Four per cent of referrals to gastroenterologists are initiated because of iron-deficiency anemia (IDA) (1). Thus, gastroenterologists need to understand more about IDA than simply reaching for an endoscope to visualize the bowel. Clinicians want to know how to establish this diagnosis, endoscopists want to know what to do when standard endoscopy results are normal, patients want to be told the likelihood that investigations will lead to benefit, and all concerned want to know how to treat the condition. Only within the past decade have systematic studies become available to answer these questions. The goal of the present article is to summarize this recent information (Figure 1).

Key Words: Endoscopy; Gastrointestinal tract; Iron-deficiency anemia

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An approach to iron-deficiency anemia

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PRESENTATION
In the 1990s, IDA was most often detected after blood tests were obtained to investigate nonspecific complaints such as weakness, lassitude, dyspnea and palpitations. This mode of presentation was observed in 63% of 371 patients with IDA (2); only 16% saw a physician because of the manifestations of the disease causing IDA.

It is difficult to know whether nonspecific complaints are due to anemia. On the one hand, a fall in hemoglobin level has been described to cause a wide range of symptoms

Figure 1) Diagnostic algorithm to iron-deficiency anemia. GI Gastrointestinal; NSAID Nonsteroidal anti-inflammatory drug
(3). On the other hand, most of these symptoms cannot be consistently correlated with anemia until the hemoglobin concentration is lower than 80 g/L (4), and the relationship between the hemoglobin concentration and the degree of symptoms is poor (3). Given the high frequency of fatigue in a general medicine clinic population without anemia (5), it is probably best to assume that correcting the anemia will lead to symptom improvement only when the hemoglobin concentration is less than 80 g/L or when the hemoglobin level has fallen rapidly.

When symptoms of IDA develop, are they secondary to the anemia or to the iron deficiency? Rector et al (6) ingeniously approached this problem by studying patients with polycythemia who were being treated solely with venesections (phlebotomies) sufficient to cause severe chronic iron deficiency but not anemia. These patients developed a compulsive craving for ice, a form of pica, but none of the other ‘classical’ manifestations of IDA such as dysphagia, glossitis, angular stomatitis or koilonychia. Thus, these problems, all of which are unusual in the modern age, must be more related to the anemia caused by low iron stores than to iron deficiency itself. In adolescents and children, there is some evidence that iron supplementation improves cognitive function when iron deficiency is present, even without anemia (7).

DIAGNOSIS

Because iron deficiency can be the only clue to curable bowel cancer and other potentially life-threatening diseases, considerable interest has developed in diagnosing iron deficiency at an early stage. As body iron reserves become depleted and even before the hemoglobin levels fall, the first diagnostic abnormality is a decrease in the serum ferritin level associated with a diminution in Prussian blue (iron stain) staining on bone marrow examination. Next, the red blood cells being produced by the bone marrow become microcytic, because sufficient iron is not available for their production. Initially, this does not show up as a decrease in the mean corpuscular volume, because the older red blood cells, which make up the majority of the cell population, still have a normal size. Instead, an estimate of the variability of red blood cell size, the red blood cell distribution width (a quantitative measurement of anisocytosis), rises. An increased red blood cell distribution width is both a sensitive and specific indicator of IDA in outpatients (8,9), but is less accurate for inpatients (10). Eventually, as the hemoglobin concentration falls, the reticulocyte count and serum iron saturation (serum iron/total iron-binding capacity) also decrease, the mean corpuscular volume drops to below 75 fl, and all of the red blood cells become obviously hypochromic and microcytic on smear, leading to a shortening of the red blood cell lifespan because of changing membrane structure. Once anemia develops from iron deficiency, there should be no iron staining at all on the bone marrow (Prussian blue staining is zero, not just ‘low’), because every molecule of iron is shunted from the bone marrow reserve to the red blood cells before the body allows the hemoglobin level to fall. However, diagnosis at this stage is usually straightforward, so that currently, bone marrow examination is only rarely necessary.

Serum ferritin has been used as an index of iron body stores (11). A number of studies have shown that serum ferritin is a specific indicator of iron deficiency, a useful screening test to detect depleted iron stores and more accurate than other blood tests (12-15). The lower limit of normal for serum ferritin is quoted to be between 12 and 20 µg/mL (45 µg/mL in patients older than age 65 years) (12), with levels below 12 µg/mL being absolutely indicative of iron deficiency. It is important to emphasize that there is no explanation for a low serum ferritin level other than iron deficiency. On the other hand, a low serum ferritin level is not sensitive for iron deficiency (ie, a level above normal does not exclude IDA), because ferritin acts as an acute phase reactant and thus rises with inflammation in virtually any organ system, even in the presence of IDA. Serum ferritin levels are commonly high in malignancy, hepatitis and rheumatoid arthritis, as well as in elderly individuals (16,17). Thus, in these conditions, the serum ferritin is not a sensitive indicator of depleted iron stores, although a low value is diagnostic of iron deficiency.

ETIOLOGY OF IDA

In North America, IDA is more commonly due to excess iron loss from bleeding than to an insufficient iron supply. It is generally believed that a steady blood loss of 3 to 4 mL/day, equivalent to 1.5 to 2 mg of iron, is sufficient to cause a negative iron balance. This degree of blood loss can only occur from the bowel, unless blood is clearly visualized in the urine or sputum, or as a hematoma (or via phlebotomy). Two exceptions to this rule, both rare, are idiopathic pulmonary hemosiderosis, in which iron is deposited in the lung (and hence cannot be reused for red blood cell production), and paroxysmal nocturnal hemoglobinuria, in which iron is lost so gradually via the urine that it is often not noticed. Pulmonary hemosiderosis should be considered when there is a history of hemoptysis without apparent cause (18). In the case of paroxysmal nocturnal hemoglobinuria, hemosiderinuria and a positive Ham’s test are considered ‘gold standards’ (19).

The average North American diet supplies 5 to 7 mg of iron/1000 kcal, more than enough to meet the requirements for adult men and postmenopausal women. Because of this dietary reserve, malabsorption leads to IDA only when the malabsorptive disease is at a well advanced stage, with the exception of celiac sprue (discussed later).

Table 1 lists the gastrointestinal conditions that have been described to cause IDA. Many of these conditions are common in the general population; thus, it is often unclear, in a specific clinical setting, whether a particular lesion is responsible for the iron loss. For example, hiatus hernias are commonly documented at endoscopy in healthy individuals; therefore, these cannot be considered a convincing cause of iron deficiency. On the other hand,
a large hiatus hernia sac associated with linear erosions (Cameron lesions) is well accepted as a cause of IDA, because surgery leads to resolution of the anemia (20,21). Similarly, hemorrhoids and diverticular disease are so common in the general population that it is difficult to determine whether either type of these lesions is responsible for the iron deficiency.

It has only been within the past decade that systematic studies have been completed to identify the causes of IDA. The seven largest prospective trials of bidirectional endoscopy in IDA are summarized in Table 2. Overall, the most common cause of IDA is gastric erosions. The most concerning diagnosis is occult cancer; this is found in up to 20% of patients. Up to 47% of cases of IDA are idiopathic, even after extensive investigations. Unfortunately, it is difficult to combine results of all the trials because of heterogeneous patient populations and nonuniform study designs.

VALUE OF COLONOSCOPY
Because colorectal cancer is the most life-threatening disease among the common causes of IDA, colonoscopy is recommended as the initial procedure. Anywhere from 16% to 30% of gastrointestinal lesions causing IDA can be identified by colonoscopy (Table 2). Hence, modern statistical studies support the traditional view of prioritizing visualization of the colon when IDA develops. Barium studies with or without sigmoidoscopy are less superior methods of examining the colon and should only be done when colonoscopy is not readily available (22,23). Endoscopy is especially superior to radiology for the diagnosis of adenoma and cancer in the presence of diverticular disease (24,25). In prospective studies, the frequency of colorectal cancer ranged from 5% to 14%, which is similar to the figures that have been quoted in the literature (26-32). The likelihood of malignancy is especially high when the patient is older than age 50 years. Classically, it is the patients with carcinoma of the right colon who present with IDA, but carcinomas in the rectum and other parts of the colon may represent a substantial proportion of the colorectal neoplasms identified in patients with IDA and no symptoms referable to the lower bowel.

Vascular malformations (angiodysplasia) have been associated with IDA in 3% to 9% of patients. One confounding variable in all the studies is that there is an uncertainty as to whether these lesions identified at endoscopy are really the cause of the IDA. For instance, angiodysplasia has been found in up to 3% of individuals with a normal hemoglobin concentration (33-35). Therefore, the conclusion that angiodysplasia is a common cause of IDA must be taken with a grain of salt. In addition, the sensitivity in identifying angiodysplasia on colonoscopy has been quoted as 68% (25,36,37). Specificity is also suboptimal because of false positive lesions from suction and other trauma-induced artifacts mimicking vascular lesions.

Other pathological lesions identified by colonoscopy include neoplastic polyps (5% to 15%), and much less commonly, colitis and colonic ulcerations. Polyps larger than 1 cm in size have been shown to cause bleeding leading to IDA (38), but it is unclear whether smaller lesions bleed sufficiently to cause IDA. IDA is rarely attributed to lesions such as diverticulosis and hemorrhoids. Only one prospective trial on IDA included patients with hemorrhoids, and even these authors emphasized the need to exclude other more significant pathology on endoscopy (26), because up to 23% of patients with hemorrhoids will have other coexisting colonic pathology (39).

VALUE OF ESOPHAGOGASTRODUODENOSCOPY
Overall, esophagogastroduodenoscopy (EGD) demonstrates pathology in 27% to 60% of individuals with IDA (Table 2). If colonoscopy is normal, there is a consensus that EGD is the next diagnostic step provided that there are symptoms of upper gastrointestinal tract disease (26,28,29). For example, Rockey and Cello (28) found a strong correlation between a positive history of upper gastrointestinal tract symptoms and consequent lesions identified on EGD. More controversial is whether EGD is necessary in individuals without upper gastrointestinal symptoms. Analysis of prospective data in this regard shows that the absolute yield of EGD is the same or even

### TABLE 1
Sources of gastrointestinal blood loss causing iron-deficiency anemia

<table>
<thead>
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<th>Source</th>
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<tr>
<td>Esophagus</td>
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<td>Ulcers</td>
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<td>Stomach</td>
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<td>Peptic ulcers</td>
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<td>Gastritis</td>
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<td>Carcinoma</td>
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<td>Polyps</td>
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<td>Angiodysplasia</td>
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<td>Hiatus hernia with ulcers</td>
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<td>Leiomyoma</td>
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<td>Small bowel</td>
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<td>Angiodysplasia</td>
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<td>Celiac disease</td>
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<td>Ulcers</td>
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<td>Carcinoma</td>
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<tr>
<td>Polyps</td>
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<td>Other small bowel tumours</td>
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<td>Regional enteritis</td>
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<td>Helminthiasis</td>
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<td>Meckel’s diverticulum</td>
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<td>Diverticulosis</td>
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<td>Hemorrhoids</td>
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<td>Idiopathic (cause of blood loss not found)</td>
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greater in asymptomatic individuals than in symptomatic individuals (26,28,29,31). On the other hand, there are no convincing data to determine whether the lesions identified in the asymptomatic group cause more clinically relevant problems than lesions in the symptomatic group. Overall, the studies suggest that upper gastrointestinal symptoms are specific but not sensitive for localizing IDA-causing lesions in the upper gastrointestinal tract. Diseases important to diagnose, such as gastric cancer (up to 7% of cases causing IDA) or peptic ulcers (7% to 21%), cannot be ruled out on the basis of whether upper gastrointestinal symptoms are present. Given the low risk of EGD presently, the expected benefit-to-risk ratio of EGD favours this procedure even in the absence of symptoms, given the grave implications of missing an early gastric cancer.

**VALUE OF SMALL BOWEL BIOPSY**

In some studies of the cause of IDA, small bowel biopsy was not performed, presumably because there was no clinical evidence of malabsorption in the patients being investigated (28). However, other trials have convincingly demonstrated that IDA may be the only manifestation of celiac sprue, and in fact, in many of the cases, none of the classical findings of celiac sprue — steatorrhea, weight loss, vitamin deficiencies — were present (40-42). Analysis of all available data shows the prevalence of celiac sprue to be as high as 6% in a population of patients with IDA, emphasizing the need for small bowel biopsy in IDA even when other features of small bowel disease are not present. Celiac sprue is important to diagnose, not only because dietary therapy is available to treat the disease, but also because, without such therapy, the risk of malignancy rises (43,44). On the other hand, the cost effectiveness of small bowel biopsy in IDA has not yet been calculated. A recent article has provided evidence to indicate that the IDA present in celiac sprue is actually due to luminal blood loss secondary to microscopic mucosal inflammation, rather than to malabsorption as was previously believed (40).

**CONCURRENT LESIONS**

A number of studies have identified patients with concurrent lesions in the upper and lower tract. The frequency of such findings ranged from 1% to 17%, with only one study quoting a frequency greater than 10% (27,29,30,32,33).
The data suggest that the older the population being investigated, the greater the chance of identifying concurrent lesions. It is often impossible to be certain which lesion is the major contributor to blood loss; therefore, both lesions often have to be treated. There is also no consensus on whether EGD is necessary after a lesion is found on colonoscopy in a patient with IDA without symptoms referable to the upper gastrointestinal tract.

SITE-SPECIFIC SYMPTOM CORRELATION
A number of studies have tried to determine whether symptoms correlate with the disease causing IDA. This is an important question to answer, because if such a correlation exists, symptoms can be used to prioritize the portion of bowel visualized endoscopically. In their prospective study of 100 patients, Rockey and Cello (28) found that symptoms do predict the location of the lesions underlying IDA. For example, in their article, the positive predictive values of history for predicting lesions in the upper and lower tract were 82% and 86%, respectively. However, virtually all other investigators have been unable to confirm such a correlation and thus do not recommend the use of symptoms to direct the initial investigation (26-30). Certainly, there is universal agreement that a lack of symptoms does not rule out disease and should not deter gastrointestinal investigation. For instance, in the absence of gut symptoms, gastric neoplasm is far less common than lower bowel tumours but still has been reported. The bulk of evidence indicates that symptoms cannot be used as a reliable guide to direct investigation in IDA. If the colonoscopy is normal, gastroscopy should follow. This can be done safely and conveniently during the same anaesthesia used for the colonoscopy (45,46).

ASSESSMENT OF PATIENTS WITH BLEEDING OF OBSCURE ORIGIN
In 7% to 47% of cases of IDA, the etiology of the anemia remains unexplained after colonoscopy, gastroscopy and small bowel biopsy. This then is referred to as ‘IDA of obscure origin’. The most important feature to emphasize about this condition is that life-threatening conditions are rare unless there are symptoms or signs present other than those caused by the anemia itself.

Several observations have been made about IDA of obscure origin by a number of long term follow-up studies. First, enteroclysis (small bowel enema) has a low yield if there are no symptoms referable to the small bowel. In fact, in one trial, the yield of this radiological investigation was zero (28), although another series reported a 10% diagnostic rate (47). Similarly, angiography only rarely reveals a lesion unless there are gut symptoms. Second, in about two-thirds of patients with IDA of obscure origin, the anemia resolves by itself after a course of oral iron supplementation (48), and in only a minority of the remainder does a life-threatening disease develop, even with long term follow-up. Third, a high yield of finding a bleeding lesion can be expected from repeating colonoscopy and gastroscopy in a specialist unit with an interest in gastrointestinal bleeds. For example, in one series of tertiary referred patients, Waye (49) reported that almost 50% of the lesions finally found to be the cause of the IDA were within reach of a standard flexible gastroscope. Last, enteroscopy shows a cause for obscure IDA in about 10% to 50% of cases (50,51). The ‘push’ technique seems to be preferable to the Sonde technique because endoscopic therapy can be offered using the endoscopy biopsy channel and less time is required for the study. Lesions detected by enteroscopy include small bowel angiodysplasia, tumours, ulcers and the ‘diaphragm’ inflammatory webs associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). With the advent of enteroscopy, laparoscopy combined with intraoperative endoscopy is less often necessary than in the past, although some authorities continue to consider this technique the ‘gold standard’ diagnostic procedure (52,53).

ASSESSMENT OF IDA IN PATIENTS ON NSAIDs
There is compelling evidence that NSAIDs are associated with IDA, and that these drugs cause mucosal ulcers and erosions in the upper gastrointestinal tract. These lesions do not correlate well with upper gastrointestinal tract symptoms that are common in patients taking NSAIDs (54). Risk factors for NSAID-induced gastric ulceration include previous history of upper gastrointestinal tract bleeding or peptic ulcer, age older than 65 years, high NSAID dose and concomitant use of corticosteroids or anticoagulants (55). Overall, about 15% of patients on NSAIDs have ulcers in their upper gastrointestinal tracts (56), and up to 20% have erosions (57). Thus, it is clear that in patients on NSAIDs, gastroscopy should be the first procedure performed when IDA develops. However, procedure is less clear if gastroscopy is normal. It is tempting to recommend no further investigations, because NSAID-induced gastric and duodenal ulcers or erosions are evanescent, disappearing (then sometimes reappearing) with time, especially if the NSAID is stopped, as is commonly done before gastroscopy. Moreover, small bowel inflammation, as assessed by measuring intestinal permeability, has been described to be a common cause of IDA in this population (58-60). This may be one reason why, in one study, only 56% of NSAID-treated patients with endoscopically documented healed upper gastrointestinal lesions showed an improvement in their anemia (54). More importantly, in at least three trials of IDA, there was no correlation between the findings at colonoscopy and NSAID use, i.e., the frequency of occult malignancy at colonoscopy was the same in patients taking NSAIDs as in those not using these drugs (26-28). It has even been suggested that the antiplatelet effect of NSAIDs causes earlier bleeding from bowel lesions, leading to earlier diagnosis of occult tumours in the bowel (61). NSAIDs have also been reported to cause ulcers and mucosal inflammation (colitis) in the colon (62). Thus, when IDA develops on the background of NSAID use, gastroscopy should be completed first. If
either an ulcer is seen and the hemoglobin does not normalize when the ulcer heals, or no significant findings are noted at upper endoscopy, colonoscopy should be done. Enteroscopy is recommended if the colonoscopy is normal and the NSAID must be continued to search for ulcers and diaphragm-like lesions in the small bowel (60).

THE SIGNIFICANCE OF IDA DURING ANTICOAGULATION THERAPY

Unfortunately, there are no prospective trials evaluating the significance of IDA in patients on long term anticoagulation therapy (heparin or warfarin). Conceptually, two possibilities exist. First, anticoagulants may cause blood loss from trivial lesions such as stercoral ulcers (mucosal denudation caused by firm stools abrading the mucosa), hemorrhoids, angiodyplasia or other entities that would not bleed without anticoagulation. In this situation, investigation of IDA in patients on anticoagulants would have a low yield of clinically significant disease. On the other hand, anticoagulants may act as a ‘stress test’, causing bleeding from tumours and ulcers before they would have bled if anticoagulants had not been given. Most of the literature supports this latter possibility. A recent study showed no significant difference in fecal occult blood loss in patients taking warfarin compared with the control group (63). Furthermore, the pathological lesions causing blood loss and, in some cases, anemia were similar to the lesions identified in patients not on anticoagulation therapy. Moreover, in a prospective trial, 15 of 16 patients on anticoagulants with occult blood in the stool (as assessed by Hemocult [Beckman Coulter, USA]), had a lesion in the intestinal tract; three of these were otherwise unsuspected cancers (64). The authors of this study concluded that anticoagulant therapy may unmask bleeding from pre-existing occult bowel lesions. It was also noted that anticoagulant treatment maintained in the therapeutic range (international normalized ratio 2.0 to 3.0) does not increase gastrointestinal blood loss without the pre-existence of an underlying pathological lesion. Thus, the literature that is available indicates that IDA should not be attributed to anticoagulation and that these patients should be investigated fully by endoscopy, especially if the international normalized ratio and/or partial thromboplastin time are/is in the therapeutic range.

THE ROLE OF FECAL OCCULT BLOOD TESTS IN IDA

Intuitively, fecal occult blood tests (FOBTs) appear to be helpful in IDA to determine whether there is a bleeding lesion in the bowel. However, the literature does not support this hypothesis, chiefly because the pretest probability of the presence of a gut lesion in IDA is almost as high as the sensitivity of the FOBT. Accordingly, it is not surprising that most studies do not show any correlation in IDA between a positive FOBT and the presence or absence of a lesion in the bowel. FOBT similarly is not helpful in determining the location of the bleeding lesion in the gut (26). FOBT is used best for screening (healthy individuals for colorectal cancer) rather than determining whether IDA is due to a bowel lesion.

IRON REPLETION THERAPY

Because iron is a natural substance, it is easy for both patient and physician to be lulled into believing that its side effects are minimal and that the formulation prescribed is inconsequential. In fact, success in repleting lost body iron is not simple. Oral iron is the treatment of choice for most patients, because it is effective, safe and economical. The goal of treatment is not only to correct the hemoglobin deficit but also to replenish iron stores. Usually, 60 mg of elemental iron is given four times daily as ferrous sulphate 325 mg 1 to 2 h before each meal and at bedtime. If taken as directed, this prescription will result in the correction of the anemia within about one month, but it is important to continue taking the oral iron until the body stores are replenished. This can take up to six months because the percentage of oral iron absorbed by the bowel mucosa falls dramatically as the iron deficiency is corrected. The reticulocyte count is often used as a convenient way of monitoring response to therapy, although it can be expected to rise only seven to 10 days after initiating therapy. By that time, the hemoglobin concentration should have risen by approximately 2 g/L. The iron replacement therapy is then continued until the serum ferritin level rises to 50 µg/L, indicating total body iron stores of about 500 mg (65).

Up to 20% of patients cannot tolerate oral iron because of symptoms referable to the bowel (66). Lower gastrointestinal symptoms include constipation and diarrhea, which do not seem to be related to dose and can be managed either symptomatically or by switching to a different formulation. On the other hand, epigastric discomfort, dyspepsia and true abdominal pain are dose-related, presumably reflecting the concentration of unbound inorganic iron in the upper gut mucosa (67). Vomiting and disabling cramping have also been described (67). To overcome these problems, the oral iron preparation can be changed to ferrous gluconate (or ferrous succinate). However, it is important to appreciate that 325 mg of ferrous gluconate contains only 35 mg of elemental iron compared with 60 mg in a 325 mg tablet of ferrous sulphate. Other strategies include trying a liquid iron formulation or recommending that the iron be taken after meals. This will decrease the proportion of iron absorbed from the tablet, but often, the increase in compliance from postprandial tablet ingestion ends up being a more important factor in achieving body iron repletion than the percentage of iron absorbed. Costly iron preparations with additives, with enteric coating or in sustained-release formulations, do not appear to offer any advantage (67). Ferrous salts should not be taken at the same time as antiulcer medications (gastric acid suppressant), because this risks decreasing iron absorption.

Parenteral iron therapy, with its risk of adverse reactions, should be reserved for the exceptional case. The indications for parenteral iron are malabsorption, severe recurrent iron deficiency due to uncontrollable blood loss and intractable, severe gastrointestinal side effects of oral iron.
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