e.g., methionine synthase and serine–glycine hydroxymethylase, have been negative. Serum vitamin B_{12} levels are also lower in the sera of mothers of NTD infants than in controls. In addition, maternal TC II receptor polymorphisms are associated with increased risk of NTD births. There are, however, no studies showing dietary fortification with vitamin B_{12} reduces the incidence of NTDs.

Cardiovascular Disease Children with severe homocystinuria (blood levels ≥100 μmol/L) due to deficiency of one of three enzymes, methionine synthase, MTHFR, or cystathionine synthase (Fig. 128-1), have vascular disease, e.g., ischemic heart disease, cerebrovascular disease, or pulmonary embolus, as teenagers or in young adulthood. Lesser degrees of raised serum homocysteine and low levels of serum folate and homozygous inherited mutations of MTHFR have been found to be associated with cerebrovascular, peripheral vascular, and coronary heart disease and with deep vein thrombosis. Prospective randomized trials of lowering homocysteine levels with supplements of folic acid, vitamin B_{12}, and vitamin B_6 against placebo over a 5-year period in patients with vascular disease or diabetes have not, however, shown a reduction of first event fatal or nonfatal myocardial infarction, nor have these supplements reduced the risk of recurrent cardiovascular disease after an acute myocardial infarct. Meta-analysis showed an 18% reduction in strokes but no significant prevention of death from any cause. Venous thrombosis has been reported to be more frequent in vitamin B_{12}–deficient subjects than in controls. This was ascribed to raised plasma homocysteine levels in vitamin B_{12} deficiency.

Malignancy Prophylactic folic acid in pregnancy has been found in some but not all studies to reduce the subsequent incidence of acute lymphoblastic leukemia (ALL) in childhood. A significant negative association has also been found with the *MTHFR* C677T polymorphism and leukemias with mixed lineage leukemia (MLL) translocations, but a positive association with hyperdiploidy in infants with ALL or acute myeloid leukemia or with childhood ALL. A second polymorphism in the *MTHFR* gene, A1298C, is also strongly associated with hyperdiploid leukemia. There are various positive and negative associations between polymorphisms in folate-dependent enzymes and the incidence of adult ALL. The C677T polymorphism is thought to lead to increased thymidine pools and "better quality" of DNA synthesis by shunting one-carbon groups toward thymidine and purine synthesis. This may explain its reported association with a lower risk for colorectal cancer. Most but not all studies suggest that prophylactic folic acid also protects against colon adenomas. Other tumors that have been associated with folate polymorphisms or status include follicular lymphoma, breast cancer, and gastric cancer. A meta-analysis of 50,000 individuals given folic acid or placebo in cardiovascular or colon adenoma prevention trials found that folic acid supplementation did not substantially increase or decrease the incidence of site-specific cancer during the first 5 years of treatment. Because folic acid may "feed" tumors, it probably should be avoided in those with established tumors unless there is severe megaloblastic anemia due to folate deficiency.

Neurologic Manifestations Cobalamin deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the posterior and pyramidal tracts of the spinal cord and, less frequently, optic atrophy or cerebral symptoms.

The patient, more frequently male, presents with paresthesias, muscle weakness, or difficulty in walking and sometimes dementia, psychotic disturbances, or visual impairment. Long-term nutritional cobalamin deficiency in infancy leads to poor brain development and impaired intellectual development. Folate deficiency has been suggested to cause organic nervous disease, but this is uncertain, although methotrexate injected into the cerebrospinal fluid may cause brain or spinal cord damage.

An important clinical problem is the nonanemic patient with neurologic or psychiatric abnormalities and a low or borderline serum cobalamin level. In such patients, it is necessary to try to establish whether there is significant cobalamin deficiency, e.g., by careful examination of the blood film, tests for serum gastrin level and for antibodies to IF or parietal cells, along with serum methylmalonic acid (MMA) measurement if available. A trial of cobalamin therapy for at least 3 months will usually also be needed to determine whether the symptoms improve.

The biochemical basis for cobalamin neuropathy remains obscure. Its occurrence in the absence of methylmalonic aciduria in TC II deficiency suggests that the neuropathy is related to the defect in homocysteine-methionine conversion. Accumulation of *S*-adenosylhomocysteine in the brain, resulting in inhibition of transmethylation reactions, has been suggested.

Psychiatric disturbance is common in both folate and cobalamin deficiencies. This, like the neuropathy, has been attributed to a failure of the synthesis of SAM, which is needed in methylation of biogenic amines (e.g., dopamine) as well as that of proteins, phospholipids, and neurotransmitters in the brain (Fig. 128-1). Associations between lower serum folate or cobalamin levels and higher homocysteine levels and the development of decreased cognitive function and dementia in Alzheimer's disease have been reported. A meta-analysis of randomized, placebo-controlled trials of homocysteine-lowering B-vitamin supplementation of individuals with and without cognitive impairment, however, showed that supplementation with vitamin B_{12}, vitamin B_6, and folic acid alone or in combination did not improve cognitive function. It is unknown whether prolonged treatment with these B vitamins can reduce the risk of dementia in later life.

HEMATOLOGIC FINDINGS

PERIPHERAL BLOOD

Oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main feature (Fig. 128-2*A*). The MCV is usually >100 fL unless a cause of microcytosis (e.g., iron deficiency or thalassemia trait) is present. Some of the neutrophils are hypersegmented (more than five nuclear lobes). There may be leukopenia due to a reduction in granulocytes and lymphocytes, but this is usually $>1.5 \times 10^9$/L; the platelet count may be moderately reduced, rarely to $<40 \times 10^9$/L. The severity of all these changes parallels the degree of anemia. In a nonanemic patient, the presence of a few macrocytes and hypersegmented neutrophils in the peripheral blood may be the only indication of the underlying disorder.

BONE MARROW

In a severely anemic patient, the marrow is hypercellular with an accumulation of primitive cells due to selective death by apoptosis of more mature forms. The erythroblast nucleus maintains a primitive appearance despite maturation and hemoglobinization of the cytoplasm. The cells are larger than normoblasts, and an increased number of cells with eccentric lobulated nuclei or nuclear fragments may be present (Fig. 128-2*B*). Giant and abnormally shaped metamyelocytes and enlarged hyperpolyploid megakaryocytes are characteristic. In severe cases, the accumulation of primitive cells may mimic acute myeloid leukemia, whereas in less anemic patients, the changes in the marrow may be difficult to recognize. The terms *intermediate*, *mild*, and *early* have been used. The term *megaloblastoid* does not mean mildly megaloblastic. It is used to describe cells with both immature-appearing nuclei and defective hemoglobinization and is usually seen in myelodysplasia.

CHROMOSOMES

Bone marrow cells, transformed lymphocytes, and other proliferating cells in the body show a variety of changes, including random breaks, reduced contraction, spreading of the centromere, and exaggeration of secondary chromosomal constrictions and overprominent satellites. Similar abnormalities may be produced by antimetabolite drugs (e.g., cytosine arabinoside, hydroxyurea, and methotrexate) that interfere with either DNA replication or folate metabolism and that also cause megaloblastic appearances.

INEFFECTIVE HEMATOPOIESIS

There is an accumulation of unconjugated bilirubin in plasma due to the death of nucleated red cells in the marrow (ineffective erythropoiesis). Other evidence for this includes raised urine urobilinogen, reduced haptoglobins and positive urine hemosiderin, and a raised