Hematologic Complications of Partial Gastrectomy

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ANEMIA is a frequent late complication of partial gastrectomy. It has mainly, and at times entirely[2] been attributed to lack of iron, relatively little significance being attached to other factors as deficiencies of vitamin B_{12} and folate. In studies of gastrectomized patients, B_{12} and folate deficiences have often been assessed on the basis of morphologic abnormalities, *i.e.*, macrocytosis and megaloblastosis[11] changes which are frequently masked by concomitant iron deficiency.[14] In other instances[10] vitamin B_{12} absorption tests (*e.g.* Schilling test) have been used, not recognizing the fact that many partially gastrectomized patients having impaired intestinal absorption of food B_{12} can effectively absorb crystalline B_{12}, the form used in these tests.[12] The criteria used for the diagnosis of B_{12} and folate deficiencies in partially gastrectomized patients have, therefore, often been less than adequate. Relatively recently studies have been published in which serum levels of B_{12} and folate were determined,[7] however, the concentrations of these vitamins in the red cells or tissue have not been systematically evaluated. This paper reports a series of 107 patients with partial gastrectomies in whom the hematologic status was investigated through morphologic and biochemical means, including measurements of B_{12} and folate levels in the red cells.

Materials and Methods

One hundred and seven men, aged 26 to 82 were studied 6 months to 24 years (average 8.2 years) following subtotal gastrectomy for benign peptic ulcer. The preoperative diagnosis was duodenal ulcer in 75 and gastric ulcer in 32. The surgical procedure used was Billroth II in 80 and Billroth I in 27. Hemoglobin, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were obtained with a Coulter S counter. Neutrophil hypersegmentation was estimated by 1) calculating neutrophil lobe index (total number of nuclear lobes per 100 PMNs/100, normal <3.25) and 2) by enumerating per cent neutrophils with 5 or more lobes (normal <5%). Serum iron (SeFe) and iron binding capacity (TIBC) were measured by the methods of Ramsay.[16,17] Serum transferrin saturation of less than 16% was regarded as definitive[1] and TIBC of greater than 400 mcg./100 ml. as probable,[20] evidence for iron deficiency. Vitamin B_{12} absorption was determined with the plasma B_{12} absorption test, in which plasma radioactivity is measured 8 hours after the oral dose of $CO^{57}B_{12}$.[6] Serum and red cell B_{12} concentrations were evaluated by the Euglena gracilis assay[13] preparing the red cells with the method of Biggs *et al.*[3] Serum and red cell folate were assayed by the lactobacillus casei method[19] using the technic of Hoffbrand *et al.*[9] for red cell preparation.

Results

Incidence of Hematologic Abnormalities

Table 1 summarizes the frequency of observed abnormalities. Forty-nine per cent of the patients were anemic. Serum transferrin saturation of less than 16% was present in 33%; however, TIBC values suggested that a greater proportion of patients (49%) were probably iron de-

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TABLE 1. *Incidence of Hematologic Abnormalties*

	Total	Billroth II	Billoth I
Anemia (Hg < 14.0 Gm./100 ml.)	49%	55%	33%
Transferrin saturation < 16%	33%	37%	19%
TIBC > 400 mcg./100 ml.	49%	53%	36%
Plasma B_{12} absorption < 2.0 pg./ml.	18%	19%	15%
Serum B_{12} < 150 pg./ml.	37%	40%	30%
RBC B_{12} < 110 pg./ml.	68%	75%	52%
Serum folate < 6.4 ng./ml.	33%	30%	40%
RBC folate < 200 ng./ml.	17%	18%	15%

ficient. Vitamin B_{12} absorption was subnormal in 18%. The most frequently observed hematologic abnormality was a decrease in red cell B_{12} concentration (68%), the serum levels of this vitamin being low in only 37%. Diminished folate levels, in contrast, were found more frequently in serum than in red cells (33% vs. 17%).

As indicated in Table I iron and B_{12} deficiencies, and anemia, were more frequent in Billroth II than in Billroth I group of patients. Billroth I patients, on the other hand, had a greater incidence of subnormal serum folate levels.

Analysis of Deficiencies

Eighty-seven, or 81% of all patients, had hematologic deficiencies (Table 2). Of these 31 had single deficiencies of iron, B_{12} or folate; in the majority, however, (56 patients) these deficiencies presented in combined forms. Iron deficient patients were more often anemic than those with B_{12} deficiencies. The incidence of anemia was: 33% in isolated B_{12} deficiency, 48% in combined B_{12} and folate deficiency, 86% in combined B_{12} and iron deficiency, and 100% when deficiencies of all three nutrients existed (Table 2). Morphologic changes characteristic of iron deficiency, *i.e.*, microcytosis and hypochromasia, were most frequently seen in pure iron deficiency. The incidence of these changes was less when B_{12} deficiency accompanied iron deficiency and least when all three deficiencies were present in combination. On the contrary, macrocytosis of B_{12} and folate deficiency was obscured by co-existing iron deficiency. Neutrophil hypersegmentation always accompanied B_{12} or folate deficiencies whether or not the patient was anemic and regardless of his iron status.

Discussion

The results indicate that in gastrectomized patients, contrary to previous assessments, vitamin B_{12} deficiency is the most frequent hematologic abnormality. Sixty-eight per cent of the patients in the present series had low red cell B_{12} levels, a finding which, along with the consistently observed neutrophil hypersegmentation in these patients, suggests a deficiency of this vitamin at tissue level. Yet, B_{12} deficiency has been thought to be unusual following partial gastrectomy, developing in 1 to 20% of the patients according to different reports.[5,7,11] The reasons for this inconsistency appear to be as follows. Macrocytosis, a commonly sought clue in the diagnosis of B_{12} (or folate) deficiency, can be masked by concomitant iron deficiency. Whereas 43% of our patients with simple B_{12} deficiency had macrocytosis, only 9% of those having a combined deficiency of B_{12} and iron exhibited this abnormality. Secondly, the B_{12} absorption tests, so heavily relied on for diagnosis of B_{12} deficiency, yielded subnormal values in only 18% of our patients, *i.e.*, in about one-fourth of those who were actually B_{12} deficient. The reason for normal B_{12} absorption in the face of B_{12} deficiency has been pointed out above. Finally, serum B_{12} levels, studied in several previous series of postgastrectomy patients, were decreased in only about half of those having low red cell B_{12} concentrations among our patients suggesting that is gastrectomized patients red cell B_{12} concentration is a better index of B_{12} deficiency than is the serum level of this vitamin. Iron deficiency, if strictly defined as transferrin saturation of less than 16%, a criterion pro-

TABLE 2. *Analysis of Hematologic Deficiencies*

	A. Single Deficiencies (31 Patients)			B. Combined Deficiencies (56 Patients)			
	Iron	B_{12}	Folate	Iron + B_{12}	Iron + Folate	B_{12} + Folate	Iron + B_{12} + Folate
No. of Patients	4	21	6	22	1	25	8
% with Anemia	100	33	33	86	(100)	48	100
% with Microcytosis	75	0	0	41	(0)	0	25
% with Hypochromasia	100	5	0	64	(100)	4	38
% with Macrocytosis	0	43	50	9	(0)	60	25
% with PMN hypersegmentation	0	100	100	100	(100)	100	100

posed by Bainten and Finch[1] was detected in 33% of the patients. However, 49% of the patients had abnormally high TIBC values (>400 mcg./100 ml.) suggesting that this deficiency was probably more prevalent; since other conditions associated with high TIBC, such as pregnancy or estrogen therapy, were not a consideration here. Iron deficiency has been described as occurring in one-third to one-half of the patients following subtotal gastrectomy,[5,7,8] except in women in whom the incidence may approach 100%.[8] The present results agree with these figures. As expected, the morphologic changes of iron deficiency, microcytosis and hypochromasia, were often masked by co-existent B_{12} and folate deficiencies (Table 2), thus lessening their diagnostic value in a combined deficiency state.

Among the 107 postgastrectomy patients, folate depletion was more marked in the serum than in red cells. Red cell folate data could not be used with confidence in the assessment of folate deficiency for two reasons. Firstly, iron deficiency has been reported to increase red cell folate levels presumably by impairing folate utilization in the red cell precursors.[15] Secondly, among our patients, depressed serum folate levels were always associated with neutrophil hypersegmentation, regardless of red cell folate concentrations. Consequently, serum folate levels appeared to be a better index of folate deficiency in gastrectomized patients. These levels were decreased in 33% of our patients. Others have reported a similar incidence.[7]

Among the morphologic abnormalities of B_{12} or folate deficiency, neutrophil hypersegmentation proved to be most valuable. It was always present whenever these deficiencies existed regardless of the patients iron status and the presence or absence of anemia.

The incidence of anemia has varied widely, from 4% to 77% in reported series of postgastrectomy patients.[4,18] A 49% incidence found in the present series is similar to one reported by Hines *et al.*[7] in a study, of approximately 300 patients. Although, percentage-wise, iron deficiency led to anemia more frequently than did B_{12} deficiency, the number of B_{12} deficient patients far exceeded those with iron deficiency. The two deficiencies, thus appeared to be equally important in the causation of anemia. The role of folate deficiency appeared to be less impressive in this regard.

The fact that Billroth II group of patients became anemic more frequently than those having had Billroth I type of resections, has been reported previously.[5] Presumably the duodenal bypass and rapid transit following Billroth II gastrectomy leads to a greater incidence of anemia. Indeed, iron and B_{12} deficiencies were noted to be more frequent in Billroth II than in Billroth I groups among our patients. Billroth I patients in contrast, had a greater incidence of folate deficiency. The reasons for this difference are not clear.

Summary and Conclusions

1. One hundred and seven men with partial gastrectomies were investigated for hematologic deficiencies on the average of 8.2 years after operation.

2. Anemia was found in 49%. It was found more frequently in Billroth II than in Billroth I patients.

3. A previously unrecognized high (68%) incidence of B_{12} deficiency in red cells was found, the serum levels of B_{12} being diminished in only 37%.

4. In patients with partial gastrectomies, plasma B_{12} absorption tests proved to be misleading. They yielded normal results in most patients with subnormal serum and red cell B_{12} levels; only 18% of the patients had low B_{12} absorption by this test.

5. Iron and folate deficiencies were each present in one-third of the patients.

6. The deficiencies of iron, B_{12} and folate were often combined (56 patients) than single (31 patients) and while those of iron and B_{12} were more frequent in the Billroth II group, folate deficiency was slightly more common following Billroth I operation.

7. Iron and B_{12} deficiencies appeared to be equally important in the causation of anemia whereas folate deficiency was less significant in this regard.

8. Neutrophil hypersegmentation appeared to be the most helpful morphologic indication of B_{12} and folate deficiencies. Macrocytosis often appeared to be masked by concomitant iron deficiency. Conversely, microcytosis and hypochromasia of iron deficiency was frequently masked by co-existent B_{12} or folate deficiencies.

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