We also investigated 6 sporadic cases with CDA I for CDAN1 gene mutations by bidirectional genomic sequencing. Six mutant alleles were found in these cases, 5 previously reported (3242A > T, 2129C > T [2 patients], 1910A > G, and 2287C > T) together with a previously unreported 3 base pairs in frame deletion. Resulting in deletion of valine 372. In 4 of the 6 sporadic cases, only 1 mutation in the CDAN1 gene could be demonstrated, a situation also seen in half of the sporadic cases described previously.3–5 and in 1 case, with multiple dysmorphic features, no mutations were detected. Mutations in regions of the CDAN1 gene that were not sequenced (promoter, introns) or in regulatory sequences may explain these findings. Given the genetic heterogeneity of this condition, however, it is plausible that a mutation in a second gene could interact with a CDAN1 mutation to result in the CDA I phenotype as a result of digenic inheritance.

A more comprehensive understanding of CDA I will require a better knowledge of the function of CDAN1 protein, its cellular distribution and intracellular localization, and the existence of any putative binding partners. The genetic heterogeneity demonstrated here indicates that this should be a fruitful field for the study of erythropoiesis.

To the editor:

Helicobacter pylori, iron deficiency, and gastric autoimmunity

We read with interest the article by Hershko et al., which reported that the hematologic presentation of autoimmune gastritis (AIG) is age-related and progresses from iron-deficiency to cobalamin depletion. This study is an important contribution to the understanding of the natural history of AIG. We wish to comment on aspects that are related to Helicobacter pylori and may have clinical relevance.

The relation between H pylori and AIG is not fully understood. AIG is mediated by CD4+ T cells reactive to the H+ K+-ATPase, and H pylori probably triggers the autoimmune process by molecular mimicry.2 Hershko and colleagues1 provide strong epidemiologic evidence in support of this model. In their study, almost 90% of AIG patients younger than 20 years were infected. The low prevalence of infection among old patients with pernicious anemia (12%) does not argue against a relation of H pylori to AIG, but can be explained by the observation that the microenvironment of the atrophic stomach is hostile to the growth and colonization of H pylori, with progressive atrophy leading to a loss of the bacterial niche.3 Indeed, in patients with pernicious anemia an anti–Helicobacter–immunoglobulin G (IgG) seroreversion rate of 6% per year has been observed.3

Although H pylori is potentially involved in the induction of AIG and has its own inhibitory effect on cobalamin absorption,4 there are no recommendations for the management of infection in AIG. The observations of Hershko and colleagues that iron-deficiency anemia (IDA) is the presenting feature in more than 50% of patients with AIG, and that these patients are mainly young and H pylori-positive, provides a basis for new therapeutic considerations. In AIG, IDA develops mainly as a consequence of reduced acid secretion. Acid is indispensable for solubilization, reduction, and subsequent absorption of nonheme dietary iron. Several lines of evidence suggest that AIG patients with IDA would benefit from H pylori eradication: (1) H pylori suppresses acid secretion through induction of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which are potent inhibitors of gastric parietal and enterochromaffin-like (ECL) cell function.5–8 H pylori causes loss of acid secreting parietal cells through induction of apoptosis.9 Thus, hypochlorhydria and atrophy, main features of AIG, are synergistically promoted by H pylori. (2) Eradication of infection restores acid secretion even in patients with severe atrophy.7 (3) H pylori inhibits secretion of ascorbic acid into the gastric juice, another important factor for iron absorption. (4) Recent studies show an association of H pylori with unexplained IDA, and antibiotic treatment frequently leads to improvement of this disease.10 Therefore, the new guidelines of the European Helicobacter pylori Study Group for the management of infection recommend bacterial eradication in unexplained IDA.11

Long-term prospective studies are needed to define the influence of H pylori eradication on the presentation and progression of AIG. Currently available data, however, suggest that at least in AIG patients with IDA, diagnosis and treatment of infection would be beneficial. Finally, the recognition of AIG and H pylori as possible causes of iron deficiency will probably have a strong impact on the clinical management of unexplained IDA.

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To the editor:

Liver therapy in anemia: a motion picture by William P. Murphy

On December 10, 1934, the Caroline Institute awarded that year’s Nobel Prize in Physiology or Medicine to 3 American investigators: George R. Minot and William P. Murphy of the Harvard Medical School (Boston, MA) and George H. Whipple of the University of Rochester School of Medicine and Dentistry (Rochester, NY), “in recognition of their discoveries respecting liver therapy in anemias.” On December 12, 1934, Murphy delivered the Nobel Lecture and in the concluding paragraph stated, “Rather than enlarge further upon the details and results of the treatment of pernicious anemia, I shall now present, with your permission, a motion picture which will illustrate many points more clearly than I could discuss them here.”1 In this letter we present what we believe was the motion picture to which Murphy referred. The motion picture, made at the Peter Bent Brigham Hospital, emphasizes the superiority of parenteral liver extract to oral whole liver and liver extract in the treatment of pernicious anemia (PA). The movie (Movie S1, available at the Blood website; click on the Supplemental Movie link at the top of the online letter) was found in the Peter Bent Brigham Hospital and given to M.A.S., but the details of its rediscovery are unknown.

In 1900, Russell gave a full account of the spinal cord involvement in PA and coined the term “subacute combined degeneration of the spinal cord.”2 It was noted that hematomatologic abnormalities in patients with tropical sprue improved with a diet containing milk, meat, cod-liver oil, and oranges.3 This observation led to successful use of similar treatments in patients with PA.4 The hematopoietic properties of liver and meat were demonstrated by Whipple while working on dogs that had been bled to produce anemia.4 Whipple demonstrated that the most effective dietary addition in chronic anemia was raw liver. Minot took detailed dietary histories from patients and noted that often his patients with PA excluded meat from their diets. Minot and Murphy started treating PA patients with liver. The diet recommended by Minot and Murphy consisted of 120 to 240 g cooked beef liver, 120 g or more of beef or mutton “muscle meat,” and some vegetables, fruits, eggs, and milk taken daily.5 They documented improvement in the red blood cell count and a sharp rise in the reticulocyte count.6

The accompanying video is approximately 7 minutes in length and is divided into 2 parts. In Part 1, Murphy illustrates the hematologic and neurologic signs and symptoms in PA. This is followed by an illustration of normal hematopoiesis and the derangements seen in PA. The last segment of the first part compares therapy with whole liver, oral liver extract, and concentrated extract for intramuscular injection. A demonstration of the intramuscular injection technique is also provided. The second part shows improvement in the peripheral smear with liver therapy. Murphy graphically illustrates the brisk reticulocytosis, the lag in increase in red cell count, and the greater effectiveness of parenteral therapy compared with oral therapy. The latter section of Part 2 deals with cost-effectiveness of the parenteral therapy and the importance of maintenance therapy.

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The online version of this letter contains a data supplement.

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To the editor:

The FIP1L1-PDGFRα T674I mutation can be inhibited by the tyrosine kinase inhibitor AMN107 (nilotinib)

A fusion of the PDGFRα and FIP1L1 genes can be detected in cases of idiopathic hypereosinophilic syndrome (HES),1 and the resulting tyrosine kinase constitutes a drug target for the treatment of this disease with the tyrosine kinase inhibitor imatinib mesylate (Gleevec; Novartis, Basel, Switzerland).2 However, a mutation leading to threonine residue 674 in the FIP1L1-PDGFRα kinase domain being replaced by isoleucine is known to give rise to resistance to imatinib mesylate in patients with HES.3,4 This T674I
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