CURRENT PROGRESS

Iron-Deficiency Anemia After Partial Gastrectomy

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Although the mechanism for its development is not well understood, iron-deficiency anemia is a well-recognized consequence of partial gastrectomy. The reported incidence varies considerably, depending upon the criteria used to define anemia, and other factors. Rapid emptying of the gastric remnant, intestinal "hurry", and borderline dietary-iron intake, with or without concomitant blood loss, produce malabsorption of some forms of iron that appears to be responsible for development of the deficiency. The diagnosis rests on hematological findings in the peripheral blood, the evaluation of iron stores, epithelial changes, and the response to adequate treatment. Oral iron therapy can be both effective and inexpensive and should form the mainstay of treatment.

Bien que le mécanisme du développement de cette déficience ne soit pas bien compris, l'anémie sidéropénique est une séquelle bien connue de la gastrectomie partielle. Sa fréquence varie considérablement selon le critère utilisé pour définir l'anémie et aussi selon d'autres facteurs. La vidange rapide du restant du chyme, le transit intestinal rapide et une alimentation limite en ce qui concerne le fer, avec ou sans hémorragie concomitante, ont pour effet de provoquer une mauvaise absorption de certaines formes de fer ce qui explique l'apparition de l'insuffisance. Le diagnostic repose sur les analyses hématoliques du sang périphérique, sur l'évaluation des réserves de fer, sur les modifications de l'épithélium et sur la réaction au traitement convenable. Une thérapeutique martiale orale est à la fois efficace et peu coûteuse et devrait constituer la pierre angulaire du traitement.

IRON-DEFICIENCY anemia is a major public health problem for many millions of the world population. Many diseases of the gastrointestinal tract cause blood loss, with subsequent iron deficiency and anemia. Those that give rise to impaired absorption of iron are relatively uncommon; in a modern society, the most important is that which follows gastric surgery.[76] After total gastrectomy, deficiency of both iron and vitamin B_{12} is expected to develop, the former quite soon after operation and the latter after a period of years, usually three or more, when reserves have been depleted.

The anemia that develops after partial gastrectomy usually is hypochromic, due to iron deficiency, and relates to such factors as the type of operation, the condition for which it was performed and, possibly, the quality of the remaining gastric mucosa. Until recently, the occurrence of megaloblastic anemia after partial gastrectomy and its degree of severity were underestimated, mainly because the simultaneous development of iron deficiency often masks megaloblastic change almost completely.[41, 54, 61, 62] Despite the publication of numerous comprehensive reports concerning iron-deficiency anemia after partial gastrectomy, including studies with modern techniques, the mechanism of its development is not well understood.

It is the purpose of this communication to discuss certain physiological aspects of iron balance and absorption, and to review the incidence, pathogenesis, diagnosis and treatment of postgastrectomy iron-deficiency anemia.

Iron Balance

Total body iron in normal adult man amounts to 45 mg./kg. body weight,[24] including the essential fraction in the form of hemoglobin, myoglobin and cell enzymes, and storage iron in the form of ferritin and hemosiderin. Good nutritional status assures normal body iron content in the absence of abnormal losses. During iron depletion the stores are affected before the essential fraction is reduced; thus, the size of the iron stores is an index of iron balance. In normal circumstances, body iron stores remain relatively constant throughout adult life although varying widely from person to person, being approximately 1200 mg. in the adult male and about half that amount in the female.

There is considerable difference in the availability of iron in various foods and the extent to which absorption of this metal may be enhanced in iron deficiency. Normal and iron-deficient subjects absorb more iron from animal tissues than from vegetable sources. The basal daily iron requirement is 1 mg. in the male and 2 mg. in the menstruating female; 1 mg. "avail-

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able" iron is roughly the equivalent of 5-10 mg. dietary iron in a balanced diet and approximately 20 mg. in a vegetarian diet.[24] Since only about 10% of food iron is effectively assimilated from a European or North American type of diet containing 12-18 mg. iron per day,[50] the daily ingestion requirements for a man will be somewhat less than 10 mg. and the menstruating woman will require 10-20 mg. In the latter it is said that the daily ingestion of at least 15 mg. iron per day is necessary to prevent the development of anemia.[51]

Iron losses in the healthy normal male are in the range of 0.5-0.1 mg. daily, mainly from exfoliation of skin and gastrointestinal mucosa, coupled with minor blood loss from the latter. In the female menstrual loss averages 0.6-1.0 mg. per day, with great variation from one person to another.

IRON ABSORPTION

Since mechanisms of iron excretion are limited, those involved in the absorption of iron from the gastrointestinal tract are primarily responsible for the maintenance of a delicate balance.[45] Several factors are known to influence iron absorption from the gut.

Total body iron content.—Studies with the double-isotope method have indicated that the larger the iron stores the less the amount of iron absorbed.[12, 23]

Blood-cell production.—The greater the red-cell production the greater the amount of iron absorbed.[12, 46]

Ingested iron.—The larger the amount of iron administered orally, the greater the amount finally absorbed.[12, 58]

Anemia.—The increased absorption of iron salts and of dietary iron in iron-deficiency states is well known.[23, 49] Correction of the anemia of iron deficiency results in a return of iron absorption to normal levels, despite depleted stores.

Transferrin.—Recent reports[29, 59] indicate that the iron-transferring system plays an important part in the regulation of iron absorption. However, other studies[55, 71] have shown that transferrin is essential for physiological iron transport but not for iron absorption, the latter appearing to be independent of the relative saturation of iron-binding protein.

Ferrous iron.—Iron is better absorbed in a ferrous form; and an absorption gradient appears to exist in the gastrointestinal tract, highest in the duodenum.[20]

Ascorbic acid.—The addition of an excess of ascorbic acid to the diet results in increased absorption of food iron,[49, 58] with the exception of hemoglobin iron.[63]

Intracellular iron stores.—Intestinal villous epithelial cells may store iron, and this is lost during desquamation;[21] the life-span of these cells is thought to be about three days,[8, 18, 19] during which time the entire epithelial covering may be renewed. Mendel[46] has presented evidence which suggests that anemia, the rate of erythropoiesis, and body iron content exert an additive effect on the absorptive mechanism of iron.

INCIDENCE

The reported incidence of postgastrectomy anemia varies from 4%[9] to 63%,[66] depending upon (1) the different criteria employed in defining anemia, (2) sex ratio in each series, (3) indication for operation, (4) type of gastrointestinal anastomosis, (5) length of time since operation, and (6) whether the patients received treatment for anemia before the institution of hematological investigation.

The highest incidence occurs in females under 50 years of age; men of all ages and older women develop the anemia less often.[2, 10] Watson[69] reported an incidence of 11% in a series of 127 cases, and Anderson and his co-workers[1] found subnormal hemoglobin levels in the majority of their patients. Wells and Welbourn,[70] who considered an arbitrary level of hemoglobin of 14 g./100 ml. as the lower limit of normal for men and 12 g./100 ml. for women, diagnosed anemia in 15% of their male patients and 30% of the females one to 10 years after operation. Mollin and Hines,[48] employing Wallensten's criteria[66] for defining anemia (hemoglobin value less than 13.6 g./100 ml. in men and 11.6 g./100 ml. in women), found an incidence of 46% in 212 unselected and previously untreated patients who were investigated one to 14 years after partial gastrectomy. Baird and his co-workers[2] recorded blood changes in 341 patients for up to 10 years after subtotal gastrectomy and found a progressive fall in hemoglobin levels in both sexes, especially in women under the age of 50 years.

The incidence of severe anemia after partial gastrectomy increases with time,[2, 22, 48] especially after Polya resection.[54] This is in striking contrast to the finding in patients with persistent peptic ulceration but with an otherwise intact stomach, in whom the incidence of anemia does not increase with time.[2]

Deller and Witts[22] studied 265 patients who had undergone partial gastrectomy in the preceding 10 years and found 54 (20.4%) to be anemic (iron deficiency in 38, vitamin B_{12} deficiency in four, and deficiency of both in 12); low serum-iron values were found more com-

monly in women and after Polya resection. The same authors analyzed data from 33 reports (7505 cases) of patients who had undergone partial gastrectomy; anemia was present in 28%, including only 0.33% of the megaloblastic type.

PATHOGENESIS

Iron deficiency after partial gastrectomy may be due to blood loss either acute and apparent or occult and chronic, or to an inadequate supply and/or impaired absorption of dietary iron.

Iron Loss Due to Hemorrhage

Some investigators consider that blood loss is an important cause of postgastrectomy anemia.[49, 57] Menstruation, parturition, epistaxis, bleeding hemorrhoids and aspirin ingestion[72] have been cited as significant contributory factors. Women lose 500-3000 ml. of blood per year during menstruation, an amount sufficient to tip the balance towards iron deficiency in anyone who is unable to compensate by increasing iron absorption.[16]

Of much greater significance, of course, in the postgastrectomy state is the occurrence of occult blood loss from the gut. Potential sites of bleeding include the lower esophagus (from esophagitis, even in the absence of acid gastric juice), the remaining gastric mucosa, the site of anastomosis,[75] and the proximal jejunum. Benedict,[6] who reviewed the findings at esophagoscopy in 1938 patients, found benign esophagitis with stenosis in 72, 10 of whom had undergone partial gastrectomy for peptic ulcer; and Cox[17] described three patients in whom esophagitis developed as early as 20 days postoperatively. Windsor[73] studied 61 unselected patients one to 12 years after partial gastrectomy: 24 showed esophageal reflux radiologically, but no precise correlation was found with the existing anemia in any case; four patients in whom esophagoscopy had shown esophagitis had chronic iron-deficiency anemia.

Gastric and jejunal biopsy studies in 58 patients after partial gastrectomy[37] failed to reveal correlation between iron-deficiency anemia, hypoferremia, or increased total iron-binding capacity with the histological picture of the gastric and jejunal mucosa. Stomal ulcer must always be considered as a potential source of occult blood, but in none of the 100 cases reported by Williams[72] was blood loss from this site considered to be the cause of the anemia. The rarity of occult blood loss after partial gastrectomy is seen in the four series listed in Table I; however, it is conceivable that the occasional rapid appearance of anemia after partial gastrectomy probably can be attributed to hemorrhage from the gastrointestinal tract.[53, 75]

TABLE I.—OCCULT BLOOD LOSS AFTER PARTIAL GASTRECTOMY

Author	*Patients tested*	*Occult blood loss detected*
Baird and Wilson[4]: Anemic	30	3
Not anemic	32	6
Stevens *et al.*[60]	55	0
Choudhury and Williams[15]	40	0
Hobbs[31]	84	1

DIETARY IRON

Supply.—The consumption of an inadequate diet after partial gastrectomy is common.[30] Unless specially advised, many patients maintain the preoperative dietary regimen of primarily milk products, low in iron content. Baird and his co-workers[2] recorded a low iron intake in female patients who had undergone gastrectomy. The combination of blood loss and inadequate diet may be a significant factor in the development of postgastrectomy iron-deficiency anemia in menstruating women. However, Hobbs[31] found evidence of possible blood loss or low dietary iron intake in only about one-third of 247 anemic postgastrectomy patients and considered that defective iron absorption probably had given rise to anemia in the others.

Absorption.—It is now generally accepted that the decreased absorption of iron is the major cause of its deficiency after partial gastrectomy in patients of either sex. Subjects with an intact stomach become adapted to depletion of iron stores and anemia with the development of enhanced absorption of dietary iron and an increase in the serum unsaturated iron-binding capacity (UIBC) to > 300 mg./100 ml.[28]—an important physiological mechanism in the prevention of iron deficiency. Iron absorption cannot be augmented in postgastrectomy patients and, therefore, iron deficiency and anemia develop.[4] However, slightly enhanced absorption has been reported[4] after administration of inorganic ^{59}Fe to fasting and postgastrectomy subjects, but not when this was given in organic combination with food, whereas absorption was greater when either preparation was given to subjects with iron deficiency and an intact stomach.

Choudhury and Williams[15] fed ^{59}Fe as ferric chloride baked into bread to patients who had undergone (1) Polya gastrectomy, (2) a Billroth-I resection, or (3) vagotomy with gastroenterostomy. Patients whose hemoglobin value was > 13.5 g./100 ml. showed similar degrees of absorption. In the anemic patients, iron ab-

sorption was reduced in the first group, somewhat reduced in the second, and altered variously in the third group. A greater decrease in absorption was observed in patients in the first group when they were fed very small amounts of iron. Stevens and his co-workers[60] have shown that postgastrectomy patients absorb inorganic iron normally, retain less than normal amounts of food iron, and absorb iron less efficiently as they become more anemic. However, Turnberg[64] showed recently that patients with postgastrectomy anemia have defective absorption of organic iron and that some may have defective absorption of inorganic iron also; absorption of iron from hemoglobin mixed with food was not enhanced in 18 patients, probably because the jejunum is less capable of absorbing organic iron than the duodenum.

Hobbs[31] considers that malabsorption of dietary iron is due chiefly to rapid emptying of the gastric remnant and by-pass of the duodenum, and that steatorrhea, jejunitis and achlorhydria are of little significance after partial gastrectomy. In fact, iron-deficiency anemia after partial gastrectomy appears to be unrelated to the malabsorption of other nutrients or to abnormal bacterial growth in the upper intestine.[74] Thus, it is reasonable to assume an additive effect of several factors: rapid emptying of the gastric remnant, resulting in intestinal hurry; duodenal by-pass; failure to render organic iron suitable for absorption; and borderline dietary intake of iron. The opinion expressed by Wallensten[68] that the incidence of the anemia is less after the Billroth-I than after the Billroth-II procedure is compatible with the known facts of iron absorption in the duodenum and upper jejunum: evacuation of the gastric remnant is slower, intestinal hurry is less pronounced, and the duodenal absorptive surface is not by-passed when gastroduodenal continuity is preserved.

Great importance has been ascribed to the part played by the hydrochloric acid present in gastric secretion, but its precise role in the absorption or iron remains unknown. Brummer[13] found no correlation between hemoglobin levels and gastric acidity in 100 women aged 20 to 60 years; and Moore[49] found no increase in absorption of radio-iron incorporated in cooked eggs given to achlorhydric or hypochlorhydric patients when hydrochloric acid was added to reduce the pH of the food to 1.5. Callender[14] detected no reduction in absorption of hemoglobin iron in patients with achlorhydria, and it was not increased when 100 ml. normal gastric juice, pH 2.0, was added to the test dose. More recently, however, Goldberg and his associates,[25] using the labelled-meal technique, demonstrated a significant difference between radio-iron absorption of achlorhydric patients (18.5% of the dose given) and of patients with acid gastric juice (57.5% of the dose). The authors were unable to establish whether the diminished absorption of ferric iron in achlorhydric subjects was due to the absence of hydrochloric acid or to associated mucosal changes. Jacobs,[36] who gave ferric chloride to 10 subjects, found mean absorption to be 2.2% with water and 9.2% with acid; in contrast, the absorption of hemoglobin iron was not increased when acid was administered. These workers suggested that hydrochloric acid facilitates the absorption of ferric iron by keeping it in solution until it reaches the absorptive area of the duodenum. Obviously the increased incidence of achlorhydria with age[65] may account partly for the increased incidence of iron-deficiency anemia in older subjects.[40]

A substantially different component has been introduced recently by Michaelides and Philis,[47] whose observations suggest that normal gastric juice contains a reducing agent necessary to the assimilation of iron. Also, Koepke and Stewart[42] have presented evidence of a factor, possibly a mucoprotein or glycoprotein, in the gastric juice of anemic dogs which significantly increases absorption of iron from the gastrointestinal tract. They postulate that the mechanism of iron absorption might well be similar to that of vitamin B_{12}, in view of the fact that deficiency of both substances develops after partial gastrectomy. Furthermore, Turnberg[64] found increased absorption of inorganic iron in three subjects with postgastrectomy anemia when whole hog-stomach extract was added to the iron ingested. These interesting data, which imply that an intrinsic substance secreted by the stomach may be necessary to iron absorption, await further documentation.

That faulty iron absorption is concerned in the development of iron deficiency after partial gastrectomy is reflected in the relationship of time since operation to the degree of severity and incidence of anemia. The progressive decline in hemoglobin concentration with the passage of time postoperatively is considered by Baird and Wilson[4] to be the characteristic feature of this condition. However, two factors that may modify this relationship are the size of the iron stores and the amount of iron administered therapeutically. If iron stores are depleted at the time of operation, iron-deficiency anemia will appear soon, whereas if they are intact at that time, anemia may not develop for six to eight years, despite impaired absorption. Moore[49] calculated that, if iron absorption ceased completely in an adult male with 2500 mg. hemo-

globin iron and 1000 mg. storage iron (hemoglobin, 15 g./100 ml., and 5000 ml. blood volume), three and one-half years would elapse before the hemoglobin value would fall below 13.6 g./100 ml., assuming the excretion of 1 mg. iron daily.

DIAGNOSIS

The diagnosis of iron-deficiency anemia after partial gastrectomy rests mainly on the hematological findings in the peripheral blood, proof that iron depletion is the limiting factor responsible for impaired erythropoiesis, and the characteristic changes in epithelial tissues. Final confirmation depends, of course, on response to adequate iron therapy.

Symptoms of iron deficiency may appear before the signs of anemia develop; they include anorexia, abdominal discomfort, epigastric distension after meals, and easy fatigability. These symptoms are quite common in postgastrectomy patients and sometimes vanish completely when iron is given.[31, 67]

Review of past records of hemoglobin and hematocrit levels, and especially of the size of iron stores at the time of operation and immediately afterwards, is important. A detailed account must be obtained of the intake of iron, protein and total calories, and of contributory causes of blood loss, especially hemorrhoids and menorrhagia. The ingestion of salicylates in any form and for an appreciable length of time must be ascertained: acetylsalicylic acid (enteric-coated, buffered, or calcium aspirin) or sodium salicylate may produce fecal blood loss and may tip the scales towards frank iron-deficiency anemia in these patients.[5, 27, 44] Serial stool examinations for occult blood are essential, and potential local causes of bleeding from the gastrointestinal tract should be ascertained radiologically and by esophagoscopy and proctosigmoidoscopy.

Laboratory Diagnosis and Evaluation of Iron Stores

Evaluation of the morphology of the erythrocytes in the peripheral blood is essential to the diagnosis of iron-deficiency anemia; early stages of the deficiency present a normochromic, normocytic picture. Hypochromia and microcytosis are usual in mild iron-deficiency anemia; as it becomes more severe, poikilocytosis, polychromatophilia and anisocytosis develop. Decrease in the red-cell indices (mean corpuscular volume and mean corpuscular hemoglobin concentration) reflect the microcytosis and hypochromia. The earliest change seen in iron deficiency is the decrease in marrow hemosiderin, followed by an increase in UIBC and reduction in serum iron.

The serum-iron value usually is below normal (60 μg./100 ml.) in iron-deficiency anemia after partial gastrectomy, and in about 15% of cases hypoferremia exists without anemia.[22] Therefore, it is important to evaluate iron stores by staining spread films or sections of bone marrow with the Prussian-blue reaction. When stainable iron is absent or considerably diminished, long-term iron therapy is essential to correct the anemia and replenish iron stores. In such cases the deficiency may mask megaloblastic changes, not only in the peripheral blood but also in the erythroblasts; such changes may become apparent only after the institution of iron therapy[41, 61] and, therefore, it is necessary to study the bone marrow at this time.

Determination of serum levels of vitamin B_{12} and folate, urinary excretion of formiminoglutamic acid (FIGLU) after histidine loading and a Schilling test also aid in detection of megaloblastic change coexistent with iron deficiency. The presence of iron-deficiency anemia after partial gastrectomy does not exclude the possibility of other coexistent anemia, and this must be borne in mind especially when the response to "adequate" iron treatment is less than expected. Hemolytic states due to a congenital abnormality (e.g. thalassemia trait), pyridoxine-responsive anemia, aplastic or hypoplastic states, anemia of chronic renal disease or infection, and iron malabsorption due to gluten sensitivity must be excluded.

Epithelial Changes

Epithelial changes include koilonychia, transverse nail ridges, brittle nails, angular stomatitis, and atrophic glossitis.[4] There are racial differences in the incidence of epithelial changes in patients with iron deficiency,[35] and it may be that genetic factors or dietary constituents other than iron may be involved; nevertheless, stomatitis, glossitis and koilonychia are corrected by iron therapy. Dysphagia suggests esophageal mucosal changes in the postcricoid region; and the absence of free acid and no appreciable change in pH of gastric secretion after maximal histamine stimulation suggest atrophic gastritis. Gastric and jejunal mucosal changes may be verified by the examination of biopsy specimens of mucosa.[3, 11, 38]

Occult Blood Loss

Occult blood loss from the gastrointestinal tract can be detected by the commonly employed chemical tests, spectroscopic examination of the

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feces, and studies with ^{51}Cr-labelled cells. The ^{51}Cr method is the most reliable, and may be of great value in selected cases.[32] The chemical tests are the most practical, but none is infallible. In the postgastrectomy patient in particular, the more sensitive procedure using benzidine base after a three-day avoidance of meat and toothbrushing may be preferable.[33]

TREATMENT

The treatment of iron-deficiency anemia after partial gastrectomy requires correction of the deficit of circulating hemoglobin, replenishment of the storage deficit (by providing an increased intake of readily absorbed iron), and correction of any treatable source of abnormal blood loss. Also, prophylactic treatment of the anticipated deficiency is of paramount importance. The time-honoured dictum that the great majority of iron-deficiency states will respond to oral iron therapy is applicable to the postgastrectomy state. Simple preparations, in the form of ferrous sulfate or gluconate, usually are effective. The ideal program is the administration of one tablet (300 mg. ferrous sulfate or 60 mg. elemental iron) between meals, three times daily. Ferrous sulfate is both inexpensive and effective and should form the mainstay of iron therapy.[56] The risk of "intolerance" is reduced when iron preparations are taken after meals, but then they are not so well absorbed. However, the incidence of side effects following oral administration is relatively low.[7, 39]

Unfortunately, iron tablets harden with age and then dissolve less rapidly, especially in postgastrectomy patients, unless they are taken when the patient is lying down; because of the rapid evacuation of the gastric remnant, tablets taken by erect subjects may reach the terminal ileum within 20 minutes.[26, 52] One tablet of ferrous gluconate or sulfate taken on retiring each night probably is adequate in the treatment of mild postgastrectomy iron-deficiency anemia. Chelated iron preparations (e.g. ferrous glycine sulfate), which are more stable in alkaline solutions,[31] may by-pass the ferritin mechanism; very high levels in the blood appear rapidly in cats,[34] and, therefore, these preparations may be termed "predigested" and thus suitable for postgastrectomy patients.

Inadequate release of ferrous ions from coated iron tablets taken after meals, and the rapid emptying of the gastric remnant, explain the poor results obtained sometimes when iron is administered orally to patients with postgastrectomy anemia. Iron given orally is not well tolerated by some of these severely anemic patients and, since iron absorption usually is reduced after the hemoglobin deficit has been corrected, replenishment of iron stores in such patients is more difficult than in those with an intact stomach. One course of iron parenterally helps to replenish iron stores, and then treatment may be continued orally.[72] Even when iron is well tolerated when given orally, it takes at least six to seven months of treatment to correct storage deficits. It may be that after partial gastrectomy most patients have partly or wholly depleted iron stores, and prophylactic postoperative iron therapy has been advocated.[43] Williams[72] recommends that a course of iron should be given orally for at least three months, followed by a maintenance dose (one tablet of 200 mg. each night) indefinitely. Many clinicians combine the iron with large doses of ascorbic acid, to increase absorption.

Hobbs[31] has outlined a scheme for the management of patients after partial gastrectomy. He recommends determination of hemoglobin values every three months for menstruating women and once a year for all other patients. Iron therapy is started for those whose hemoglobin level is less than 13.6 g./100 ml. and for all menstruating women.

Vitamin B_{12} or folic-acid deficiency coexisting with iron-deficiency anemia should be treated accordingly, and a well-balanced diet secured. Blood transfusion is rarely necessary in the treatment of anemia after partial gastrectomy, and should never be employed unless there is urgent need for rapid restoration of hemoglobin levels.

SUMMARY

Iron balance and iron absorption under normal conditions and following partial gastrectomy have been discussed. It is likely that iron-deficiency anemia occurs less frequently after gastrectomy when gastroduodenal continuity is preserved. Inadequate absorption of dietary iron, which appears to be the main factor contributing to the development of anemia, is attributed to rapid evacuation of the gastric remnant, by-pass of the duodenum, and failure to render organic iron available for absorption because of impairment of digestion. The inability of these patients to increase their absorption or iron from food as they become anemic probably is the most significant factor. Borderline dietary intake or iron in both sexes and blood loss in menstruating women are important contributory causes, and the possibility of occult blood loss must be borne in mind. The size of iron stores at time of operation appears to be the main determinant of how soon iron-deficiency anemia will develop. The diagnosis and treatment of this type of anemia have been outlined.

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