antibodies are not specific, in that they are found in as many as 50% of older adults with idiopathic chronic gastritis not associated with pernicious anemia.

Autoantibodies are of diagnostic utility, but they are not thought to be the primary cause of the gastric pathology; rather, it seems that an autoreactive T-cell response initiates gastric mucosal injury and triggers the formation of autoantibodies. When the mass of intrinsic factor-secreting cells falls below a threshold (and reserves of stored vitamin B_{12} are depleted), anemia develops. The common association of pernicious anemia with other autoimmune disorders, particularly autoimmune thyroiditis and adrenalitis, is also consistent with an underlying immune basis. The tendency to develop pernicious anemia (as well as other autoimmune disorders) is linked to genetic variants involving the inflammasome, suggesting that altered innate immunity may also play some role.

Vitamin B_{12} deficiency is associated with disorders other than pernicious anemia. Most of these impair absorption of the vitamin at one of the steps outlined earlier (Table 14-5). With achlorhydria and loss of pepsin secretion (which occurs in some older adults), vitamin B_{12} is not readily released from proteins in food. With gastrectomy, intrinsic factor is not available for uptake in the ileum. With loss of exocrine pancreatic function, vitamin B_{12} cannot be released from haptocorrin-vitamin B_{12} complexes. Ileal resection or diffuse ileal disease can remove or damage the site of intrinsic factor-vitamin B_{12} complex absorption. Certain tapeworms (particularly those acquired by eating raw fish) compete with the host for B_{12} and can induce a deficiency state. In some settings, such as pregnancy, hyperthyroidism, disseminated cancer, and chronic infection, an increased demand for vitamin B_{12} can produce a relative deficiency, even with normal absorption.

MORPHOLOGY

The findings in the bone marrow and blood in pernicious anemia are similar to those described earlier for all megaloblastic anemias. The stomach typically shows diffuse chronic gastritis (Chapter 17). The most characteristic alteration is **fundic gland atrophy**, affecting both chief cells and parietal cells, the latter being virtually absent. The glandular epithelium is replaced by mucus-secreting goblet cells that resemble those lining the large intestine, a form of metaplasia referred to as **intestinalization**. Some of the cells as well as their nuclei may increase to double the normal size, a "megaloblastic" change analogous to that seen in the marrow. With time, the tongue may become shiny, glazed, and "beefy" **(atrophic glossitis)**. The gastric atrophy and metaplastic changes are due to autoimmunity and not vitamin B_{12} deficiency; hence, parenteral administration of vitamin B_{12} corrects the megaloblastic changes in the marrow and the epithelial cells of the alimentary tract, but gastric atrophy and achlorhydria persist.

Central nervous system lesions are found in about three fourths of all cases of florid pernicious anemia but can also be seen in the absence of overt hematologic findings. The principal alterations involve the cord, where there is **demyelination of the dorsal and lateral spinal tracts,** sometimes followed by loss of axons. These changes give rise to spastic paraparesis, sensory ataxia, and severe paresthesias in the lower limbs. Less frequently, degenerative changes occur in the ganglia of the posterior roots and in peripheral nerves (Chapter 28).

Clinical Features

Pernicious anemia is insidious in onset, and the anemia is often quite severe by the time it comes to medical attention. The course is progressive unless halted by therapy.

The diagnosis is based on (1) a moderate to severe megaloblastic anemia, (2) leukopenia with hypersegmented granulocytes, (3) low serum vitamin B_{12}, and (4) elevated serum levels of homocysteine and methylmalonic acid. The diagnosis is confirmed by an outpouring of reticulocytes and a rise in hematocrit levels beginning about 5 days after parenteral administration of vitamin B_{12}. Serum antibodies to intrinsic factor are highly specific for pernicious anemia. Their presence attests to the cause rather than the presence or absence of vitamin B_{12} deficiency.

Persons with atrophy and metaplasia of the gastric mucosa associated with pernicious anemia have an increased risk of gastric carcinoma (Chapter 17). Elevated homocysteine levels are a risk factor for atherosclerosis and thrombosis, and it is suspected that vitamin B_{12} deficiency may increase the incidence of vascular disease on this basis. With parenteral or high-dose oral vitamin B_{12}, the anemia is cured and the progression of the peripheral neurologic disease can be reversed or at least halted, but the changes in the gastric mucosa and the risk of carcinoma are unaffected.

Anemia of Folate Deficiency

A deficiency of folic acid (more properly, pteroylmonoglutamic acid) results in a megaloblastic anemia having the same pathologic features as that caused by vitamin B_{12} deficiency. FH_4 derivatives act as intermediates in the transfer of one-carbon units such as formyl and methyl groups to various compounds (Fig. 14-20). FH_4 serves as an acceptor of one-carbon fragments from compounds such as serine and formiminoglutamic acid. The FH_4 derivatives so generated in turn donate the acquired one-carbon fragments in reactions synthesizing various metabolites. FH_4, then, can be viewed as the biologic "middleman" in a series of swaps involving one-carbon moieties. The most important metabolic processes depending on such transfers are (1) purine synthesis; (2) the conversion of homocysteine to methionine, a reaction also requiring vitamin B_{12}; and (3) deoxythymidylate monophosphate (dTMP) synthesis. In the first two reactions, tetrahydrofolate (FH_4) is regenerated from its one-carbon carrier derivatives and is available to accept another one-carbon moiety and reenter the donor pool. In the synthesis of dTMP, a dihydrofolate (FH_2) is produced that must be reduced by dihydrofolate reductase for reentry into the FH_4 pool. The reductase step is significant, because this enzyme is susceptible to inhibition by various drugs. Among the molecules whose synthesis is dependent on folates, dTMP is perhaps the most important biologically, because it is required for DNA synthesis. It should be apparent from this discussion that **suppressed synthesis of DNA, the common denominator of folic acid and vitamin B_{12} deficiency, is the immediate cause of megaloblastosis**.

Etiology. The three major causes of folic acid deficiency are (1) decreased intake, (2) increased requirements, and (3) impaired utilization (Table 14-5). Humans are entirely dependent on dietary sources for their folic acid