Nutritional Problems Associated with Gastrointestinal and Genitourinary Cancer

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Summary

Cancer involving the alimentary tract may produce significant effects on the nutritional status of the patient. The organs in the gastrointestinal system are among the most metabolically active in the body. Consequently, food deprivation may adversely affect absorptive capacity and contribute to malabsorption by its effect on intestinal mucosal enzymes. Mucosal changes associated with malnutrition may occur in the presence of cancers outside the alimentary tract ("cancer enteropathy"), but such changes appear to be the result of and not the cause of cachexia. Long-term preexisting celiac disease is associated with the development of intestinal lymphoma and carcinoma. Intestinal lymphoma itself can present as a celiac syndrome. The most common direct effect of alimentary tract neoplasms on nutritional status relates to partial or complete obstruction at 1 or more sites. In addition to impaired food intake, fluid and electrolyte and acid base problems may result from persistent vomiting and/or diarrhea. Malabsorption may occur as a result of gastric hypersecretion, pancreatic exocrine insufficiency, or bile insufficiency. The malabsorption occurring from these various conditions can lead to deficiencies of a variety of nutrients. Hepatoma may be associated with severe hypoglycemia, and liver failure leads to progressive malnutrition. Ovarian tumors exert an adverse effect with the development of ascites or intestinal obstruction. Cervical and bladder carcinoma may obstruct the ureters causing renal dysfunction.

Neoplasia of the Digestive Tract

Because of the fundamental roles of the gastrointestinal tract related to ingestion, digestion, and absorption of food, the occurrence of cancer anywhere in that system may produce significant effects on the nutritional status of the patient (Table 1). Included in this system are the entire alimentary tract from the lips to the anus, the liver, gallbladder, pancreas, and the ducts connecting them to the alimentary tract proper.

There is a close interrelationship between the function of the components of the gastrointestinal tract and the behavior of the patient in relation to food and nutrition. In addition, there is an important "reverse" relationship between the ability of the patient to consume food in adequate amounts and the subsequent behavior of the gastrointestinal tract. It is a dictum in medicine that when a patient has an unexplained loss in appetite and body weight one should look for an occult neoplasm. Often such neoplasms are in the gastrointestinal tract. Table 2 summarizes some data on the incidence of weight loss and anorexia on presentation of patients with primary alimentary tract cancers.

Malnutrition and Intestinal Function

Any tumor, although related to the gastrointestinal tract, or treatment of that tumor which leads to profound anorexia or in other ways interferes seriously with the ingestion of food can adversely affect the absorption of food. The organs in the gastrointestinal system are among the most metabolically active in the body. It is therefore not surprising to learn that marked intestinal changes occur with starvation or protein deficiency (Table 3).

In the fasting adult rat, for example, nitrogen losses after 24 hr were 15% of the original content in small intestine and liver and were approximately double this after 4 days at which time pancreas loss was also 30% and stomach loss 11%. When calories were supplied as a protein-free diet, nitrogen losses were very high at 24 hr for pancreas and liver (25 and 20%, respectively, of the control values). Small bowel losses were appreciably less than with fasting (18).

In recent years attention has been directed to specific changes in structure, composition, and absorption. There is a diminution in mitotic figures in crypt regenerative areas, a reduction of cells in the crypts and villi, and cytological alterations after 4 to 5 days of starvation (7, 26).

McManus and Isselbacher (37) noted decreases after overnight fasts in weight of the bowel and DNA content (apparently related to the smaller cell mass of the mucosal fraction of the small bowel) and in amino acid and hexose transport in the fasted animals as compared to the fed animals together with decreased activity of the enzyme palmitoyl thiokinase (an enzyme used as an index of microsomal activity). While there was no difference in the measured length of intestine between fasted and fed young adult rats after 3 days, the wet weight of the mucosa in the first 30 cm of intestine dropped to one-third the control value in the fasted rat, and the total mucosal protein fell to approximately one-half of control values (42). However, mucosal protein expressed per g of wet weight of mucosa actually increased slightly. There were similar changes observed throughout the small intestine. There were also marked decreases in total sucrose, maltase, and monoacylglycerol acyltransferase activities. However, specific activi-
that of lactase was increased while that of the acyltransfer
jects significantly decreased the activities of certain jejunal
These results appear most consistent with the hypothesis of
had anorexia.
3. Decreased total enzyme activity with a few exceptions
4. Little or no change of specific enzyme activity
5. Function deteriorates before morphological changes appear
6. Increased gluconeogenic and lysosomal enzyme activities
7. Hormonal effects related to route of feeding and starvation

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Weight loss, anorexia, and dysphagia in patients presenting with carcinomas of the alimentary tract</th>
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<tbody>
<tr>
<td>Site</td>
<td>No. of patients</td>
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<tr>
<td>---------</td>
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<tr>
<td>Esophagus</td>
<td>60</td>
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<tr>
<td>Stomach</td>
<td>1112</td>
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<tr>
<td>Pancreas</td>
<td>255</td>
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<tr>
<td>Liver (primary)</td>
<td>53</td>
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Change in the gastrointestinal tract during starvation

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<td>1. Decreased weight thickness and protein content</td>
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<td>2. Decreased DNA, RNA, and protein synthesis in gastric parietal cells, pancreas, and small intestine</td>
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3rd day (30). Four obese fasting subjects on prolonged fasts were found to have abnormal villi on biopsy; however, the periods of starvation prior to biopsies are not stated (48).
Observations have been made on protein- and calorie-malnourished children and adults. Intestinal malabsorption and jejunal histological abnormalities have been amply documented (8, 46, 53). Viteri et al. (53) studied absorption of a number of nutrients in 32 protein-calorie malnourished children on admission to hospital and throughout recovery. Severe malabsorption of all substances was present initially. As nutritional recovery progressed, absorption of nitrogen, p-xylene, and vitamin A palmitate recovered soon after initiation of therapeutic diets while absorption of fat and vitamin B₁₂ recovered more slowly.

Changes in Small Intestine Mucosa Related to Extraintestinal Tract Cancers

Creamer (12) studied the small bowel mucosa in 9 patients with cancer. In 3 of 6 subjects in whom the neoplasm arose outside the intestinal tract there was a flat mucosa, and in the 4th there was a hypoplastic mucosa. The other 3 patients had cancer in the stomach, small intestine, and cecum; the 1st 2 had abnormal mucosa. Of the 6 patients with abnormal mucosa, 5 had lost weight and 4 had steatorrhea. He suggested that "some of the ill-health and loss of weight in malignancy is caused by an abnormal small intestinal mucosa." A number of papers then followed supporting this suggestion of a "cancer enteropathy" (14, 15, 21, 35, 55); however, other investigators have been unable to confirm these findings (4, 18, 29).
In the paper of Gilat et al. (21), 82 patients with cancers (in
M. E. Shils

57 of this group, the alimentary tract was involved) were compared with 73 patients without neoplasia, malabsorption, or other disease involving the small bowel. No mention is made of weight in comparison with normal weight or preillness weight. Ten patients with cancer had partial villous atrophy and 1 had subtotal villous atrophy. None of the benign group had any villous atrophy. Of interest is the finding that 8 of the 10 patients having partial villous atrophy had a tumor involving the gastrointestinal tract and the 1 patient with subtotal villous atrophy had carcinoma of the ovary with a single metastasis in the small bowel.

In a more definitive study Barry in essence asked the question: if mucosal changes occur in malignant diseases (as they appear to do), how much of these changes is associated with weight loss and how much with cancer (4)? Three groups of patients were studied; 1 group consisted of 32 patients, with minimum weight loss of 21 pounds with biopsy-proved malignant disease occurring anywhere in the body but not involving the gastrointestinal tract either primarily or secondarily. This group was compared with a 2nd group of 20 patients matched for age who were hospitalized for investigation of vague abdominal symptoms but who had no evidence of organic disease or weight loss. A 3rd group was a population of 15 wasted patients who were ill and had lost more than 28 pounds for reasons other than cancer or gastrointestinal disease. Lactose utilization, epithelial cell loss rate, and the appearance of fresh peroral biopsies were examined. They found abnormal changes in these parameters in patients with cancer. However, these same abnormalities were present in the wasted patients without cancer; in fact, the wasting illnesses appeared to have a more marked effect on intestinal appearance than did cancer. In addition, mucosal morphology was studied in 3 groups at necropsy. One group consisted of 23 individuals dying of extensive malignant disease not affecting the gastrointestinal tract. The 2nd group consisted of 36 patients dying suddenly and without cancer. A 3rd postmortem group consisted of 52 patients dying after illnesses other than cancers or gastrointestinal disease with a weight loss of 28 pounds or greater. There was a highly significant difference between the mucosal architecture in "normal controls" and those with wasting diseases; a very similar trend was shown in malignant disease but did not reach a level of statistical significance with the numbers available. The author concludes "although mucosal changes undoubtedly occurred in malignant disease, the changes are not specific for malignancy and the concept of "cancer enteropathy" is not tenable. It is suggested that mucosal changes are the effect of and not the cause of cachexia."

Association of Carcinoma and Intestinal Mucosal Abnormalities

The literature on the association among villous atrophy, steatorrhea, and primary small bowel tumors was reviewed up to 1966 by Brzechwa-Ajdukiewicz et al. (10); a table modified from their paper is presented as Table 4. Bossaket et al. (6) reviewed 94 patients with celiac disease (gluten enteropathy, nontropical sprue), 5 of whom had intestinal carcinomas. Harris et al. (25) reported 202 patients with adult celiac disease or sprue of whom 14 had carcinomas of the alimentary tract, 6 of which were in the esophagus. Eighteen of 26 patients with such cancers were males. Various hypotheses have been suggested for the carcinomatous involvement in these patients including possibilities that the abnormal small bowel epithelium permits increased absorption of carcinogens, that the chronic inflammation of the lamina propria or lymphoid hyperactivity somehow plays a role, or that environmental factors such as prolonged nutritional deficiency secondary to malabsorption or intestinal organisms may account for the malignant changes.

Celiac Syndrome and Intestinal Lymphomas

Prior to 1962 steatorrhea in lymphomatous patients was considered to be the consequence of mesenteric lymphoma causing obstruction of lymphatic flow or of diffuse lymphomatous infiltration of the small bowel. In 1962 Gough et al. (23) advanced the hypothesis that small bowel reticulosis may develop as a complication in patients with celiac syndrome. Austed et al. (3) found a 10% incidence of lymphoma in their celiac patients. Benson et al. (5) reported an incidence of 6.2%, and Harris et al. (25) reported an incidence of 6.9% (with a similar incidence of carcinoma in their series of 202 patients). Nine of the 14 patients of Harris et al. (25) had lymphoma involving the stomach, jejunum, or ileum; 12 of the 14 had celiac disease diagnosed for more than 5 years (the average being 21 years for the group of 14). Of the 14, 4 had Hodgkin's disease in none of whom the intestine was involved. The others had reticulum cell sarcoma with the intestine involved in 8 patients. Many of the older studies had no histological proof of villous atrophy by biopsy and the diagnosis of celiac syndrome was made by history or abnormal fat absorption and/or in response to gluten-free diets.

Lymphoma involving the small bowel mesenteric lymph nodes may present as malabsorption (9, 17, 39). Patients with abdominal lymphomas and malabsorption often present with abdominal pain, weight loss, anorexia, and bulky stool suggestive of steatorrhea. They may have clubbing, glossitis, angular stomatitis, and peripheral edema. Laboratory findings may include abnormal D-xylOse absorption, flat glucose tolerance curves, hypoalbuminemia, and fat and B12 malabsorption; megaloblastosis may be present (9, 17, 39). There may be deficits in fat-soluble vitamins. Folic acid deficiency may occur on occasion (41).

Because of this relationship lymphoma should be suspected with the onset of the celiac syndrome in middle age especially, but also in young people particularly in certain areas and in certain racial backgrounds (17, 27). Males above 40 years of age with long-standing celiac syndrome who are not on a gluten-free diet are a major risk group.

Primary lymphomas originate in the intestinal tract in approximately 10 to 20% of reported cases (38). A majority of these tumors are lymphocytic lymphomas, with approximately twice (38) or 2.5 times as many (34) occurring in the stomach as in the small intestine. Disseminated lymphoma often secondarily involves 1 or more sites along the gastrointestinal tract; tumor, ulcerations, erosions, and infection may occur with deleterious effects to the patient (16).

The mechanisms for the development of malabsorption...
are several. The intestinal epithelium may be disrupted by the generalized villous atrophy found in association with lymphomatous involvement. Infiltration of the lamina propria and draining lymph nodes can lead to obstruction of mesenteric lymph channels and dilation of the lymphatics within the intestinal villi which in turn can lead to development of a protein-losing enteropathy with hypoalbuminemia, hypoglobulinemia, and lymphocytopenia (54). Protein-losing enteropathy has also been described with cases of gastric carcinoma (54).

The blind loop syndrome in the upper small bowel secondary to partial obstruction with bacterial overgrowth may also result in steatorrhea and vitamin B12 deficiency. Recent evidence indicates that the blind loop syndrome involves not only direct interaction of bacteria with certain nutrients but also the development of abnormalities of the intestinal epithelium to account for associated malabsorption (50).

Nutritional replacement and support in such malabsorption syndromes are useful while direct antineoplastic treatment with radiation and chemotherapy are undertaken.

### Obstruction along the Alimentary Tract

The most common direct effect of alimentary tract neoplasms on nutritional status relates to partial or complete obstruction at 1 or more sites.

It is estimated that about 20% of surgical admissions for acute abdominal conditions are associated with intestinal obstruction and that the 3rd most common cause of obstruction is neoplasm of the bowel (45). When obstruction occurs acutely, medical attention is very likely to be sought immediately. However, most neoplasms obstruct slowly and progressively. It is a common observation that a significant number of patients will defer seeking medical care until their dysphagia, anorexia, pain, nausea, vomiting, diarrhea, or anemia from chronic blood loss have persisted to the point where weight loss and weakness are prominent (Table 2). In addition to weight loss secondary to poor intake of food there are fluid, electrolyte, and acid-base problems that result from persistent vomiting or diarrhea or as a consequence of malnutrition per se.

#### Endocrine and Paracrine Production by Tumors

A number of biologically active agents are formed by neoplasms of the gastrointestinal tract in amounts which may create serious problems in fluid and electrolyte balance (44). These endocrine and paracrine substances have been described by Lipsett (33) at this conference.
Pancreatic Exocrine Insufficiency

A marked decrease in the secretion or activities of pancreatic enzymes results in maldigestion and consequent malabsorption of fats, proteins, and long-chain carbohydrates.

Carcinoma of the pancreas may cause enzyme deficiency, especially when there is extensive involvement of this organ, particularly in the head region. Although the number of such patients that has been reported is small (56), it is my experience that malabsorption in this condition is not uncommon. The resulting malabsorption combined with anorexia frequently apparent in such patients contributes to progressive weight loss. Treatment with pancreatic replacement is indicated if there is any suspicion of enzyme deficiency. Despite a priori supposition that vitamin $B_{12}$ absorption would be normal in pancreatic insufficiency, there have been reports indicating that there may be reduction in vitamin $B_{12}$ absorption in approximately 40 to 50% of patients with this condition (51, 52) and in partially pancreatectomized rats (49). Where pancreatic insufficiency exists with pancreatic carcinoma, there may be a role for pancreatic enzymes in improving the absorption of vitamin $B_{12}$ as well as protein, fat, and carbohydrate.

Irreversible denaturation and dilution of pancreatic enzymes in proximal small intestine in the Zollinger-Ellison syndrome as a result of excess gastric acid production may be a contributing factor in the malabsorption noted in this condition (22).

Conjugated bile salts play an important role in the absorption of fat; hence, any condition that reduces the concentration of such bile salts below the critical level for adequate micellar formation will lead to steatorrhea. This may occur with obstruction or diversion of biliary flow. Concentrations of conjugated bile salts may decrease as the result of bacterial action in the blind loop syndrome or following precipitation of glycine-conjugated bile salts into a microcrystalline phase as a result of a low pH in the Zollinger-Ellison syndrome (22). Bile insufficiency reduces intestinal absorption of vitamin K and leads to reduction in plasma levels of the vitamin K-dependent coagulation factors. This can be overcome by parenteral administration of relatively small amounts of vitamin K$_2$ oxide. There is recent evidence that lack of bile in the small intestine depresses the lipid-reesterifying capacity of the small bowel (47).

Bypass of significant portions of small bowel as a result of gastrocolic, enteroentero-, enterocolic, or enterocolic fistulas secondary to tumor can induce malabsorption, the severity of which depends upon the extent of small bowel bypass. The rather abrupt occurrence of diarrhea or of steatorrheic stools in the patient with suspected or known abdominal tumors, particularly where there has been previous surgery or radiation, should include this possibility in the differential diagnosis and work-up.

Liver Carcinoma

Weight loss, weakness, and ascites occur in approximately 79% and jaundice occurs in 41% of patients with primary carcinoma in whom there is preexisting cirrhosis; the incidences are lower in those with noncirrhotic livers (13). In poorly differentiated hepatoma, which is the common type, weight loss is early and severe; hypoglycemia occurs late and in about 17% of these cases. In well-differentiated tumors weight loss is late but hypoglycemia is very common, manifests itself early, and is difficult to control. The hypoglycemia does not result from ectopic insulin production but appears to be related to the deletion in the tumor cells of normal enzyme systems for glycolysis and gluconeogenesis and to rapid tumor growth (36).

The liver is second only to regional lymph nodes as a site of metastases for various tumors. Fifty % of patients with gastrointestinal tumors have hepatic metastases at autopsy. Clinical manifestations when such metastases are widely disseminated in the liver are similar to those occurring with primary carcinoma. Hypoalbuminemia and hypoprothrombinemia occur progressively as the result of progressive malnutrition with jaundice. Renal failure without apparent cause may develop in the course of liver decompensation. The development of azotemia under these circumstances bears with it a very poor prognosis (40). Serum vitamin $B_{12}$ levels are often excessively high (>1000 mg/ml) in patients with liver disease (29). Mild folate deficiency appears to be common in patients with disseminated cancer, either as a result of decreased intake, increased need, or both (29).

Tumors of the Reproductive System

Tumors arising from the organs of this system in males and females do not have a direct effect on nutrition per se other than through endocrine changes. They may have secondary effects through local spread or distant metastases. Ovarian tumors have a propensity for seeding the peritoneum and peritoneal cavity with the development of ascites and its resultant problems in terms of hypoalbuminemia and fluid retention or of obstruction of the intestine. Cervical carcinoma in its spread laterally may obstruct the ureters with resultant impairment of renal function. The effect of metastatic spread to liver has been described earlier.

Tumors Affecting the Urinary Tract

Nutritional consequences of involvement of this tract relate primarily to the effects of interference with normal renal function. Primary tumors of the kidney such as Wilms', neuroblastoma, and clear cell carcinoma will progressively damage the involved kidney or kidneys. Metastases to the kidney do occur although they are not common. More common is the development of ureteral obstruction secondary to encroaching pelvic tumors or to primary bladder cancer. In his review of the causes of death in 150 cases of bladder cancer, Cooling (11) noted that 25% were directly attributable to renal damage and electrolyte disturbances.

With destruction of renal tissue there is progressive deterioration with its usual consequences of azotemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, and the hematological and neurological problems attendant on progressive renal failure. Partial obstruction of urine outflow from both kidneys may lead to back pressure and impairment of both glomerular and tubular function resulting in
azotemia and associated changes, polyuria, and electrolyte problems. Total obstruction causes anuria and the danger of nephron destruction if not relieved. The sudden relief of severe urinary tract obstruction can lead to very large fluid and electrolyte output (postobstructive diuresis) which, although self-limiting, may be life-threatening during its course and requires careful fluid and electrolyte management of the patient until kidney function is restored. Diet therapy can play an important role in the care of patients with significant renal failure. Restriction of the intakes of protein, potassium, phosphate, and sulfate and careful management of fluid and electrolytes are often of major concern. When renal tubular dysfunction occurs recognition must be given to the possibilities of increased losses of sodium, magnesium, and phosphorus. With advanced renal disease there is an increased need for histidine (19).

Renal tubular disorders may occur secondarily as a result of tumor activities elsewhere. For example, chronic potassium depletion may result from excessive potassium losses in diarrhea as a result of the excessive production of certain intestinal hormones. The hypokalemia may be severe enough to damage renal tubules with resultant impaired ability to reabsorb other ions and water. Similarly, hypercalcemia secondary to either ectopic production by tumors of parathyroid hormone-like substance or parathyroid hormone itself, or from lytic lesions of bone, can impair tubular function with inability to concentrate urine.

References


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