeloid and platelet lines are unaffected.
The bone marrow is normocellular. All elements present
are normal, but erythroid precursors are markedly reduced
or absent. In some cases, chest imaging studies will reveal a
thymoma.

The disorder is distinguished from aplastic anemia (in
which the marrow is hypopcellular and all cell lines are
affected) and from myelodysplasia. This latter disorder is
recognized by the presence of morphologic abnormalities
that should not be present in pure red cell aplasia.

Possible offending drugs should be stopped. With thy-

### Hemolytic Anemias

The hemolytic anemias are a group of disorders in which red
blood cell survival is reduced, either episodically or continu-
ously. The bone marrow has the ability to increase erythroid
production up to eightfold in response to reduced red cell
survival, so anemia will be present only when the ability of
the bone marrow to compensate is outstripped. This will occur
when red cell survival is extremely short or when the ability
of the bone marrow to compensate is impaired for some
reason.

Since red blood cell survival is normally 120 days, in the
absence of red cell production the hematocrit will fall at the
rate of approximately 1/100 of the hematocrit per day,
which translates to a decrease in the hematocrit reading of
approximately 3% per week. For example, a fall of hemat-
crit from 45% to 36% over 3 weeks need not indicate
hemolysis, since this rate of fall would result simply from
cessation of red blood cell production. If the hematocrit is
falling at a rate faster than that due to decreased produc-
tion, blood loss or hemolysis is the cause.

Reticulocytosis is an important clue to the presence of
hemolysis, since in most hemolytic disorders the bone mar-
row will respond with increased red blood cell production.
However, hemolysis can be present without reticulocytosis
when a second disorder (infection, folate deficiency) is super-
imposed on hemolysis; in these circumstances, the hematocrit
will fall rapidly. However, reticulocytosis also occurs during
recovery from hypoproliferative anemia or bleeding. Hemol-
ysis is correctly diagnosed (when bleeding is excluded) if the
hematocrit is either falling or stable despite reticulocytosis.

Hemolytic disorders are generally classified according to
whether the defect is intrinsic to the red cell or due to some
external factor (Table 13–8). Intrinsic defects have been
described in all components of the red blood cell, including
the membrane, enzyme systems, and hemoglobin; most of

### Table 13–8. Classification of hemolytic anemias.

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane defects: hereditary spherocytosis, hereditary elliptocytosis, paroxysmal nocturnal hemoglobinuria</td>
<td>Immune: autoimmune, lymphoproliferative disease, drug toxicity</td>
</tr>
<tr>
<td>Glycolytic defects: pyruvate kinase deficiency, severe hypophosphatemia</td>
<td>Microangiopathic: thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, valve hemolysis, metastatic adenocarcinoma, vasculitis</td>
</tr>
<tr>
<td>Oxidation vulnerability: glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia</td>
<td>Infection: Plasmodium, Clostridium, Borrelia</td>
</tr>
<tr>
<td>Hemoglobinopathies: sickle cell syndromes, unstable hemoglobins, methemoglobinemia</td>
<td>Hypersplenism</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Burns</td>
</tr>
</tbody>
</table>

Zecca M et al. Anti-CD20 monoclonal antibody for the treatment of
severe immune-mediated pure red cell aplasia and hemolytic
because of trapping of red blood cells within the spleen. Fenestrations in the splenic red pulp. Hemolysis takes place
results in a spherical shape of the cell. These spherical cells
The result is a decrease in surface-to-volume ratio that
most of the scaffolding for the red blood cell membranes.
abnormality in spectrin or actin, the proteins providing
these characteristics of strength and deformability.

Hereditary spherocytosis is a disorder of the red blood cell
membrane, leading to chronic hemolytic anemia. Normally,
the red blood cell is a biconcave disk with a diameter of 7–8
mcm. The red blood cells must be both strong and deform-
able—strong to withstand the stress of circulating for 120 days
and deformable so as to pass through capillaries 3 mcm in
diameter and splenic fenestrations in the cords of the red pulp
and deformation occurs. Hemoglobin is filtered through the glomerulus and
is usually reabsorbed by tubular cells. Hemoglobinuria will
be present only when the capacity for reabsorption of
hemoglobin by these cells is exceeded. In its absence,
evidence for prior intravascular hemolysis is the presence
of hemosiderin in shed renal tubular cells (positive urine hemosiderin).
With severe intravascular hemolysis, hemoglobinemia and methemalbuminemia may be present. Hemolysis increases the indirect bilirubin, and the total bilirubin may rise to 4 mg/dL. Bilirubin levels higher than this may indicate some degree of hepatic dysfunction. Serum LDH levels are strikingly elevated in cases of microangiopathic hemolysis (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome) and may be elevated in other hemolytic anemias.

**HEREDITARY SPHEROCYTOSIS**

**ESSENTIALS OF DIAGNOSIS**

- Positive family history.
- Splenomegaly.
- Spherocytes and increased reticulocytes on peripheral blood smear.
- Microcytic, hyperchromic indices.

**Clinical Findings**

**A. Symptoms and Signs**

Hereditary spherocytosis is an autosomal dominant disease of variable severity. It is often diagnosed during childhood, but milder cases may be discovered incidentally late in adult life. Anemia may or may not be present, since the bone marrow may be able to compensate for shortened red cell survival. Severe anemia (aplastic crisis) may occur in folic acid deficiency or when bone marrow compensation is temporarily impaired by infection. Chronic hemolysis causes jaundice and pigment (calcium bilirubinate) gallstones, leading to attacks of cholecystitis. Examination may reveal icterus and a palpable spleen.

**B. Laboratory Findings**

The anemia is of variable severity, and the hematocrit may be normal. Reticulocytosis is always present. The peripheral blood smear shows the presence of spherocytes, small cells that have lost their central pallor. Spherocytes usually make up only a small percentage of red blood cells on the peripheral smear. Hereditary spherocytosis is the only important disorder associated with microcytosis and an increased mean corpuscular hemoglobin concentration (MCHC), often greater than 36 g/dL. As with other hemolytic disorders, there may be an increase in indirect bilirubin. The Coombs test is negative.

Because spherocytes are red cells that have lost some membrane surface, they are abnormally vulnerable to swelling induced by hypotonic media. Increased osmotic fragility merely reflects the presence of spherocytes and does not distinguish hereditary spherocytosis from other spherocytic hemolytic disorders such as autoimmune hemolytic anemia. In some laboratories, the osmotic fragility test has been supplanted by ektacytometry, which has the advantages of better reliability and the ability to distinguish spherocytes from other red blood cell abnormalities such as elliptocytosis.

**Treatment**

These patients should receive uninterrupted supplementation with folic acid, 1 mg/d. The treatment of choice is splenectomy, which will correct neither the membrane defect nor the spherocytosis but will eliminate the site of hemolysis. In very mild cases discovered late in adult life, splenectomy may not be necessary.


**PAROXYSMAL NOCTURNAL HEMOGLOBINURIA**

Paroxysmal nocturnal hemoglobinuria is an acquired clonal stem cell disorder that results in abnormal sensitivity of the red blood cell membrane to lysis by complement. The underlying cause is a defect in the gene for phosphatidylinositol class A (PIG-A), which results in a deficiency of the glycosylphospho-
phatidylinositol (GPI) anchor for cellular membrane proteins. In particular, the complement-regulating proteins CD55 and CD59 are deficient. Paroxysmal nocturnal hemoglobinuria should be suspected in confusing cases of hemolytic anemia or pancytopenia. The best screening test is flow cytometry to demonstrate deficiency of CD59 on red blood cells. This test has largely replaced the classic sucrose hemolysis test.

**Clinical Findings**

### A. Symptoms and Signs

Classically, patients report episodic hemoglobinuria resulting in reddish brown urine. Hemoglobinuria is most often noticed in the first morning urine, probably because of its increased concentration. In addition to being prone to anemia, these patients are prone to thrombosis, especially mesenteric and hepatic vein thromboses. Other common sites of thrombosis include the central nervous system (sagittal vein) and the skin, with formation of painful nodules. This hypercoagulopathy may be related to platelet activation by complement. As this is a stem cell disorder, paroxysmal nocturnal hemoglobinuria may progress either to aplastic anemia, to myelodysplasia, or to acute myelogenous leukemia.

### B. Laboratory Findings

Anemia is of variable severity, and reticulocytosis may or may not be present. Abnormalities on the blood smear are nondiagnostic and may include macro-ovalocytes. Since the episodic hemolysis in paroxysmal nocturnal hemoglobinuria is intravascular, the finding of urine hemosiderin is a useful test. Serum LDH is characteristically elevated. Iron deficiency is commonly present and is related to chronic iron loss from hemoglobinuria, since hemolysis is primarily intravascular. The white blood cell count and platelet count may be decreased. A decreased leukocyte alkaline phosphatase—evidence for a qualitative abnormality in the myeloid series—may be seen. Bone marrow morphology is variable and may show either generalized hypoplasia or erythroid hyperplasia. Flow cytometric assays may confirm the diagnosis by demonstrating the absence of CD59.

### Treatment

Iron replacement is often indicated for treatment of iron deficiency. This may improve the anemia but may also cause a transient increase in hemolysis. For unclear reasons, prednisone is effective in decreasing hemolysis, and some patients can be managed effectively with alternate-day steroids. In severe cases and cases of transformation to myelodysplasia, allogeneic bone marrow transplantation has been used to treat the disorder. The anti-complement C5 antibody eculizumab has been shown to be effective in reducing hemolysis and transfusion requirements.

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**GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY**

**ESSENTIALS OF DIAGNOSIS**

- X-linked recessive disorder seen commonly in American black men.
- Episodic hemolysis in response to oxidant drugs or infection.
- Minimally abnormal peripheral blood smear.
- Reduced levels of glucose-6-phosphate dehydrogenase between hemolytic episodes.

**General Considerations**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary enzyme defect that causes episodic hemolytic anemia because of the decreased ability of red blood cells to deal with oxidative stresses. Oxidized hemoglobin denatures and forms precipitants called Heinz bodies. These Heinz bodies cause membrane damage, which leads to removal of these cells by the spleen. Numerous types of G6PD enzymes have been described. The normal type found in whites is designated G6PD-B. Most American blacks have G6PD-A, which is normal in function. Ten to 15 percent of American blacks have the variant G6PD designated A−, in which there is only 15% of normal enzyme activity, and enzyme activity declines rapidly as the red blood cell ages past 40 days, a fact that explains many of the clinical findings in this disorder. Many other G6PD variants have been described, including some Mediterranean variants with extremely low enzyme activity.

### Clinical Findings

G6PD deficiency is an X-linked recessive disorder affecting 10–15% of American black males. Female carriers are rarely affected—only when an unusually high percentage of cells producing the normal enzyme is inactivated.

#### A. Symptoms and Signs

Patients are usually healthy, without chronic hemolytic anemia or splenomegaly. Hemolysis occurs as a result of oxidative stress on the red blood cells, generated either by infection or exposure to certain drugs. Common drugs initiating hemolysis include dapsone, primaquine, quinidine, quinine, sulfonamides, and nitrofurantoin. Even with continuous use of the offending drug, the hemolytic episode is self-limited because older red blood cells (with low enzyme activity) are removed and replaced with a