

## THE PREVALENCE OF OCCULT GASTROINTESTINAL BLEEDING IN CELIAC SPRUE

KENNETH D. FINE, M.D.

**Abstract Background.** Iron deficiency complicating celiac sprue is usually attributed to the malabsorption of dietary iron or the loss of iron from the intestinal mucosa. There has been little investigation of the role of intestinal loss of blood in patients with this condition. The purpose of this study was to determine the prevalence of occult gastrointestinal bleeding in patients with celiac sprue.

**Methods.** We tested one 48- or 72-hour stool collection from each of 8 patients with partial villous atrophy and 28 patients with total villous atrophy using a guaiac-impregnated card (Hemoccult). Serving as controls were 18 normal subjects, each studied before and during laxative-induced diarrhea; 17 patients with idiopathic chronic diarrhea; 63 patients with microscopic colitis; 23 patients with pancreatic steatorrhea; and 7 patients with treated celiac sprue who had normal intestinal histologic features. All the patients underwent a diagnostic workup

IRON deficiency is frequent in patients with celiac sprue<sup>1-3</sup> and may rarely cause anemia in such patients in the absence of diarrhea and steatorrhea.<sup>4-9</sup> Malabsorption of dietary iron is presumed to be the predominant cause of this iron deficiency,<sup>10-12</sup> with the loss of iron contained in rapidly proliferating and sloughing enterocytes a less important factor.<sup>13,14</sup> Only rarely has gastrointestinal bleeding been mentioned as a possible factor contributing to iron deficiency in patients with celiac sprue.<sup>15,16</sup> In two small studies in which this question was addressed with the use of intravenously injected red cells labeled with chromium-51, fecal excretion of chromium-51 in amounts indicative of gastrointestinal bleeding occurred in two of six patients in one study<sup>15</sup> and in one of six patients in the other.<sup>14</sup> There have been no studies of the prevalence of gastrointestinal bleeding in large groups of patients with celiac sprue.

The purpose of this study was to determine the prevalence of gastrointestinal blood loss in patients with a lesion on biopsy of the small intestine consistent with celiac sprue. Because tests using guaiac as a reagent have been the mainstay in detection of occult gastrointestinal bleeding for over 130 years,<sup>17</sup> widely available, guaiac-impregnated cards (Hemoccult) were used to detect fecal occult blood in stool samples collected over 48 or 72 hours. In addition to its relevance to the pathophysiology of negative iron balance in patients with celiac sprue, the frequency of Hemoccult positivity is also important in terms of the predictive value of this test

that included esophagogastroduodenoscopy, colonoscopy, and barium radiography of the small bowel.

**Results.** Positive Hemoccult tests were infrequent in each of the control groups, occurring in 0 to 8 percent of the subjects, whereas 2 of the 8 patients with partial villous atrophy (25 percent) and 15 of the 28 patients with total villous atrophy (54 percent) had positive tests. When the patients with total villous atrophy were classified according to their subsequent responses to a gluten-free diet, 7 of the 17 who were responsive to gluten withdrawal (41 percent) were Hemoccult-positive, as compared with 8 of the 11 who did not respond to the diet (73 percent).

**Conclusions.** Occult gastrointestinal bleeding can be detected in about half of patients with celiac sprue and should be added to the list of factors that can contribute to iron deficiency in patients with this disorder. (N Engl J Med 1996;334:1163-7.)

©1996, Massachusetts Medical Society.

for gastrointestinal cancer, which is disproportionately frequent in such patients.<sup>18-20</sup>

### METHODS

#### Patients with Villous Atrophy

Thirty-six patients (21 women and 15 men, 18 to 76 years of age) who were evaluated between 1985 and 1995 and who had small-intestinal biopsies showing pathological features of celiac sprue had tests for occult blood in stool samples collected over 48 or 72 hours. Eight of these patients, who had been given a diagnosis of celiac sprue years earlier and were already eating a gluten-free diet, had partial villous atrophy. Although their health had improved after the diagnosis and the initiation of dietary therapy, they were still having symptoms, including intermittent diarrhea in five, probably due to admitted dietary indiscretions. The remaining 28 patients, whose celiac sprue had been diagnosed recently, had total villous atrophy. Five had nonspecific abdominal symptoms, bone pain, or iron-deficiency anemia but no diarrhea; the other 23 were evaluated mainly for diarrhea, with or without weight loss. These patients were treated with a gluten-free diet; 17 had rapid clinical improvement, which is consistent with a diagnosis of celiac sprue, whereas 11 had no clinical improvement during treatment with a gluten-free diet and corticosteroids for at least six months, which is consistent with a diagnosis of refractory sprue.<sup>21</sup>

#### Control Groups

Tests for occult blood in quantitative stool collections were also done in the following control groups: group 1 — 18 normal subjects (11 women and 7 men, 23 to 62 years of age) who had no gastrointestinal symptoms or other medical problems; group 2 — the same 18 normal subjects during a period of diarrhea induced with either 60 g of sorbitol per day or 720 mg of phenolphthalein per day for four consecutive days; group 3 — 17 patients (10 men and 7 women, 33 to 72 years of age) given a diagnosis of chronic idiopathic diarrhea after an extensive diagnostic evaluation for other causes of diarrhea was negative (this entity was chosen because it is a clinical diarrheal state not associated with anatomical or pathologic abnormalities of the gastrointestinal tract; the clinical features of these patients [excluding the results of the fecal guaiac tests] have been reported previously<sup>22</sup>); group 4 — 63 patients (51 women and 12 men, 28 to 84 years of age) with microscopic colitis (these patients also had extensive evaluations ruling out other causes of chronic diarrhea, including small-intestinal villous atrophy; this disease was chosen because some patients with

From the Department of Gastrointestinal Research, Baylor University Medical Center, 3500 Gaston Ave., Dallas, TX 75246, where reprint requests should be addressed to Dr. Kenneth Fine.

Supported by a Public Health Service grant (5-R01-DK37172-05) from the National Institute of Diabetes and Digestive and Kidney Diseases and by the Southwest Digestive Disease Foundation.

celiac or refractory sprue have microscopic colitis<sup>23,24</sup>); group 5 — 23 patients (17 men and 6 women, 34 to 77 years of age) with steatorrhea due to chronic pancreatitis, representing a control group with nutrient malabsorption but normal intestinal histologic features; and group 6 — 7 patients (5 women and 2 men, 29 to 62 years of age) with a previous diagnosis of celiac sprue who had followed a gluten-free diet for a minimum of six months (documented by the disappearance of anti-gliadin IgA antibodies in serum) and who had biopsy-proved normalization of histologic findings in the small intestine.

These studies were approved by the institutional review board for the protection of human subjects of Baylor University Medical Center, and informed consent was obtained from all subjects.

### Diagnostic Evaluation

The patients with villous atrophy and the patients in control groups 3, 4, and 5 underwent extensive diagnostic evaluation for chronic diarrhea that included esophagogastroduodenoscopy, colonoscopy, and barium radiography of the small intestine. Blood was drawn from patients with villous atrophy and normal subjects for measurement of hemoglobin and serum iron by routine clinical methods.

Each study subject collected all stools passed over a 48- or 72-hour period. (Some normal subjects collected stools for more than one period when diarrhea was induced experimentally.) Immediately after a sample was brought to the laboratory, two sites within the undisturbed specimen container were tested for occult blood with Hemocult II (specimens analyzed between 1985 and 1990) or Hemocult Sensa (specimens analyzed between 1991 and 1995) (SmithKline Diagnostics, San Jose, Calif.).

### Statistical Analysis

Fisher's exact test was used to compare the rates of positive Hemocult tests in the patients with villous atrophy and the control groups. The two-tailed Student's t-test was used to compare the means of hematologic variables in patients with villous atrophy who were Hemocult-positive and those who were Hemocult-negative. Nonlinear regression analysis of the relation between hematologic variables and fecal weight was performed with the use of JMP Statistics and Graphics, version 3.1 (SAS Institute, Cary, N.C.).

## RESULTS

### Control Groups

Six percent of the normal subjects (1 of 18) had positive Hemocult tests at base line (Table 1). When diarrhea was induced in these subjects, the percentage with Hemocult-positive stool samples did not change, despite a threefold increase in fecal weight and mean ( $\pm$ SD) fecal frequency (from  $1.4 \pm 1.4$  to  $3.7 \pm 2.1$  bowel movements per day). The percentage of patients in the various control groups with positive Hemocult tests was similar. All the patients with previously diagnosed and treated celiac sprue had negative tests for fecal occult blood. The results of upper and lower gastrointestinal endoscopy and radiography of the small intestine were normal in all these patients.

### Patients with Villous Atrophy of the Small Intestine

#### Positivity of Hemocult Tests

The percentage of positive Hemocult tests in patients with villous atrophy of the small intestine was significantly higher than that in either the normal subjects or the control patients and increased along a continuum from previously treated patients with celiac sprue who had partial villous atrophy (25 percent), through patients with a new diagnosis of celiac sprue who had total villous atrophy (41 percent), to patients with refrac-

tory sprue who had total villous atrophy (73 percent) (Table 1). The percentage of positive tests among the 28 patients with total villous atrophy was 54 percent, and among all 36 patients with partial or total villous atrophy it was 47 percent.

#### Results of Diagnostic Evaluations

None of the patients with villous atrophy had any lesions visible on upper or lower gastrointestinal endoscopy that would be expected to cause gastrointestinal blood loss, such as mucosal ulceration or vascular malformations. Radiographs of the small intestine were normal in 11 patients and abnormal in the remaining 25, showing some combination of intestinal dilatation, irregularity or loss of the mucosal pattern, increased luminal fluid, edematous folds, and flocculation of the barium column. No patient had ulcers, masses, or any other evidence of a small-intestinal tumor or other source of bleeding.

#### Results of Hemocult Tests in Patients with and Those without Diarrhea

Because the presence of fluid and electrolyte malabsorption in patients with the pathologically determined lesion of celiac sprue correlates with more extensive villous atrophy in the small intestine and the absence of such malabsorption with a more limited extent of atrophy,<sup>25,26</sup> the prevalence of positive Hemocult tests was compared in patients with celiac or refractory sprue who had symptomatic diarrhea and those who did not have it. Among the eight patients with no diarrhea (who presented mainly with abdominal pain or were found to be iron-deficient), only one had Hemocult-positive stools (12 percent). Among the 28 patients with diarrhea, 16 had Hemocult-positive stools (57 percent;  $P=0.04$  for the comparison with patients with sprue who had no diarrhea).

#### Relation of Hemocult-Test Results to Hematologic Values

The mean values for hemoglobin and serum iron concentrations between the patients with villous atrophy who were Hemocult-negative and those who were Hemocult-positive are shown in Table 2. The mean concentrations of both hemoglobin and serum iron were lower in the Hemocult-positive patients, but only the difference in hemoglobin concentration was statistically significant ( $P=0.04$ ).

To determine whether the hemoglobin or serum iron values in the patients with villous atrophy were in any way related to a variable other than the Hemocult-test result, such as the severity of diarrhea (one marker of disease severity), these hematologic values were plotted against fecal weight (Fig. 1). The values on both blood tests correlated with fecal weight in a curvilinear manner.

## DISCUSSION

The main finding of this study is that patients with celiac or refractory sprue often have Hemocult-positive stools. Although the cause of the positive Hemoc-

Table 1. Fecal Weight, Fecal Fat, and Hemocult-Test Positivity in the Control Groups and in Patients with Villous Atrophy.

GROUP OF SUBJECTS	NO. OF STOOL SPECIMENS*	FECAL WEIGHT†	FECAL FAT†	NO. (%) OF HEMOCULT-POSITIVE SUBJECTS	P VALUE‡	ODDS RATIO (95% CI)‡
<b>Control group</b>						
Normal subjects (n = 18)						
With normal stools	18	133±55	—§	1 (6)		
With induced diarrhea	50	361±156	—§	3 (6)		
Patients with idiopathic secretory diarrhea (n = 17)	17	627±252	6±4	0 (0)		
Patients with microscopic colitis (n = 63)	63	537±341	5±3	5 (8)		
Patients with pancreatic insufficiency (n = 23)	23	562±412	43±34	1 (4)		
Patients with previously treated celiac sprue and normal small-intestinal histology (n = 7)	7	188±89	3±2	0 (0)		
All control subjects (n = 128)	178	—	—	10 (6)		
<b>Patients with villous atrophy</b>						
Previously treated patients with celiac sprue and partial villous atrophy (n = 8)	8	499±223	21±17	2 (25)	0.09	5.7 (1.0–34.5)
Patients with celiac sprue and total villous atrophy (n = 17)	17	724±907	21±16	7 (41)	<0.001	12.0 (3.5–41.7)
Patients with refractory sprue and total villous atrophy (n = 11)	11	1054±718	29±20	8 (73)	<0.001	45.4 (10.0–200.0)
All the patients with total villous atrophy (n = 28)	28	865±830	25±18	15 (54)	<0.001	20.0 (6.9–58.8)
All the patients with partial or total villous atrophy (n = 36)	36	762±864	24±18	17 (47)	<0.001	15.4 (5.6–41.7)

\*Number of stool specimens tested per group.

†Plus-minus values are means ±SD.

‡These values pertain to 128 independent tests in the control groups (excluding the group with induced diarrhea) by Fisher's exact test. CI denotes confidence interval.

§Not measured.

cult tests in our patients was not investigated directly, there are several reasons to believe that it was probably occult bleeding from the histopathological abnormalities of the small intestine itself — that is, mucosal inflammation and villous atrophy. The low frequency of positive tests in the control groups makes it unlikely that the positive tests in patients with villous atrophy were due to perianal bleeding due to diarrhea, bleeding due to microscopic colonic inflammation, or false positive Hemocult reactions due to the malabsorption of meat fibers or peroxidase-containing foodstuffs. In the patients with celiac or refractory sprue, there was no evidence of ulcers or other macroscopic lesions of the gastrointestinal tract. Although measured in only 50 percent of the patients with villous atrophy, the prothrombin time was not prolonged in any patients with occult bleeding. Positive Hemocult tests were less frequent in patients with previously diagnosed and treated celiac sprue who had normal small-intestinal histologic features or partial villous atrophy than in untreated patients with total villous atrophy. Finally, positive Hemocult tests were more prevalent (57 percent) in patients with sprue who had diarrhea — that is, those with more of their small-intestinal absorptive surface involved pathologically<sup>25,26</sup> — than in those without this symptom (12 percent), a group that usually has disease limited to the proximal intestine. The higher frequency of positive Hemocult tests among patients with refractory sprue may also have been related to the pathologic involvement of a greater amount of small intestine.

One can only speculate on how the small-intestinal abnormalities that characterize sprue result in increased gastrointestinal blood loss. One possibility is that the

chronic inflammation causes microerosions that escape detection by endoscopic and radiographic methods. Alternatively, the rapid rate of enterocyte turnover may intermittently compromise the epithelial-cell barrier, allowing red cells that may have leaked into deeper layers of the mucosa to find their way into the intestinal lumen.

Because the Hemocult test is qualitative and becomes positive only above a critical concentration of fecal hemoglobin,<sup>17</sup> it cannot be used to measure fecal losses of blood or iron. Furthermore, the results of Hemocult testing of stools collected for two or three days will not necessarily correlate with the presence or absence of anemia or hypoferrremia in a patient with villous atrophy, because there are many other variables that can influence hemoglobin and serum iron values (such as the intake and absorption of hematic nutrients and the severity of diarrhea) and because gastrointestinal blood loss may be intermittent.<sup>15</sup> Thus, the relative con-

Table 2. Relation of the Results of Hemocult Tests to Hemoglobin and Serum Iron Concentrations in Patients with Villous Atrophy.\*

GROUP	HEMOGLOBIN	SERUM IRON
	g/dl	µg/dl
Normal subjects (n = 18)	14.2±1.3	91±25
Patients with villous atrophy		
Fecal Hemocult-negative (n = 19)	12.9±1.7	64±44
Fecal Hemocult-positive (n = 17)	11.3±2.5†	47±37

\*Plus-minus values are means ±SD. To convert serum iron values to micromoles per liter, multiply by 0.179.

†P = 0.04 for the comparison with the patients with Hemocult-negative stools.

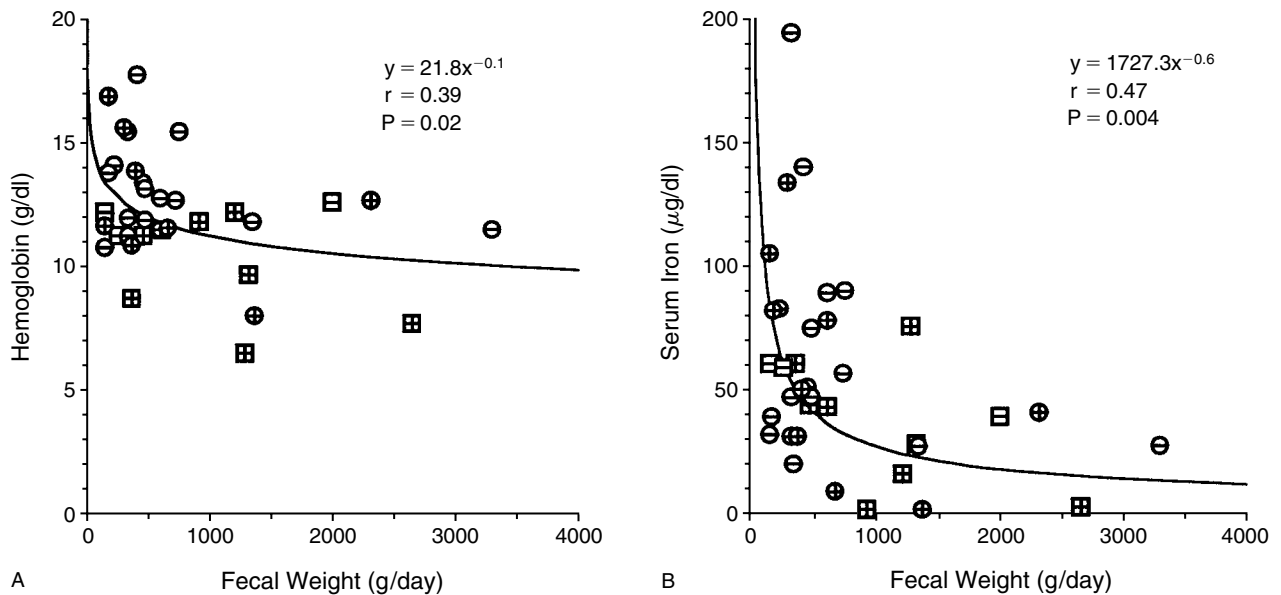


Figure 1. Values for Hemoglobin (Panel A) and Serum Iron (Panel B) as a Function of Fecal Weight in 36 Patients with Partial or Total Villous Atrophy.

The circles represent patients with celiac sprue, and the squares those with refractory sprue. Patients with Hemocult-positive stools are denoted by +, and those with Hemocult-negative stools by -. To convert serum iron values to micromoles per liter, multiply by 0.179.

tribution of occult gastrointestinal bleeding to the iron deficiency and anemia that so commonly complicate celiac and refractory sprue is not known. Nevertheless, any amount of blood lost in stool will increase the chance that patients with total villous atrophy will become iron-deficient and perhaps anemic because of their limited ability to absorb dietary or supplemental oral iron.

An important aspect of this study relates to the question, How should a positive Hemocult test in a patient with celiac or refractory sprue be interpreted in clinical practice in the light of the increased incidence of gastrointestinal lymphomas and carcinomas in such patients?<sup>18-20</sup> Although these tumors can obviously cause a positive Hemocult test, no malignant lesions were found in this study in the 15 untreated patients with celiac or refractory sprue or in the 2 patients with partially treated celiac sprue who had Hemocult-positive stools. Since treatment of celiac sprue that results in restoration of villous architecture seems to reduce the amount of occult gastrointestinal blood loss, a patient with a positive Hemocult test at the time of diagnosis might be followed expectantly through the early phases of treatment with a gluten-free diet, provided he or she has no constitutional symptoms suggestive of cancer and the test becomes negative. If at any time an endoscopic or radiographic evaluation is undertaken because of a positive Hemocult test and is unrevealing, the results of this study suggest that rather than a missed tumor, some degree of small-intestinal villous atrophy may still be present and causing occult bleeding.

Perhaps the most useful clinical lesson of this study is that the Hemocult test should not be used as a screening test for cancer in patients with celiac or refractory

sprue because of its poor predictive value. Although a negative result can be reassuring, a positive result could cause unnecessary worry for doctor and patient alike and increase the use of expensive and invasive diagnostic tests.

I am indebted to Ms. Diana Santa Ana for her help in preparing the manuscript; to Ms. Carol Santa Ana and Dr. Don McIntire, University of Texas Southwestern, for their help with the statistical analyses; and to Ms. Beverly Peters for assistance with graphics.

## REFERENCES

1. Stevens D, Harkness C, Burman D. Anaemia in childhood coeliac disease. *Arch Dis Child* 1979;54:648-9.
2. Bonamico M, Vania A, Monti S, et al. Iron deficiency in children with celiac disease. *J Pediatr Gastroenterol Nutr* 1987;6:702-6.
3. Cooke WT, Holmes GKT. Coeliac disease. Edinburgh, Scotland: Churchill Livingstone, 1984:128.
4. McGuigan JE, Volwiler W. Celiac-sprue: malabsorption of iron in the absence of steatorrhea. *Gastroenterology* 1964;47:636-41.
5. Whitehead R, Carter RL, Sharp AA. Anaemia in occult intestinal malabsorption. *J Clin Pathol* 1965;18:110-3.
6. Kilpatrick ZM, Katz J. Occult celiac disease as a cause of iron deficiency anemia. *JAMA* 1969;208:999-1001.
7. Depla ACTM, Bartelsman JFWM, Mulder CJJ, Tytgat GNJ. Anemia: monosymptomatic celiac disease: a report of 3 cases. *Hepatogastroenterology* 1990;37:90-1.
8. Gostout CJ. Enteroscopy for unexplained iron-deficiency anemia: identifying the patient with sprue. *Gastrointest Endosc* 1993;39:76-9.
9. Brady CE. Occult celiac sprue masquerading as severe iron deficiency anemia. *J Clin Gastroenterol* 1994;18:130-2.
10. Badenoch J, Callender ST. Iron metabolism in steatorrhea: the use of radioactive iron in studies of absorption and utilization. *Blood* 1954;9:123-33.
11. *Idem*. Effect of corticosteroids and gluten-free diet on absorption of iron in idiopathic steatorrhea and coeliac disease. *Lancet* 1960;1:192-4.
12. Hoffbrand AV. Anaemia in adult coeliac disease. *Clin Gastroenterol* 1974; 3:71-89.
13. Webb MGT, Taylor MRH, Gatenby PBB. Iron absorption in coeliac disease of childhood and adolescence. *BMJ* 1967;2:151-2.
14. Sutton DR, Stewart JS, Baird IM, Coghil NF. "Free" iron loss in atrophic gastritis, post-gastrectomy states, and adult coeliac disease. *Lancet* 1970;2:387-9.
15. Giuliani ER, Hagedorn AB, Owen CA Jr, Scudamore HH. Anemia of nontropical sprue studied with radioiron and radiochromium. *J Nucl Med* 1961; 2:297-313.

16. Kosnai I, Kuitunen P, Siimes MA. Iron deficiency in children with coeliac disease on treatment with gluten-free diet: role of intestinal blood loss. *Arch Dis Child* 1979;54:375-8.
  17. Simon JB. Occult blood screening for colorectal carcinoma: a critical review. *Gastroenterology* 1985;88:820-37.
  18. Cooper BT, Read AE. Coeliac disease and lymphoma. *Q J Med* 1987;240:269-74.
  19. Holmes GKT, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease — effect of a gluten free diet. *Gut* 1989;30:333-8.
  20. Holmes GKT, Thompson H. Malignancy as a complication of coeliac disease. In: Marsh MN, ed. *Coeliac disease*. Oxford, England: Blackwell Scientific, 1992:105-35.
  21. Trier JS, Falchuk ZM, Carey MC, Schreiber DS. Celiac sprue and refractory sprue. *Gastroenterology* 1978;75:307-16.
  22. Afzalpurkar RG, Schiller LR, Little KH, Santangelo WC, Fordtran JS. The self-limited nature of chronic idiopathic diarrhea. *N Engl J Med* 1992;327:1849-52.
  23. DuBois RN, Lazenby AJ, Yardley JH, Hendrix TR, Bayless TM, Giardiello FM. Lymphocytic enterocolitis in patients with "refractory sprue." *JAMA* 1989;262:935-7.
  24. Sylwestrowicz T, Kelly JK, Hwang WS, Shaffer EA. Collagenous colitis and microscopic colitis: the watery diarrhea-colitis syndrome. *Am J Gastroenterol* 1989;84:763-8.
  25. Marsh MN. Mechanisms of diarrhoea and malabsorption in gluten-sensitive enteropathy. *Eur J Gastroenterol Hepatol* 1993;5:784-95.
  26. Kagnoff MF. Celiac disease. In: Yamada T, Alpers DH, Owyang C, Powell DW, Silverstein FE, eds. *Textbook of gastroenterology*. Philadelphia: J.B. Lippincott, 1991:1503-20.
-