Is achlorhydria a cause of iron deficiency anemia?1

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ABSTRACT
We re-evaluated the old hypothesis that gastritis-induced achlorhydria is a cause of iron deficiency anemia (IDA) in humans. First, we analyzed the currently available research on the association between achlorhydria and IDA. When gastric acid secretion was measured after maximal stimulation, the frequency of achlorhydria (or severe hypochlorhydria) was 44% in patients with idiopathic IDA and 1.8% in healthy controls. In some patients with pernicious anemia, presumed achlorhydria preceded the development of IDA in time. However, we found no credible evidence that IDA caused gastritis or that IDA preceded the development of achlorhydria. Thus, correlational results favor achlorhydria as the causal factor in the association between achlorhydria and IDA. Second, we sought to determine whether gastritis and achlorhydria cause negative iron balance. When biosynthetic methods were used to isotopically label iron in food, achlorhydric patients were found to have severe malabsorption of nonheme iron, which persisted after the development of IDA. In 1 study, achlorhydria reduced the normal increase in heme-iron absorption from hemoglobin in response to iron deficiency. After an injection of isotopic iron into normal men, the physiologic loss of iron from the body was found to be 1 mg/d. Patients with chronic gastritis had excess fecal loss of isotopically tagged plasma iron. Calculations based on these results indicate that the absorption of iron from a typical Western diet by achlorhydric patients would be less than physiologic iron losses, creating a negative iron balance that could not be overcome by the adaptive increase in duodenal iron absorptive capacity that occurs in response to iron deficiency. The combination of results from these correlational and pathophysiologic studies supports the hypothesis that gastritis-induced achlorhydria can be an independent cause of IDA. Am J Clin Nutr 2015;102:9–19.

Keywords: achlorhydria, chronic atrophic gastritis, iron deficiency anemia, iron malabsorption, pernicious anemia

INTRODUCTION
In the early 1900s it was discovered that patients with idiopathic microcytic anemia had a high frequency of chronic gastritis and achlorhydria. The anemia was corrected by oral iron therapy, and the etiology of the underlying gastritis was considered to be idiopathic or related to pernicious anemia (PA) (1, 2). In the 1930s, this syndrome was embraced by prominent clinical investigators throughout the world, and it was diagnosed more frequently than PA. It was most commonly assumed that the iron deficiency anemia (IDA) was caused by achlorhydria-induced malabsorption of dietary iron (3–11).

Starting in the 1950s, clinical researchers began to believe that achlorhydria could not cause enough malabsorption of dietary iron to be a primary etiology of iron deficiency (12–16). The most influential statement was by Moore (12), whose opinion is paraphrased as follows:

The human organism has little ability to rid itself of iron through ordinary excretory channels. When achlorhydria is present, there is almost certainly less ionization of iron in food and more prompt precipitation of iron in the small intestine. But although poor absorption can contribute to the pathogenesis of iron deficiency, it is not enough to precipitate its development unless iron losses from the body are also excessive due to repeated pregnancies, menstrual blood flow, or intermittent hemorrhage. No carefully studied patient has ever been shown to provide an exception to these statements.

Other investigators reported results that suggested that iron deficiency was the cause rather than the result of atrophic gastritis (17–21), which further eroded the concept of achlorhydric anemia. Within a few years, achlorhydria was no longer considered by clinicians to be one of the causes of IDA. The last original research article we found on the quantitation of iron absorption in relation to gastric acidity was published in 1981 (22). In 1991, Finch and Huebers (23) wrote in an authoritative review that “achlorhydria in the human does not appear sufficient to produce iron deficiency.”

Even though the case was closed on achlorhydric anemia, an association between IDA and PA continued to be reported between 1963 and 1988 (24–27). In 1997, Dickey et al. (28) reported on a group of patients presenting with idiopathic IDA in whom endoscopic biopsies revealed a high frequency of atrophic gastritis. Although acid secretion was not measured, serologic testing of their patients with gastritis often revealed suggestive

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evidence of achlorhydria due to PA. They proposed that achlorhydria was the cause of idiopathic IDA in these patients. Other clinical researchers recently confirmed that patients who present with idiopathic IDA often have gastritis by endoscopic biopsy and/or serologic abnormalities suggestive of achlorhydria, and they also endorsed the old concept of achlorhydric anemia (29–32). However, none of these authors discussed the research findings that provoked earlier investigators to abandon this syndrome. More importantly, they did not provide evidence that achlorhydria was the causal factor in the association between achlorhydria and IDA, and they did not show that achlorhydria causes enough iron malabsorption to produce IDA. Currently, clinicians in the United States rarely, if ever, make a diagnosis of achlorhydric anemia, and a 2014 review did not mention achlorhydria as a cause of iron deficiency or IDA (33).

We therefore decided to re-evaluate the hypothesis that gastritis-induced achlorhydria is a cause of IDA. To do this, we analyzed currently available research on the association between achlorhydria and IDA and the extent to which achlorhydria causes negative iron balance. We paid attention to specific reasons why earlier researchers rejected this hypothesis.

METHODS

We sought to examine all of the research related to the question posed in the title of this article. Because of substantial species differences (23) and the clinical nature of the questions, we almost exclusively confined our review to research in humans. Recently published articles were found via various search engines. Articles not available electronically were obtained through interlibrary loan. Older articles were found by reviewing the references of more recent articles, books, and symposiums. The effect of achlorhydria on food-iron absorption was evaluated by experiments in which the gain of iron to the body was measured quantitatively. We did not consider articles in which iron absorption was inferred from blood concentrations after the ingestion of iron. We focused on the absorption of iron contained in foods rather than on the absorption of soluble iron salts, which are not an important component of food iron.

ASSOCIATION BETWEEN ACHLORHYDRIA AND IDA

Defining achlorhydria

In the 1930s, the presence or absence of achlorhydria was mainly defined by the concentration of acid in gastric fluid aspirated after the ingestion of various test meals. The parietal cell stimulus was submaximal and variable, and the acid concentration in aspirated stomach contents was influenced by the buffer content of the meal as well as by the amount of acid that was secreted. The augmented histamine test (34) was introduced in 1953 as a measure of maximal gastric acid secretion, with results expressed as quantity of acid secreted per unit of time. There was no meal buffer to reduce acid concentration. Subsequently, a maximal dose of pentagastrin became the preferred stimulus, with similar results compared with histamine (35). The maximal acid secretory response was reproducible (35, 36) and was correlated with the number of parietal cells in the stomach (37) and with the amount of acid secreted after the ingestion of a steak meal (38). This test quantitatively identifies patients with achlorhydria, severe hypochlorhydria, and high-normal gastric acid secretion. Results obtained by maximal stimulation with histamine or gastrin analogs will be used to establish the strength of the association between achlorhydria and IDA.

Increased frequency of achlorhydria in patients with IDA

As shown in Figure 1A, none of 146 European control subjects were achlorhydric, but 3 were severely hypochlorhydric (39, 40).
One study in patients with IDA contained an internal control group of healthy women (third column of Figure 1A), none of whom were achlorhydric or severely hypochlorhydric (41). The next 3 columns show results in groups of European patients with idiopathic IDA in whom the frequency of achlorhydria or severe hypochlorhydria was 37% (41), 40% (42), and 75% (43), respectively. Among these 3 studies, 27 of 61 patients (44%) with idiopathic IDA were either achlorhydric or severely hypochlorhydric compared with 1.8% in all healthy subjects shown in Figure 1, a ratio of 24:1. The final column of Figure 1A shows results in patients with IDA attributed to excess bleeding or idiopathic IDA were either achlorhydric or severely hypochlorhydric. The median acid secretion rate was significantly lower in control women than in control men and was lower in patients with IDA than in control groups (for all comparisons, \( P < 0.01 \)).

Figure 1B shows results of 2 studies from India (44, 45). The first 2 columns show that no instance of achlorhydria was found in a group of Indian control subjects or in a group of Indian patients with IDA due to hookworm infection. However, the median acid secretion rate was lower in those with hookworm than in controls (\( P < 0.01 \)). The last 2 columns of Figure 1B document a high frequency of achlorhydria in patients with idiopathic IDA (45%) or IDA attributed to excess blood loss (30%). The difference between the median acid secretion rate in patients with idiopathic and hemorrhagic IDA was not significant (\( P = 0.054 \)).

**Does achlorhydria precede the development of iron deficiency or IDA?**

It is known that patients with megaloblastic anemia due to autoimmune gastritis are achlorhydric and that achlorhydria associated with autoimmune gastritis precedes the development of megaloblastic anemia. Therefore, if achlorhydria is a cause of IDA, patients who present with megaloblastic anemia due to autoimmune gastritis should be prone to subsequent development of iron deficiency.

In 1965, Callender (46) briefly described 55 patients with PA who had never received iron therapy. Seven of these patients (12.7%) had low serum iron, which in most cases was attributed to menstrual blood loss. In only 2 patients was the low serum iron unexplained, leading the author to conclude that achlorhydria contributes little to the development of iron deficiency.

Two years before Callender’s report, Gibson et al. (24) examined the frequency of new-onset iron deficiency in 138 patients with PA receiving long-term vitamin B-12 maintenance therapy. Fifty-six of these patients (41%) developed iron deficiency at some stage after the first year of treatment, and in 43 of these patients the cause of the iron deficiency was not apparent. The PA was well controlled at the time that iron deficiency developed. Of the 20 women who developed iron deficiency, 17 were postmenopausal. Carmel et al. (26) studied 96 patients with PA who did not have iron deficiency at the time of PA diagnosis. During future therapy with vitamin B-12, 27 (28%) developed iron deficiency. The authors concluded that patients with PA are at high risk of iron deficiency. Atrah and Davidson (27) studied 150 patients with a definitive diagnosis of PA. All had unequivocal megaloblastic bone marrow and vitamin B-12 malabsorption, and all had responded to parenteral vitamin B-12 therapy. Blood samples were examined when the mean duration of PA from diagnosis was 5.8 y, while the patients were receiving maintenance therapy with parenteral vitamin B-12. Hypoferritinemia was found in 23.7% of these patients, and hypochromic microcytic anemia was present in 16.6%. The authors concluded that iron deficiency is a common complication of long-standing treated PA.

In other patients, iron deficiency or IDA occurred before diagnosis of PA or iron deficiency and PA coexisted at the time of clinical presentation (26, 32). However, these sequences do not prove which came first, achlorhydria or iron deficiency.

**Is IDA a cause of gastritis and achlorhydria?**

The consensus opinion in the 1950s and 1960s that IDA was the cause rather than the result of gastritis and achlorhydria was based on 4 observations. First, IDA was an accepted cause of glossitis and stomatitis, and this led to the hypothesis that IDA caused similar epithelial changes in gastric mucosa (17, 21). However, these nongastric lesions reversed with correction of IDA (21), whereas gastritis associated with IDA did not (47).

Second, Leonard (20) found that achlorhydria associated with hypochromic anemia in young men was reversed in 6 of 13 cases by correction of IDA with intravenous iron therapy. This suggested that the achlorhydria associated with idiopathic IDA was often due to iron deficiency. However, in this experiment, gastric acidity was evaluated by a gruel and alcohol test meal, and there was no distinction made between hypochlorhydria and normal gastric acidity. Therefore, this study did not define the degree to which iron therapy increased acid secretion in some achlorhydric patients with idiopathic IDA. Subsequently, maximal gastric acid secretion before and after correction of IDA was measured in 4 experiments (41, 43, 44, 48), the results of which are summarized in **Figure 2**. In 3 studies there was a significant increase (\( P < 0.05 \)) in average maximal acid output after correction of IDA. A total of 22 of the patients shown in Figure 2 were achlorhydric before iron therapy. After correction of IDA, 18 of these 22 patients remained achlorhydric. The other 4 had acid secretion rates of 0.3, 1.0, 1.5, and 1.8 mEq/h, indicating marked hypochlorhydria. Thus, 100% of achlorhydric patients with IDA remained achlorhydric or markedly hypochlorhydric after correction of IDA. These findings do not support the hypothesis that IDA causes chronic gastritis and achlorhydria. It seems likely that the reduced availability of energy to parietal cells in iron-deficient states (49) causes a modest functional reduction in gastric acid secretion, and that correction of iron deficiency allows a small increase in acid secretion in some patients.

Third, Davidson and Markson (19) showed that 50% of patients with IDA without achlorhydria had abnormal gastric biopsy samples, suggesting that gastritis-induced achlorhydria develops after IDA. However, in this study, patients without achlorhydria may have had severe hypochlorhydria, which could have contributed to the development of IDA.

Fourth, groups of patients with IDA attributed to chronic bleeding were found to have a high frequency of achlorhydria (18, 19, 43, 45). If IDA in such patients was exclusively due to bleeding, this would suggest that IDA caused achlorhydria. However, if achlorhydria is a cause of iron malabsorption, this could result in a high frequency of achlorhydria in groups of patients in whom IDA had been attributed solely to blood loss. In this situation, achlorhydria would be a contributor to IDA rather than a consequence of it.

Thus, experimental results previously used to support IDA as a cause of gastritis and achlorhydria have other plausible explanations.
explanations. In reviewing the evidence available today on this question, we found no studies showing that groups of normal acid-secreting patients with IDA later developed a high frequency of achlorhydria. Two experiments in rats revealed no evidence that nutritionally induced IDA caused gastritis or achlorhydria (50, 51). Patients with chronic anemia due to sickle cell disease had a normal average rate of gastric acid secretion, and none were achlorhydric (52). Patients with chlorosis had severe long-standing IDA, but they did not have a high frequency of achlorhydria or hypochlorhydria (3, 7, 10, 53). No achlorhydria was identified in groups of patients with chronic IDA related to hookworm infection (44). We therefore found no convincing evidence that IDA is a cause of gastritis and achlorhydria. This is consistent with the fact that current experts in gastric pathology do not consider IDA to be a cause of chronic gastritis (54).

EFFECT OF ACHLORHYDRIA ON IRON BALANCE

Iron losses from the body

Normal individuals lose iron from exfoliation of cells that contain iron. Such losses are excreted in stool, urine, and sweat or shed from skin and hair. Small additional losses of iron in stool originate from digestive secretions. Normal individuals also have small losses of iron from intestinal bleeding, and iron is lost through menstruation. In 1968, Green et al. (55) measured losses of iron from all body sources in healthy men by injecting radioactive iron intravenously and following the decline in red blood cell activity over several years. The average iron loss was ~1 mg/d in white men (range: 0.63–1.63 mg/d). Comparable studies were not conducted in women, but iron loss due to menstruation is equivalent to 0.5 mg/d (56). Average total iron losses in women who menstruate have been estimated to be 1.4 mg/d (57).

Sutton et al. (58, 59) studied patients with atrophic gastritis and IDA after anemia and iron deficiency had been corrected by iron therapy. Red blood cells were labeled with isotopic chromium and plasma iron was labeled with isotopic iron. Fecal loss of red blood cells did not increase in patients with gastritis. However, daily fecal loss of iron from plasma was almost 2 times higher in patients with gastritis than in control subjects (P < 0.01). The authors calculated that most iron-replete patients with severe atrophic gastritis have at least 0.4 mg excess fecal loss of plasma iron/d (59). It was suggested that this excess loss was derived from an exudate of atrophic and inflamed gastric mucosa (i.e.,

FIGURE 2 Maximal gastric acid secretion (mEq/h) in patients with IDA before and after correction of anemia by treatment with iron (A–D). Results in patients who secreted acid before or after treatment are shown as closed circles. Results in patients who were achlorhydric both before and after treatment are shown in a single open circle; the number of patients in each study who were achlorhydric before and after treatment is shown in the insets. A line of identity is included for each study. P values were determined by Student’s paired t test. IDA, iron deficiency anemia.
an iron-losing enteropathy). There was no explanation of how the authors determined the milligram quantity of plasma iron lost in stool from the quantity of isotopic iron recovered in stool.

Dubach et al. (60) measured fecal iron losses in 4 normal women and in 3 women with severe iron deficiency. After intravenous injection of radiolabeled iron, the amount of isotopic iron excreted in feces was determined. From this, and from the ratio of total hemoglobin iron to total hemoglobin radioiron, the authors calculated that fecal iron loss averaged 0.4 mg/d in healthy women and only 0.04 mg/d in women with severe iron deficiency. Iron losses from nonfecal routes were not measured.

Chemical measurement of iron intake and iron excretion in stool and urine

These studies are conducted in a metabolic ward, where under steady state conditions iron output in stool and urine are subtracted from the iron content of ingested food. The meticulous requirements for accurate measurement of iron intake and output by this method have been well described (61). In one such experiment (62), iron intake averaged 11 mg/d and average iron balance was +0.5 mg/d in normal subjects and −2 mg/d in achlorhydric subjects (P = 0.01). However, for 2 reasons these results cannot be accepted as evidence that achlorhydria reduces iron balance. First, the experimental periods were too short (only 6 d) to guarantee steady state conditions and there was only 1 balance period for each subject. Second, in some subjects, the measured output of iron in stool was unrealistically high. This suggests that the intake of iron was higher than the investigators intended, either due to contamination of food or surreptitious protocol deviations. We found no other such studies in achlorhydric patients.

Use of isotopes to measure absorption of food iron

There are 2 main types of iron in foods, each of which can be tagged with an iron isotope (63–67). Nonheme iron is mainly composed of inorganic ferric salts (e.g., ferric oxides) that are not soluble in water. Most dietary nonheme iron is contained in plants (fruit, vegetables, grains, nuts), but meats (especially poultry) also contain considerable amounts of nonheme iron. Heme iron is an organic form of iron that exists mainly in the porphyrin ring of myoglobin and hemoglobin in meats. When meats are cooked, a variable fraction of their heme iron is converted to nonheme iron (68). Trace amounts of heme iron are also present in plants. Björn-Rasmussen et al. (63) calculated iron consumed by Swedish military recruits from a 6-wk master menu. The total intake of dietary iron was 17.4 mg/d. Nonheme iron constituted 16.4 mg/d (94%) and heme iron constituted 1 mg/d (6%) of total dietary iron intake. As pointed out by Finch and Huebers (23), the importance of heme to total iron absorption is often limited by the relatively small amount that is present in the diet.

Nonheme food iron can be labeled with an iron isotope in 2 ways. With intrinsic labeling, using bread as an example, wheat is grown in soil containing an iron isotope. Consequently, the flour’s iron content is biosynthetically tagged with the isotope. Iron in bread made from this flour is uniformly labeled with the isotope (69) and no food-free isotope is present. With extrinsic labeling, the isotope is mixed with foods before a meal is eaten and it is assumed that the isotope equilibrates with all of the nonheme iron contained in the various foods that comprise the meal (63, 70). With either method of tagging, the absorption of the isotope can be accurately measured by the body content of the isotope several weeks after the ingestion of a test meal (66). The absorption of isotopic iron can also be calculated from fecal isotopic excretion, but this method is less accurate because it depends on complete stool collection.

Effect of achlorhydria on solubility and absorption of isotopically labeled nonheme iron

Bezwoda et al. (69) incubated intrinsically labeled bread in vitro with gastric juice that had been aspirated from different subjects after the injection of histamine, and measured the fraction of isotopic iron that became soluble. As shown in Figure 3A, when the pH of gastric juice was between 4 and 7 isotopic iron solubility was near zero. As the pH of gastric juice decreased below 4, iron solubility increased to as high as 52%.

In additional experiments by Bezwoda et al., patients with IDA consumed a test meal containing this tagged bread iron plus a hamburger steak. In vivo absorption of isotopic iron in a given patient was well correlated with in vitro solubility of the bread iron in gastric juice taken from that patient (Figure 3B). These

![Figure 3](https://academic.oup.com/ajcn/article-abstract/102/1/9/4564242/4564242/fi03.png)
results indicate that nonheme iron in bread that is not made soluble by acid gastric juice remains virtually unabsorbable in the small intestine, even in patients with IDA whose duodenal mucosa is primed to absorb iron at a high rate. Note that in this experiment the meal contained a hamburger steak. This meal did not prevent severe malabsorption of nonheme iron by achlorhydric patients. Also important, when gastric juice from patients with IDA had higher than average amounts of acid there was a corresponding increase in the solubility and absorption of nonheme iron.

As shown in the first section of Table 1 and Figure 4A, the effect of achlorhydria on nonheme-food-iron absorption was measured in 10 studies by using radioactive iron (14, 15, 69, 71–78). In comparison to acid-secreting subjects, all of the studies showed at least some reduction in nonheme-iron absorption by achlorhydric patients. Combining results from all 10 studies, isotopic iron absorption in achlorhydric patients averaged 12%. If achlorhydric patients absorbed 12% of nonheme iron from a typical Western diet, they would absorb enough iron to balance normal iron losses, which would mean that achlorhydria could not be an independent cause of IDA. All of the information in Table 1 and Figure 4A was potentially available to Finch and Huebers in 1991 (23), and this may explain why they concluded that, in humans, achlorhydria does not appear sufficient to produce iron deficiency.

Another feature of the results shown in Figure 4A is large variation in nonheme-iron absorption, both in acid secretors and in achlorhydric patients. This variation was present even when patients with normal iron status and patients with IDA were considered separately. In searching for an explanation, in Figure 4B we plotted the results of isotopic iron absorption as measured by intrinsic tagging. In 4 such studies, the average absorption of isotopic nonheme iron by achlorhydric patients was 0.9%. In contrast, as shown in Figure 4C, with extrinsic tagging the average absorption of isotopic nonheme iron by achlorhydric patients was 18.7%. The examination of data from 2 studies in iron-deficient patients revealed that extrinsic tagging produced approximately equal high values of isotopic iron absorption in comparison to intrinsic tagging at all amounts of gastric acid secretion (from achlorhydria to hyperchlorhydria) (69, 75).

In our opinion, the most likely explanation for the discrepancy between intrinsic and extrinsic tagging is the frequent failure of an extrinsic tag to be totally and exclusively incorporated into nonheme food iron, so that a variable fraction of water-soluble isotopic iron is not tagged to nonheme food iron and is freely available for absorption in the duodenum. This potential source of error with extrinsic tagging was emphasized by Moore (70) in 1968, but other researchers later found similar results with intrinsic and extrinsic tagging (76, 77, 79). Nevertheless, the results shown in Figure 4 suggest that the absorption of nonheme iron in food is substantially underestimated in some studies that use extrinsic tagging. This could explain the paradox noted by Cook et al. (80), in which ascorbic acid given to normal volunteers caused a 5-fold increase in the absorption of isotopic iron that had been extrinsically tagged to nonheme iron in test meals, yet failed to result in any increase in iron reserves over a long period of time. In other words, ascorbic acid caused a marked increase in the retention of an iron isotope added to meals, but ascorbic acid did not cause increased retention of nonsotopic iron contained in foods that were eaten.

Intrinsic tagging is the gold standard for quantitating the fraction of physical nonheme iron in food that is absorbed and retained in the body (70, 79), and results with this method indicate that fractional nonheme food iron absorption is only ~1% in achlorhydric patients, even in those who have IDA (69). Conversely, patients with IDA who secreted gastric acid at high-normal rates absorbed as much as 56% of intrinsically labeled nonheme iron (Figure 3B).

As shown in the second section of Table 1, in normal subjects, the inhibition of gastric acidity with an H2 receptor antagonist or with a liquid antacid reduced nonheme iron absorption (22). We found no quantitative studies on the effect of proton pump inhibitors on the absorption of nonheme dietary iron.

The absorption of isotopically labeled ferric iron salts or nonheme food iron increased in achlorhydric patients when test meals were premixed with acid or with gastric juice from normal individuals (73, 81, 82). The stimulating effect of normal gastric juice was due mainly to hydrochloric acid, but to a lesser extent neutralized normal gastric juice also increased isotopic iron absorption by achlorhydric patients (82).

**Effect of achlorhydria on ascorbic acid stimulation of nonheme iron absorption**

As shown in the third section of Table 1, in acid-secreting subjects ascorbic acid markedly stimulated the absorption of an iron isotope that had been intrinsically tagged to nonheme iron in bread (Δ = +53%). In achlorhydric patients, ascorbic acid stimulated nonheme-iron absorption to a much lesser extent (71). Thus, a powerful stimulant of nonheme-iron absorption in acid-secreting individuals is markedly attenuated in achlorhydric patients. However, ascorbic acid promoted nonheme-iron absorption in achlorhydric patients from 0.1% to 11.3%, indicating that this acidic substance promoted the solubility of nonheme iron even in the absence of secreted gastric acid. The chemistry underlying the effects of ascorbic acid on iron solubility and absorption has been well described by Conrad and Schade (83).

**Effect of achlorhydria on iron absorption from heme and hemoglobin**

Isotopically labeled pure heme iron from hemolyzed erythrocytes is absorbed normally by achlorhydric patients (69). With the use of a test meal containing isotopically labeled heme iron in hemoglobin, Biggs et al. (16) found that iron absorption in achlorhydric and acid-secreting patients was similar. These results are questionable because isotopic absorption was measured by subtracting isotopic recovery in stool from oral intake of isotope and because there is no evidence that stools were collected under closely supervised conditions. Waxman et al. (84) used whole-body counting to measure the absorption of isotopically labeled heme iron in hemoglobin. Absorption in iron-deficient patients who secreted gastric acid averaged 19.6%, whereas achlorhydric patients with iron deficiency absorbed 10.4%. This malabsorption was corrected by normal gastric juice (10.4–23.3%) but not by gastric juice from patients with PA (10.4–11.9%). Thus, in the setting of iron deficiency, achlorhydric patients absorbed pure heme iron normally (69), but they malabsorbed heme iron contained in hemoglobin (84).

The combination of normal absorption of pure heme iron and malabsorption of heme iron contained in hemoglobin by achlorhydric patients might be explained by a reduction in peptic activity...
TABLE 1
Effect of achlorhydria on absorption of isotopic nonheme iron

<table>
<thead>
<tr>
<th>Authors, year, country (ref)</th>
<th>Subjects</th>
<th>Food, tag, iron intake</th>
<th>Average radioiron absorption, %</th>
<th>P (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotope tagged to nonheme iron in food</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moore and Dubach, 1951, USA (14)</td>
<td>Achlorhydric patients vs. normal subjects</td>
<td>2–3 Eggs, intrinsic tag Iron: 3–4 mg</td>
<td>Secretors (n = 10): 4.00 Achlorhydria (n = 3): 1.20</td>
<td>P = 0.135 (−70%)</td>
</tr>
<tr>
<td>Pirzio-Birolli et al., 1958, USA (15)</td>
<td>Achlorhydric patients with PA in remission vs. normal students</td>
<td>Standard mixed meal, extrinsic tag Iron: 4.6 mg/meal</td>
<td>Secretors (n = 8): 6.35 Achlorhydria (n = 4): 3.50</td>
<td>P = 0.734 (−17%)</td>
</tr>
<tr>
<td>Williams, 1959, England (71)</td>
<td>Achlorhydric vs. acid-secreting patients</td>
<td>Bread with high PO4/Fe, intrinsic tag Iron: 0.6–0.7 mg</td>
<td>Secretors (n = 4): 6.40 Achlorhydria (n = 4): 0.10</td>
<td>P = 0.01 (−98%)</td>
</tr>
<tr>
<td>Goldberg et al., 1963, Scotland (72)</td>
<td>Iron-deficient patients with and without achlorhydria</td>
<td>Normal foods, extrinsic tag Iron: 12.5 mg/meal</td>
<td>Secretors (n = 8): 57.5 Achlorhydria (n = 7): 18.5</td>
<td>P &lt; 0.01 (−68%)</td>
</tr>
<tr>
<td>Cook et al., 1964, Canada (73)</td>
<td>Achlorhydric patients with PA in remission vs. controls</td>
<td>Bread (low-iron), extrinsic tag Iron: 170 µg/meal</td>
<td>Secretors (n = 9): 35.2 Achlorhydria (n = 9): 19.8</td>
<td>P = 0.01 (−44%)</td>
</tr>
<tr>
<td>Turnbull, 1965, England (74)</td>
<td>Patients with IDA with and without achlorhydria</td>
<td>Standard mixed meal, extrinsic tag Iron: 8 mg; ascorbic acid, 25 mg</td>
<td>Secretors (n = 10): 54.1 Achlorhydria (n = 7): 29.3</td>
<td>P &lt; 0.001 (−46%)</td>
</tr>
<tr>
<td>Jacobs et al., 1966, Wales (75)</td>
<td>Twenty patients with IDA, maximal acid secretion measured</td>
<td>Mixed meal, extrinsic tag Iron: 10 mg/meal</td>
<td>Secretors (n = 15): 44.8 Achlorhydria (n = 5): 39.0</td>
<td>P = 0.652 (−13%)</td>
</tr>
<tr>
<td>Björn-Rasmussen et al., 1973, Sweden (76, 77)</td>
<td>Achlorhydric patients with PA in remission vs. student controls</td>
<td>Soybean meal, intrinsic tag Iron: 2.2 mg/meal</td>
<td>Secretors (n = 15): 2.62 Achlorhydria (n = 5): 0.70</td>
<td>P = 0.067 (−73%)</td>
</tr>
<tr>
<td>Bezwoda et al., 1978, South Africa (69)</td>
<td>Twenty-four patients with IDA, gastric acidity after maximal dose of pentagastrin</td>
<td>Bread, intrinsic tag Iron: 1.4 mg/meal</td>
<td>Secretors (n = 20): 24.1 Achlorhydria (n = 4): 1.5</td>
<td>P &lt; 0.001 (−94%)</td>
</tr>
<tr>
<td>Björn-Rasmussen and Hallberg, 1979, Sweden (78)</td>
<td>Achlorhydric patients with PA in remission vs. normal subjects</td>
<td>Maize porridge, ferrous sulfate; extrinsic tag Iron: 5.0 mg/meal</td>
<td>Secretors (n = 8): 1.69 Achlorhydria (n = 4): 0.65</td>
<td>Unknown (−62%)</td>
</tr>
</tbody>
</table>

Effect of cimetidine and antacid

| Skikne et al., 1981, USA (22) | Normal volunteers with and without drug-induced inhibition of gastric acidity | Beef, potatoes, milkshake; extrinsic tag Iron: 4.8 mg | Control (n = 8): 3.72 | P < 0.05 (−65%) |
| Björn-Rasmussen and Hallberg, 1979, Sweden (78) | Achlorhydric patients with PA in remission vs. normal subjects | Maize porridge, ferrous sulfate; extrinsic tag Iron: 5.0 mg/meal | Secretors (n = 8): 1.69 Achlorhydria (n = 4): 0.65 | Unknown (−62%) |
| Effect on ascorbic acid stimulation of iron absorption | Four achlorhydric patients and 4 normal subjects | Bread with intrinsic tag ≥ ascorbic acid Iron: 0.6–0.7 mg | Secretors: 6.4→59.0 | P = 0.002 (−79%) |
| Italo et al., 1989, Italy (13) | Patients with IDA, maximum acid secretion measured | Mixed meal, extrinsic tag Iron: 10 mg/meal | Secretors (n = 15): 44.8 Achlorhydria (n = 5): 39.0 | P = 0.652 (−13%) |
| Williams, 1959, England (71) | Four achlorhydric patients and 4 normal subjects | Bread with intrinsic tag ≥ ascorbic acid Iron: 0.6–0.7 mg | Secretors: 6.4→59.0 | P = 0.002 (−79%) |

1This table does not include 2 studies in which test meals contained soluble iron salts without food, because the relevance of such studies to the development of IDA due to achlorhydria is questionable. One of these studies showed no effect of achlorhydria on iron absorption, whereas the other showed a marked reduction in iron absorption in achlorhydric patients (Boddy K, Will G. Iron absorption in Addisonian pernicious anemia. Am J Clin Nutr 1969;22 (12):1555–58; Celada A, Rudolf H, Herreros V, Donath A. Inorganic iron absorption in subjects with iron deficiency anemia, achyilia gastrica and alcoholic cirrhosis using a whole-body counter. Acta Haematol 1978;60:182–92.) We did not consider indirect methods for estimating iron absorption, such as serum concentrations after ingestion of iron. IDA, iron deficiency anemia; PA, pernicious anemia; ref, reference.

2We used the authors’ uncorrected data; “corrected” data were also presented where isotopic iron absorption was adjusted for the assumed effects of iron status. The results of corrected data were qualitatively similar to uncorrected results.

3The authors did not give a P value, and we were unable to calculate it with the data that were presented.

of gastric juice that contains no acid. The resulting reduction in gastric digestion of hemoglobin would delay the release of free heme from hemoglobin. Subsequent digestion of hemoglobin by pancreatic enzymes might release free heme in a region of the small intestine that is not optimally designed for heme absorption. As with nonheme iron, heme iron is absorbed preferentially in the duodenum, at least in rats (85). Unfortunately, we found no study on the effect of achlorhydria on the absorption of heme iron contained in natural meats. Presumably, the reduced acidity and peptic activity of gastric juice would result in an even greater reduction in heme absorption from meat than was observed with hemoglobin.

Does gastritis-induced achlorhydria produce enough iron malabsorption to cause iron deficiency?

For achlorhydria to be an independent cause of iron deficiency or IDA, iron malabsorption due to achlorhydria would have to be severe enough to result in negative iron balance, in which physiologic losses of iron from the body exceed the absorption of
iron from the diet. Because metabolic balance studies have not been successfully carried out in patients with achlorhydria, the absorption of dietary iron has only been accurately measured by fractional absorption of isotopes by using biosynthetic tagging. Fractional isotopic absorption, multiplied by the milligram per day amounts of iron in the diet, provides a measure of the milligram per day quantity of food iron that is absorbed into the body.

In the following analysis, we assumed consumption of a typical Western diet (63, 66, 86) containing 15 mg iron/d, 90% as nonheme iron and 10% as heme iron. We used absorption of intrinsically labeled bread iron as a surrogate for nonheme-iron absorption because results with bread are available in both normal subjects (71) and patients with IDA (69) and because wheat is a major source of dietary nonheme iron (87–89). As shown in Table 1, subjects without IDA absorbed 6.4% of nonheme iron in bread if they secreted gastric acid and 0.1% if they were achlorhydric (71). Acid-secreting patients with IDA absorbed an average of 24.1% of nonheme iron in bread and absorbed 1.5% if they were achlorhydric (69). As a surrogate for the absorption of heme iron from natural meat we used the absorption of heme iron contained in hemoglobin as reported by Waxman et al. (84) (i.e., 10.0% in normal subjects, 19.6% in acid-secreting patients with iron deficiency, and 10.4% in achlorhydric patients with iron deficiency). No information was found with regard to heme-iron absorption in achlorhydric non–iron-deficient patients, so we assumed their absorption would be equal to that in normal acid-secreting subjects (i.e., 10%).

Using this meal and these fractional absorption values, we calculated that iron absorption in a normal man would be 1.01 mg/d. This is almost identical to the average daily loss of iron from the body in healthy men who are considered to be in iron balance (55). Next, we assumed that this man developed a transient episode of bleeding that depleted his iron stores. While consuming the same diet his iron absorption would be 3.54 mg/d. This is much higher than his physiologic iron losses of 1 mg/d, and his iron balance would be +2.54 mg/d. Over time, his iron stores would be restored.

If a man with normal iron stores developed gastritis and achlorhydria, while consuming this same diet he would absorb 0.16 mg iron/d. Iron losses would initially be 1 mg/d and iron balance would be −0.84 mg/d. Over time, iron stores would be reduced. His heme- and nonheme-iron absorption would then increase from 10% to 10.4% and from 0.1% to 1.5%, respectively, leading to iron absorption of 0.36 mg/d. When physiologic iron losses ultimately decreased from 1 to 0.36 mg/d because of reduced iron stores (60), the patient would again be in iron balance. From that point on there would be no further depletion of body iron, and no recovery from his iron-deficient state.

**DISCUSSION**

With the use of data based on maximal stimulation of gastric acid secretion, previous work showed that the frequency of achlorhydria (or severe hypochlorhydria) in groups of patients with idiopathic IDA was 44% compared with 1.8% in groups of control subjects. In the absence of an identifiable spurious third factor that simultaneously causes both achlorhydria and IDA, the strength of this association suggests either that IDA is a cause of gastritis and achlorhydria or that gastritis and achlorhydria is a cause of IDA. To establish which is cause and which is effect on the basis of correlational data, the supposed cause must be shown to precede the supposed effect in time (90, 91). In this regard, patients who presented with megaloblastic anemia due to autoimmune gastritis were followed longitudinally in 4 studies, and a high frequency of iron deficiency was documented in 3 of them (24, 26, 27). Because achlorhydria is present in most if not all patients with autoimmune gastritis and megaloblastic anemia, achlorhydria must have preceded the development of iron deficiency.
in other foods. We found only 1 valid measurement on the effect of achlorhydria on heme-iron absorption from hemoglobin (84), and no study on the effect of achlorhydria on absorption of heme iron in natural meat. Further human research with radioactive iron isotopes may not be forthcoming because of concerns about radiation toxicity.

Despite these limitations, in our opinion there are 3 research findings that, in combination, strongly indicate that gastritis and achlorhydria can be an independent cause of IDA. First, correlational data suggest that achlorhydria is the causal factor in the association between IDA and achlorhydria. Second, experimental results with intrinsically labeled radioisotopes indicate that achlorhydria causes food-iron absorption to decrease below the generally accepted rate of physiologic iron loss from the body, which would cause negative iron balance. And third, there is no evidence that iron deficiency or IDA can cause gastritis and achlorhydria.

If achlorhydria becomes an accepted cause of IDA there are several clinical and pathophysiologic issues that deserve mention. First, in adult patients who present with idiopathic IDA, the differential diagnosis would need to be expanded to include achlorhydria in addition to undiscovered intermittent hemorrhage (12). However, it is only after an age-appropriate search for potential bleeding lesions has been conducted, with negative results, that achlorhydria should be considered as the primary cause of idiopathic IDA. The main goal of such caution is to avoid missing occult colonic or gastric carcinoma (96). Second, at the present time, it is not possible to make a definitive diagnosis of achlorhydria in an individual patient due to lack of histamine or pentagastrin to stimulate gastric acid secretion. Therefore, gastric biopsy alone is not a reliable indicator of the presence or absence of achlorhydria in an individual patient. Unless new gastric stimulants become available, serologic tests for pepsinogens (98) in combination with gastric biopsy and pH of fasting gastric juice obtained during endoscopy will have to suffice. Third, although the association between IDA and achlorhydria is stronger in women than in men, achlorhydria is a common finding in young healthy men with idiopathic IDA (20). Fourth, on average, patients with achlorhydria and IDA respond somewhat slower to oral therapy than in men, achlorhydria is a common finding in young healthy

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According to our interpretation, the main reason why achlorhydria causes negative iron balance is because the stimulation of duodenal iron absorptive capacity in response to iron deficiency cannot compensate for the lack of solubility of dietary iron (Figure 3). This is different from reduced iron absorption caused by a reduction in dietary iron intake (61), which is common in underdeveloped countries (87). In this condition, stimulated duodenal iron transport mechanisms can increase the fraction of iron absorbed from an iron-deficient diet. However, the degree to which fractional absorption actually increases would be dependent on the amount of gastric acid that is secreted (Figure 3). Individuals with low acid secretion would be more likely to develop IDA than those with high-normal acid secretion. In Scotland, 2 patients with severe IDA attributed primarily to reduced iron intake had maximal gastric acid outputs of only 0 and 4.8 mEq/h (43).

Much of the evidence on which our conclusions are based can be criticized. The studies that showed a strong association between achlorhydria and idiopathic IDA rarely contained an internal control group of healthy subjects without IDA who had their secretory status measured contemporaneously. However, results with maximal stimulation of acid secretion are reproducible (35, 36) and should allow valid comparison between normal subjects in one study with achlorhydric patients in another. Although we know of no one who has criticized the validity of nonheme-food-iron absorption measured with intrinsic isotope tagging, the available results with this method have 2 limitations. The number of achlorhydric subjects studied by the intrinsic tagging method is quite small, as shown in Table 1. In addition, intrinsic tagging involves labeling only 1 food source of nonheme iron, and results obtained with 1 food do not necessarily apply to nonheme iron in other foods.
a recurrence of IDA within the next 5–10 y. Sixth, the underlying chronic gastritis in patients with achlorhydria has only 2 known causes, autoimmunity and Helicobacter pylori. Patients with IDA associated with achlorhydria should be examined for evidence of these 2 diseases. Seventh, in addition to IDA and PA, patients with gastritis and achlorhydria often develop bacterial overgrowth in the stomach and upper small intestine, they have reduced defense against some infections, they absorb some drugs poorly, and they may have an increased likelihood of developing gastric malignancies. Eighth, prolonged treatment with drugs that reduce gastric acid secretion may contribute to the development of IDA. However, in clinical practice, an association between antisecretory drugs and IDA might be due to the prescription of such drugs for gastrointestinal symptoms, rather than because these drugs reduce iron absorption. Ninth, as suggested by others (100), the suppression of gastric acid secretion might be helpful in reducing iron absorption in some patients with iron overload. Tenth, high-normal gastric acid secretion mitigates the development and severity of iron deficiency and IDA in patients with excess bleeding, poor dietary iron intake, or increased demands for iron.

The authors’ responsibilities were as follows—ALB and JSF: designed the research and interpreted the results; CASA: analyzed data and was responsible for the final content. The authors declared no conflicts of interest.

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