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NUTRITIONAL ASPECTS OF INFLAMMATORY BOWEL DISEASE

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INTRODUCTION

The term *inflammatory bowel disease* is a designation commonly used for two related but distinct chronic inflammatory conditions affecting the gastrointestinal tract, Crohn's disease and ulcerative colitis. Crohn's disease may involve any segment of the gastrointestinal tract with a chronic granulomatous in-

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flammatory process of all layers of the bowel wall. Characteristically, the region of greatest involvement is the distal one quarter of the small intestine and the proximal colon. In ulcerative colitis the inflammation is, by definition, limited to the mucosa of the large bowel. The chronic, full thickness, inflammation of Crohn's disease commonly leads to scarring and fistula formation and obstruction so that 50–70% of patients will require intestinal resections of varying extent at some time in the course of this disease for which there is no cure. Recurrences after resection may be delayed by some years but are highly predictable. Similarly, a chronic and unrelenting course of ulcerative colitis will lead to total proctocolectomy and ileostomy since at present there is no medical cure. In both diseases chronic use of corticosteroids, often for extended periods, is common as an approach to the control of intestinal inflammation. Sulfasalazine is widely used in both ulcerative colitis and in some patients with Crohn's disease; however, the mechanism of action of this drug, which consists of 5-amino salicylate and sulfapyridine in azo linkage, is still not fully established. Antibiotics are used intermittently, particularly in presence of severe exacerbations as are other drugs including antispasmodics and anticholinergics.

It is currently held that the pathogenesis of inflammatory bowel disease involves a complex interaction of host responses, some immunologic and some genetically determined, and external influences including microbial and dietary factors (53). Food allergy was suggested early as a possible trigger for the inflammatory response; however, no firm evidence has been gathered over the years to substantiate this possibility. On the contrary, normal levels of circulating diet-specific IgE immunocytes have been recorded in ulcerative colitis (47). The possibility that patients with Crohn's disease may have an unusual premorbid pattern of dietary intake has also been examined. Several groups of investigators report an increased intake of refined sugar in patients with Crohn's disease; the significance of this observation remains unclear (48, 64, 75, 93). No preexisting nutritional abnormality has been identified consistently in patients who later develop inflammatory bowel disease.

Taken together these diseases represent a major cause of morbidity, particularly in countries with populations of northern European origin. Given the locus of these diseases in the gastrointestinal tract, their tendency to begin in the second or third decades of life, their chronic nature, the characteristic worsening of symptoms of diarrhea and abdominal pain by eating, the loss of functional intestinal absorptive surface area by inflammation or resection, the tendency to lose either blood or plasma across damaged and inflamed epithelium, the potential for loss of fluid, electrolytes, and minerals in chronic diarrhea, and the potential for unwanted drug-nutrient interactions in patients on multiple drugs, it is not surprising that this group of patients presents major continuing problems in the maintenance of adequate nutrition. This review presents a

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conceptual approach to the pathogenesis and management of nutritional complications of inflammatory bowel disease.

MECHANISMS OF NUTRITIONAL DEFICIENCY

Diminished Food Intake

The major mechanisms that contribute to nutritional depletion in patients with inflammatory bowel disease are listed in Table 1. Most important is a diminished food intake in the face of pain and diarrhea and sometimes nausea, symptoms that are characteristically worsened by meals. Often the diminution in dietary intake is subtle, especially in prepubertal patients, but can nonetheless result in inadequate intake of total calories and other nutrients. Dietary imbalance or inadequacy may result from restrictive dietary prescriptions directed toward control of symptoms. Legitimate withdrawal or decrease of lactose-containing foods in patients with lactose intolerance and the diminution of intake of fiber in patients with narrowing and partial obstruction may improve symptomatic management. However, such deletions are often un-

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Table 1 Causes of malnutrition in inflammatory bowel disease

Decreased oral intake
Disease-induced (abdominal pain, diarrhea, nausea, anorexia)
Iatrogenic (restrictive diets without supplementation)
Malabsorption
Decreased absorptive surface due to disease or resection
Bile salt deficiency after ileal resection
Bacterial overgrowth
Drugs (see below)
Increased secretion and nutrient loss
Protein-losing enteropathy
Electrolyte, mineral, and trace metal loss in diarrhea
GI blood loss
Drug-nutrient effects
Corticosteroids and calcium absorption/protein metabolism
Sulfasalazine and folate absorption/hemolysis
Cholestyramine and fat-soluble vitamin absorption
Increased utilization and increased requirements
Inflammation, fever, infection
Increased intestinal cell turnover
Hemolysis (see sulfasalazine)

accompanied by instructions to restore the calorie and nutrient adequacy of the restricted diet.

Malabsorption

Malabsorption can be anticipated in those patients with extensive mucosal involvement of the small intestine and especially in those who have had resections of segments of the small bowel.

In most instances carbohydrate malabsorption plays only a secondary role to inadequate intake in decreasing energy availability. Jejunal function determined by D-xylose absorption is preserved in most patients with Crohn's disease (6, 35). Lactose malabsorption was initially reported to be very high in patients with ulcerative colitis, but more recent studies in ethnically homogeneous groups of patients detected hypolactasia in jejunal biopsy specimens in 12.5% of patients in England (74) and in 9.2% in Denmark (12). During an acute attack of ulcerative colitis, a temporary reduction in lactase activity may be seen in some patients (74); other researchers find no such relationship (12). The activity of other disaccharidases, sucrase and maltase, are unaffected in ulcerative colitis (3). In children, lactose malabsorption as detected by hydrogen breath test was seen in 15% of cases with ulcerative colitis and in 34% with Crohn's disease (51). Interestingly, lactose malabsorption was found in 46% of children with Crohn's disease from Jewish or black descent, in contrast to only 15% of Caucasian gentile children (51). Therefore the prevalence of lactose malabsorption does not seem to be increased in inflammatory bowel disease, provided extensive small intestinal involvement is not present.

Fat malabsorption results in caloric loss as well as loss of other nutrients such as fat-soluble vitamins and minerals. A coefficient of fat absorption of less than 94% was found in 31% of patients with Crohn's disease (6), and a strong correlation of fecal fat with length of disease and/or resection was reported in another study (35). Steatorrhea may result from jejunal mucosal disease or resection in Crohn's disease or from a decrease in luminal bile acid concentration after ileectomy. Bile acids are actively absorbed in the terminal ileum, hence disease or resection of the ileum may result in bile acid malabsorption (41). Malabsorbed bile acids may contribute to watery diarrhea by their cathartic effect on the colon. With greater ileal resections, bile acid malabsorption will be so severe as to eventually deplete the bile acid pool and steatorrhea will aggravate diarrhea.

Increased Secretion and Nutrient Loss

One of the prominent features of active Crohn's disease or ulcerative colitis is an exudative enteropathy that may result in extensive loss of plasma proteins across the inflamed mucosa. This loss of proteins may exceed the ability of the

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liver to replace plasma proteins even when protein intake is adequate. This process may lead to hypoalbuminemia and eventually to peripheral edema.

The extent of protein-losing enteropathy can be assessed by measurement of fecal radioactive chromium after intravenous injection of $^{51}CrCl_3$ or by determination of the intestinal clearance of alpha-1-antitrypsin (32). A linear relationship has been established between intestinal protein loss and the Crohn's disease activity index (31).

In addition to increased loss of protein into the intestine, there is also chronic loss of blood leading to iron depletion and anemia. Electrolytes and trace minerals are lost in the face of chronic diarrhea. Clinically this excessive loss may lead to hypokalemia, hypomagnesemia, and zinc depletion. Indeed some studies show a predictable relationship between the volume of diarrhea and the amount of zinc lost from the body (97). In the presence of significant steatorrhea there will also be loss of excessive calcium and magnesium in the form of calcium and magnesium soaps of fatty acids.

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Drug-Nutrient Effects

While the judicious use of drug therapy may help to control symptoms in most patients and thereby improve well-being and even dietary intake, many of the drugs in common use by these patients have negative effects on nutritional metabolism. Corticosteroids, particularly when used in high daily doses, can exert an additional catabolic effect on patients who may already be under stress. In addition, corticosteroids have negative effects on bone mass by a variety of mechanisms, not least an inhibition of calcium absorption by the intestine. Another example of a potentially negative drug-nutrient interaction is the established interference with folate absorption by sulfasalazine via a mechanism of competitive inhibition (33).

Energy and Protein Utilization

One additional consideration in the mechanism of nutritional depletion is the question of increased nutrient requirements in these chronic inflammatory conditions. Certainly when there is frank infection or abscess formation as may occur with local perforation, and when there is a fever, there will be an increased requirement for calories and protein as well as for certain micronutrients. In the absence of fever and sepsis, however, the best current evidence indicates that there is not a remarkable increase in calorie utilization and requirement in patients with chronic inflammatory bowel disease (4).

A method designed for use in a clinical setting is now available for determining rates of protein synthesis and breakdown (95). Whole-body protein turnover was measured in nineteen patients with inflammatory bowel disease after intravenous infusion of a tracer dose of ^{15}N-glycine, with urinary ammonia as the end product (77). The results showed a correlation between the rates of

protein synthesis and breakdown and the erythrocyte sedimentation rate. In severely ill patients with an elevated sedimentation rate, both protein synthesis and breakdown increased. The rates were about two times those of patients with mildly active inflammatory bowel disease and those of normal subjects (77). Protein requirements may indeed be greater in patients with acute exacerbations of inflammatory bowel disease as a result of excess intestinal loss and increased protein turnover rate.

PREVALENCE OF NUTRITIONAL DEFICIENCIES

Table 2 presents a tabulation of the reported nutritional deficiencies in patients with inflammatory bowel disease, with some estimates of the prevalence of these deficiencies. It should be emphasized that these prevalence figures refer principally to hospitalized patients. Although the management of nutritional problems in ambulatory patients is a continuing challenge, prevalence of nutritional and metabolic derangements is obviously lower than in patients ill enough to require hospitalization.

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Table 2 Prevalence of nutritional deficiency in hospitalized patients with inflammatory bowel disease[a]

Evidence of	Prevalence (%)
Macronutrient deficiency	
Weight loss	65–75
Growth retardation	40
Hypoalbuminemia	25–80
Micronutrient deficiency	
Anemia	60–80
Iron deficiency	40
Low serum vitamin B_{12}	48
Low serum folate	54–64
Low serum magnesium	14–33
Low serum potassium	6–20
Low serum vitamin A	21
Low serum vitamin C	12
Low serum 25-OH-vitamin D	25–65
Low serum zinc	40–50
Vitamin K deficiency	[b]
Low serum copper	[b]
Metabolic bone disease	[b]
Pellagra	[b]
Vitamin E deficiency	[b]

[a] Modified from Driscoll, R. H., Rosenberg, I. H. 1978. *Med. Clin. North Am.* 62:185–201.
[b] Reported, but prevalence not described.

Energy-Protein Deficits

The most common nutritional deficit in patients who require hospitalization is a deficiency of calorie intake. This usually presents as weight loss in adults and may present as growth retardation as well in children. Under those circumstances in which the patient is unable to meet calorie and nutritional needs by mouth the question of intensive parenteral or enteral nutrition support becomes central. A great deal of experience has accrued in the use of intensive nutrition support in the management of patients with inflammatory bowel diseases. (See the section on this below.)

Patients suffering from chronic diseases with acute exacerbations such as Crohn's disease and ulcerative colitis may seek medical attention at any point in their disease course. Thus the prevalence of protein-energy deficiencies may vary widely. At the University of Chicago we recently evaluated a consecutive series of 133 hospitalized patients with inflammatory bowel disease who were referred to the Nutrition Consultation Service for evaluation. In this severely ill group of patients, anthropometric measurements confirmed a high prevalence of protein-energy malnutrition (Table 3).

Nitrogen balance may be negative in about two thirds of patients with inflammatory bowel disease (6). While protein malabsorption may play a secondary role, excess protein loss through the inflamed enteric mucosa, demonstrated in one study in 76% of patients (6), is a major factor in depleting body protein.

Electrolyte and Mineral Deficiencies

POTASSIUM Diarrheal diseases are associated with variable losses of water and electrolytes. In a study of 57 patients with Crohn's disease, total-body potassium (TBK) was significantly lower than in controls or starving patients matched for weight (59). An inverse correlation was established between TBK and the Crohn's disease activity index so that an activity index higher than 225 corresponded to a TBK lower than 70%. As previously shown, no correlation was demonstrable between serum potassium and TBK. Although clinical

Table 3 Prevalence of decreased anthropometric measurements in 133 hospitalized patients in a University of Chicago series.

	Percent < 80% of standard	
Measurement	Crohn's disease	Ulcerative colitis
Ideal body weight[a]	31	30
Muscle area	61	56
Fat area	64	60

[a] From the Metropolitan Life Table, 1983.

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symptoms of potassium deficiency, such as muscle weakness, were seen in only one case, intensive preoperative nutritional support to correct potassium deficiency resulted in a reduced surgical complication rate, particularly of postoperative paralytic ileus (59).

MAGNESIUM Symptomatic hypomagnesemia has been reported in many patients with Crohn's disease (34). It is seen after extensive small bowel resection in patients with chronic diarrhea who manifest hyperirritability, paresthesias, muscle weakness, tetany, cardiac arryhthmias, and finally convulsions and coma. A poor correlation exists between plasma levels, which may be decreased in only a minority of patients (6), and intracellular magnesium, which is commonly decreased in ulcerative colitis and Crohn's disease (71, 94). Magnesium supplementation is important in patients with active inflammatory bowel disease; however, oral supplementation is different because of the cathartic action of magnesium and the poor absorption in patients with a short bowel (57).

CALCIUM Hypocalcemia is often found in patients with inflammatory bowel disease, and often reflects hypoproteinemia. Nevertheless a high risk for calcium depletion exists in this patient group because of decreased intake of dairy products, loss of absorptive surface (57) and steatorrhea in which calcium is lost in complex with unabsorbed fatty acids. Calcium malabsorption has been demonstrated in Crohn's disease (56). Moreover calcium absorption may be decreased by corticosteroid treatment (50, 61) and vitamin D deficiency (see below).

Fat-Soluble Vitamin Deficiencies

Malabsorption of fat-soluble vitamins in Crohn's disease is the principal cause of deficiencies of these nutrients.

VITAMIN A A high frequency of subclinical vitamin A deficiency has been found in patients with chronic small intestinal disease including Crohn's disease (82). Although only one patient complained of night blindness, a functional deficit was uncovered by dark-adaptation testing in all 13 patients tested. In a study of 52 patients with Crohn's disease, low plasma retinol levels were found in 21% (63). Impaired dark adaptation was present in three patients who also had low levels of plasma proteins and retinol-binding protein.

VITAMIN D Vitamin D status depends on adequate sun exposure and dietary intake. In patients with Crohn's disease malabsorption of vitamin D may also produce deficiency. As an index of vitamin D status, serum levels of 25-hydroxyvitamin D were measured in 82 patients with Crohn's disease (22).

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Low 25-hydroxyvitamin D levels were found in 65% of patients and in 25% the values were in the deficiency range. Low serum levels and diminished absorption of 25-hydroxyvitamin D have also been reported in Crohn's disease patients after intestinal resection (15).

Metabolic bone disease appears to be a frequent complication of Crohn's disease (87). Nine patients in the above series had transiliac needle bone biopsies for histologic and histomorphometric analysis (22). Six patients had increased fractional osteoid surface diagnostic of osteomalacia, four with diminished trabecular bone volume (osteopenia) also. Most of these patients had low serum 25-hydroxyvitamin D concentrations. Supplementary vitamin D therapy improved the osteomalacia as demonstrated on a second bone biopsy in three patients. Two patients with osteomalacia but normal serum 25-hydroxyvitamin D concentrations showed no improvement on the second biopsy after vitamin D treatment. Three patients had only osteoporosis. In these cases, previous long-term treatment with corticosteroids and other factors including calcium, phosphorus, and magnesium deficiency could have been operative.

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VITAMIN E A single case report convincingly documents reversible neurological manifestations caused by vitamin E deficiency in a patient with a 25-year history of Crohn's disease with multiple small bowel resections (45). The patient had bilateral visual field scotomata, generalized motor weakness, a broad-based gait with marked ataxia, brisk reflexes, and a bilateral Babinski response. Serum vitamin E concentration was 0.03 mg/dl (normal 0.8–1.2 mg/dl) and in vitro peroxide hemolysis was 100% (normal < 10%). Aggressive vitamin E supplementation permitted recovery, which was not complete until two years later, however.

VITAMIN K As with the other fat-soluble vitamins, dietary vitamin K malabsorption can occur in Crohn's disease. Depression in the plasma level of the vitamin K–dependent coagulation factors may be a consequence of malabsorption of fats, as well as broad spectrum antibiotic treatment, which reduces endogenous vitamin K synthesis by the gut flora.

Water-Soluble Vitamin Deficiencies

FOLIC ACID Low serum concentrations of folic acid are variably reported in 15% (6, 35), 25–44% (43), and 63% (33) of patients with inflammatory bowel disease. Macrocytosis may be seen in 10% of patients (33). Folic acid absorption was impaired in patients with ulcerative colitis and granulomatous colitis, and further reduced in patients taking the drug sulfasalazine (33). This drug interferes with folate-dependent enzymes and with the intestinal transport

system for folate (84). A clear relation between the use of sulfasalazine and the incidence of folate deficiency has been established in patients with ulcerative colitis (39).

VITAMIN B_{12} A significant correlation is reported between vitamin B_{12} absorption and the extent of terminal ileal disease and/or resection (35). In another study, the correlation between the Schilling test and the length of resection was confirmed but correlation of vitamin B_{12} absorption with the extent of disease was poor when the extent of the inflammatory lesion was less than 60 cm (27). Overall, abnormal Schilling tests are found in 48% of patients with Crohn's disease (6). With an ileal resection exceeding 90 cm, the Schilling test is abnormal in all patients (35). Furthermore, no compensatory mechanism seems to develop since absorption of vitamin B_{12} does not improve with time after resection (27).

OTHER B VITAMINS Specific deficiencies in thiamin, riboflavin, and pyridoxine have not been demonstrated in inflammatory bowel disease. However, case reports of pellagra in Crohn's disease appear in the literature. In one patient who presented with brown pigmentation on the dorsa of the hands typical of pellagra and an acute attack of psychosis, both responsive to vitamin B therapy, Crohn's disease was also demonstrated in small and large bowel (76). Malabsorption of nicotinic acid was suggested by oral and intramuscular loading tests. Recurrent pellagrous, a scaly rash on the face and hands, was observed in a patient concurrent with flares of Crohn's disease (60). The rash responded to nicotinamide replacement.

ASCORBIC ACID A low vitamin C intake is common in patients with Crohn's disease, particularly with a low residue diet. Serum and leukocyte ascorbic acid concentrations were significantly lower in twenty patients with Crohn's disease compared to controls (36). Among the clinical observations, the investigators noted that patients with fistulous tracts had lowest serum ascorbate levels.

Trace Element Deficiencies

IRON Iron deficiency anemia is very frequent in inflammatory bowel disease, largely because of chronic blood loss through the gut (5, 23, 59). A decreased ratio of iron to iron-binding capacity was found in 35% of Crohn's disease patients (6). Low serum hemoglobin and iron concentrations have been measured in about 80% of patients with predominantly colonic disease and in 30 to 60% of patients with predominantly ileal disease (43).

Iron deficiency may be difficult to diagnose by routine serum tests in patients with inflammatory bowel disease, since inflammation itself may affect the

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serum ion, transferrin, or ferritin levels. Serum ferritin levels are the most useful of these indices. A concentration greater than 55 ng/ml indicates adequate bone marrow iron reserves and a ferritin concentration of less than 18 ng/ml is highly predictive of iron deficiency (92).

ZINC Zinc deficiency in Crohn's disease is a result of reduced intake, impaired absorption, and most importantly gastrointestinal loss in diarrheal stool. Significant reductions in plasma and hair zinc have been documented, particularly in children with Crohn's disease and growth retardation (89). In a series of 52 patients with Crohn's disease, 40% had low serum zinc concentrations (65). Two other patients developed acrodermatitis-like skin lesions that responded to zinc treatment. A strong correlation exists between plasma zinc and albumin levels (99). The combination of decreased serum and urinary zinc found in 19% of Crohn's disease patients has been proposed as a better predictor of zinc deficiency (30). Zinc absorption was studied in seven patients with Crohn's disease using a short-lived isotope of zinc and was found considerably reduced: to a range of 8–45% compared to 38–75% in normal controls (91). In patients with diarrhea or high output fistulae, zinc balance was achieved parenterally with 6–12 mg of zinc per day. In patients without diarrhea, balance was achieved with 3 mg of zinc per day (97).

OTHER TRACE ELEMENTS Increased gastrointestinal losses of other trace elements is likely in patients with inflammatory bowel disease. In Crohn's disease patients with total gastrointestinal secretions above 300 g/day (including stool, fistulas, and stoma drainage), the mean copper loss was 0.30 mg/day, significantly higher than in patients with gastrointestinal secretions less than 300 g/day (86). In one study, plasma copper levels were no different in inflammatory bowel disease and control subjects (75). The same investigators report lower whole-blood concentrations of selenium in Crohn's disease but not in ulcerative colitis. However, the difference with controls was eliminated by correction for plasma albumin (75).

NUTRITIONAL ASSESSMENT OF A SERIES OF PATIENTS

At the University of Chicago, data on 133 consecutive in-patients with inflammatory bowel disease referred for nutritional consultation was evaluated. Ninety-nine patients had Crohn's disease and 34 had ulcerative colitis. All were severely ill and most were possible candidates for intensive nutritional support, i.e. enteral or parenteral nutrition. Anthropometric measurements are reported in Table 3, which reports the percentage of patients with values below 80% of standard. The frequency of decreased serum vitamin levels is given in Table 4

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Table 4 Prevalence of decreased serum vitamin levels in 133 hospitalized patients[a] in a University of Chicago series

Vitamin	Crohn's disease (%)	Ulcerative colitis (%)
Vitamin A	27	26
Vitamin D	23	35
Folic acid	42	41
Thiamin	5	11
Riboflavin	10	0
Pyridoxine	14	13
Vitamin B_{12}	5	0
Ascorbic acid	7	0

[a] Including patients receiving supplements before hospitalization.

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for both groups of patients. Vitamin A and D levels were obtained in all patients, folate levels in 80% of the group, and water-soluble vitamin concentrations in 43 patients with Crohn's disease and 17 cases with ulcerative colitis. Many patients had been treated with vitamin B_{12}, folic acid, and vitamin D, which may explain a lower frequency of deficient values than previously reported.

PRINCIPLES OF NUTRITIONAL THERAPY

The importance of correcting nutritional deficiencies in patients with inflammatory bowel disease cannot be overemphasized. Protein calorie malnutrition and deficiency of micronutrients also have documented effects on gastrointestinal function and structure (10, 55, 69, 80). The patient with inflammatory bowel disease who becomes significantly malnourished, therefore, may enter a vicious cycle where the secondary effects of malnutrition on gastrointestinal function and structure may lead to a further increase in gastrointestinal symptoms and malabsorption, which further worsens nutrient balance. In addition, it may be assumed that malnutrition will significantly depress the patient's ability to heal the inflammatory and structural changes in the bowel.

The overall therapeutic strategy must be to ensure adequate intake of nutrients while often modifying dietary intake to decrease gastrointestinal symptoms. The composition and pattern of nutrient intake must be adjusted to minimize stress on the bowel, which may be inflamed and in some cases narrowed. As with many gastrointestinal disorders, it is often useful to divide the diet into frequent, small meals to decrease the amount of food and gastrointestinal secretions that the diseased bowel must handle at any one point in time. Because enteric protein losses are almost always increased in active inflammatory bowel disease, such patients should be on a diet that provides perhaps 25% more than the usual recommended allowance of protein. Although patients with

inflammatory bowel disease have often been characterized as "catabolic" in the literature, recent studies indicate that for most patients energy expenditure is no greater than would be predicted for a healthy individual, unless the disease is complicated by marked fever or sepsis (4). Additional caloric intake, however, may need to be provided for patients who are severely ill or for those who have substantial gastrointestinal calorie losses because of malabsorption.

Micronutrient deficiencies have received less attention in this patient group. It must be recognized that many patients with inflammatory bowel disease will have subclinical micronutrient deficiency that can only be detected by measurement of appropriate serum nutrient levels, functional measurements, or coenzyme-dependent enzyme assays using circulating cells. In general, patients with inflammatory bowel disease should be placed on therapeutic multivitamins that provide one to five times the recommended dietary allowance. Patients with malabsorption, particularly those with intestinal resection, will often require even higher doses to correct micronutrient deficiency. In patients with significant ileal disease or resection, vitamin B_{12} should be provided by intramuscular injection providing at least 100 micrograms per month or 500–1000 micrograms every three months.

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Diet Modifications

Modifications in dietary intake are often recommended to patients with inflammatory bowel disease. Such changes in diet may have an impact on the adequacy of intake of various nutrients. A low-fiber diet is often recommended for patients with stenotic segments of the bowel and symptoms of obstruction in an effort to decrease obstructive symptoms. Some clinicians argue that a low-fiber diet may also be useful for decreasing symptoms of inflammatory disease by diminishing mechanical stimulation and irritation of the bowel. A recent study, however, suggested that patients receiving a high-fiber diet may actually experience a diminution of gastrointestinal symptoms (42). It should be noted that dietary fiber represents several different types of lignins and carbohydrates that have varying effects on gastrointestinal function (25). Whereas insoluble fibers increase gastrointestinal transit time and therefore may increase bowel frequency, soluble fibers such as guars and pectins may decrease transit time and because of their water-retaining capacity be useful in patients who are bothered by frequent watery bowel movements (2).

Lactose intolerance has been thought to be common in patients with inflammatory bowel disease. Recent studies, however, suggest that the prevalence of lactose malabsorption may parallel the prevalence in the appropriate ethnic group (12, 74, 51). Although some studies suggested that transient lactose malabsorption may be associated with flares in symptomatic inflammatory bowel disease, this has not been universally observed (12, 74). Since lactose-containing dairy products may be an important source of protein and the

predominant source of calcium in the diets of patients with inflammatory bowel disease, it is important to document accurately lactose malabsorption before simply removing these foods from the patient's dietary intake. This can be most effectively done by the use of a lactose hydrogen breath test, which allows the determination of the dose of lactose that is tolerated by the patient (70). In those patients who are lactose intolerant, it is often possible to select low lactose-containing dairy products to ensure continuing calcium and protein intake. The use of bacterial lactases such as Lactaid in dairy products may effectively improve the patient's tolerance of these foods (73).

Patients with Crohn's disease who have had substantial ileal resection or disease may develop steatorrhea. The fat malabsorption will also contribute to the patient's diarrhea, predominantly because fatty acids and their hydroxy fatty acid derivatives produced by colonic bacteria will stimulate fluid and electrolyte secretion by the colon (9). For this reason, a low fat diet is often recommended for patients who have substantial ileal resection or disease and a preserved colon. Recent reports have emphasized that patients with ileostomies will have similar fluid and electrolyte losses when consuming either high-fat or low-fat diets, presumably because the unabsorbed fat does not stimulate fluid and electrolyte secretion by the small intestine to the degree that it does in the colon (72, 98). Even in patients with ileostomies, however, the fat malabsorption may have undesirable nutritional effects (99). Some studies documented increased fecal losses of divalent cations such as calcium, magnesium, zinc, and copper that presumably bind unabsorbed fatty acids, although other investigators have not found increased divalent cations loss (72, 98). In addition, fat-soluble vitamins may be lost in greater amounts in patients having steatorrhea, although this loss has not been measured directly.

In general, we recommend a modest fat restriction to the level of about 70 g/day even in patients with ileostomy. This degree of fat restriction is tolerated well by the patient, can be met by the judicious use of commonly available foods, and does not require special nutritional supplements. More severe fat restrictions may be required in some patients with more extensive intestinal resections (96), but this will often make the diet unpalatable and may severely compromise the ability of the patient to meet his total caloric goals.

Calcium oxalate kidney stones are a common complication in patients with Crohn's disease who have had ileal resection (88). Such patients have increased urinary oxalate concentrations due to increased absorption of dietary oxalate (14). Studies in experimental animals and in man emphasize that the colon is the major site for oxalate absorption (21), and that most oxalate is absorbed by passive diffusion (20). Steatorrhea increases enteric hyperoxaluria by two mechanisms: (*a*) The unabsorbed fatty acids bind calcium, and therefore more oxalate is free in solution and available for colonic absorption. (*b*) Studies in rats show that the fatty acids increase the colonic permeability to oxalate (20).

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Dietary fat restriction lessens steatorrhea and is an effective approach toward lessening absorption and urinary supersaturation with oxalate (24).

Special attention must be paid to patients who are taking drugs that interfere with the absorption or metabolism of certain nutrients. For example, sulfasalazine has been shown to be a competitive inhibitor of intestinal folate absorption, and folate deficiency is common in patients who are taking this medication even while eating an unrestricted diet that is adequate in folate (33). Patients taking sulfasalazine should usually receive one milligram of folic acid per day. The bile salt-binding resin cholestryramine, used in patients with bile salt malabsorption and watery diarrhea, binds several nutrients such as folic acid and vitamin D, as well as potentially increasing steatorrhea (78). Patients on large doses of cholestryramine must therefore be monitored for the development of fat-soluble vitamin or folate deficiency and supplemented as needed. Accelerated osteomalacia has been described in patients with Crohn's disease and intestinal resections taking cholestyramine, and can be reversed by vitamin D treatment (16).

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Intensive Nutrition Support

For some patients with more severe intestinal disease or extensive resection, it is impossible to meet nutritional goals by a diet alone. Such patients can often be treated with various formula diets and supplements, which may be used as their total dietary intake or as a supplement to their diet. Types of enteral supplements available include meal replacement formulae, which are similar in composition to the normal diet, defined formula or elemental diets, which are generally low in fat and contain other nutrients in predigested or easily digested forms, and modular supplements, which are not complete feedings but are used to provide a specific nutrient (44). In patients with a more moderate disease and those who have not had extensive intestinal resection, modular feedings or meal replacement supplements are used since they are more palatable and are less costly for the patient. Defined formula diets should be reserved for those patients with severe malabsorption who will not tolerate the fat content of the meal replacement supplement. Useful modular supplements to be added to the patient's diet include medium-chain triglyceride oil as a source of calories in patients with steatorrhea, protein supplements as either powdered or liquid protein, and glucose polymer or partially hydrolyzed corn starch, which can provide well-tolerated carbohydrate calories.

There is now considerable experience with patients with active Crohn's disease and nutritional deficiencies who have been effectively treated by enteral supplements. Because of the lesser risk of serious complications compared with total parenteral alimentation, this approach is preferred whenever tolerated. A recent controlled trial emphasized the ability of a 500-calorie formula supplement to achieve nutritional repletion in patients with Crohn's disease, but

evidence for a decrease in gastrointestinal symptoms was less apparent (40). These low-residue formulas may be useful in the treatment of patients with Crohn's disease with enteocutaneous fistulae because nutrients are almost completely absorbed in the more proximal bowel and such diets might decrease the flow of intestinal contents past fistulae in the more distal bowel (11).

Difficulty in tolerating the taste of some of these supplements may limit the patient's ability to meet caloric requirements; this is sometimes circumvented by administering formulas via tube feeding. In addition, some patients who have excessive gastrointestinal symptoms when attempting to drink the formulae may be able to tolerate them as administered via tube at a slow, constant rate. The diarrhea that often accompanies the use of tube feedings in patients with inflammatory bowel disease can generally be controlled by administration of adequate amounts of antidiarrheal agents during the feeding. When possible, feedings should be done via nasointestinal tube, since this approach carries a lesser risk of aspiration than nasogastric feedings (13). For some patients, however, it may be preferable to take supplement via tube feedings at night (37). This allows them to eat a restricted diet during the day. Some patients may be taught to insert nasogastric feeding tubes for nocturnal nutrient infusions nightly (7).

Special mention should be noted of the usefulness of enteral supplements for children and adolescents with growth retardation due to inflammatory bowel disease (52). Several centers have documented that caloric deficiency is common in patients with growth retardation, and that nutritional supplementation, which allows the patient to achieve caloric goals, often results in resumption of growth (49, 52). Studies at the University of Chicago have emphasized the efficacy of nutritional supplements in the treatment of children with inflammatory bowel disease and growth retardation (52).

Total Parenteral Nutrition

Total parenteral alimentation has been an important advance in the management of patients with severe inflammatory bowel disease. Some patients with significant nutritional defects, who require surgery, are treated with total parenteral alimentation prior to operation. Several studies in patients with inflammatory bowel disease and other gastrointestinal disorders emphasize that a period of preoperative total parenteral nutrition (TPN) may be useful in reversing some of the immunologic and other abnormalities associated with malnutrition, and may be capable of reducing postoperative morbidity and mortality (68, 79). Further work needs to be carried out, however, to determine more accurately which patients will benefit from perioperative TPN, and to investigate the nutritional parameters that should be followed to indicate adequate nutritional repletion prior to surgery. At present, we recommend preoperative total parenteral alimentation for approximately seven to ten days

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in patients with significant nutritional depletion. We are unaware of evidence that longer periods of preoperative nutrition support are justified.

Our studies and those from a number of other centers stress the role of total parenteral alimentation and bowel rest in the management of patients with inflammatory bowel disease that has not responded to conventional medical treatment with corticosteroids, sulfasalazine, and other measures (83). Various series indicate that 40–80% of patients with serious Crohn's disease poorly responsive to medical treatment will experience a decrease in symptoms during a three- to four-week period of total parenteral alimentation and bowel rest (8, 26, 28, 38). Although long-term followup of patients who responded to this modality of treatment is incomplete, some patients have a prolonged clinical remission. Further studies are required to determine the optimal length of treatment with total parenteral alimentation and bowel rest, but many centers are now using home parenteral nutrition in order to decrease the cost and disruption of the patient's employment and other activities (29, 90). In addition, controlled clinical trials comparing total parenteral alimentation with modified bowel rest provided by the use of liquid supplements are needed to determine which patients will benefit most from each of these modes of treatment.

The retrospective experience with TPN and bowel rest in the treatment of severe exacerbations of ulcerative colitis is far less encouraging than that with Crohn's disease, by which one in three patients avoid colectomy (26, 28, 83). The only randomized, controlled study in patients with colitis demonstrated no advantage of TPN over standard hospital therapy (19).

Enterocutaneous fistulae are a common and debilitating complication of Crohn's disease and do not respond well to conventional medical treatment. Initial reports of total parenteral alimentation and bowel rest were optimistic; some patients experienced a permanent closure of these fistulae (38, 62, 68). More recent studies, however, show that total parenteral alimentation is less effective in causing permanent closure of fistula, with such closure occurring in only 30% of patients (8, 26). Some patients with Crohn's disease who have been treated surgically may develop postoperative enterocutaneous fistulae that tend to heal better with total parenteral alimentation and bowel rest; the more optimistic reports may have been describing patients with this type of fistula rather than those caused primarily by transmural inflammation due to Crohn's disease. Although fistulae due to Crohn's disease do not regularly close with total parenteral alimentation, it should be emphasized that patients with fistulae are often severely nutritionally depleted because of inability to eat and because of nutrient losses through the fistula track. A period of preoperative nutritional support prior to attempting to close the fistula and resect affected bowel is often useful.

As previously mentioned, growth retardation affects about 25% of patients with inflammatory bowel disease, and calorie insufficiency is a major factor in

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producing the delayed growth (49, 58, 90). Several recent studies have emphasized the utility of total parenteral alimentation in achieving calorie restitution and stimulating growth (52). It must be noted, however, that the use of modified diets or enteral supplements to meet the patient's caloric requirements will also result in improved growth. We therefore recommend total parenteral alimentation only for those patients with severe enough inflammatory bowel disease so as to preclude adequate oral caloric intake even with formula diets. For those patients with advancing bone age in whom the time available for growth is limited, we favor the use of parenteral alimentation to achieve caloric requirements if prospects for success by the enteral route are unlikely.

Long-term home parenteral alimentation has been used to meet nutrient requirements of patients with Crohn's disease who have had extensive intestinal resection resulting in the short bowel syndrome (29). Such patients can be safely and effectively maintained on home total parenteral alimentation, allowing nutritional and social rehabilitation in some of these patients. Study of such individuals on long-term home total parenteral nutrition has provided examples of some newly recognized micronutrient deficiency syndromes, such as vitamin E, biotin, selenium, and molybdenum deficiency (1, 45, 46, 67). In addition, metabolic bone disease consisting of both osteoporosis and osteomalacia appears in this patient group, although the cause of these disturbances in bone and mineral metabolism remains controversial (54, 85). It was recently emphasized that such patients are susceptible to formation of gall stones, presumably because the lack of stimulation by food results in stasis in the gall bladder, and because many of these patients have had ileal resections with depletion of bile salts and the related tendency toward lithogenic bile (66, 81). Home TPN patients may also develop chronic liver disease. Recent reports describe steatonecrosis in a rare patient on long-term total parenteral nutrition (17); children on long-term TPN often develop severe cholestasis, which may lead to portal hypertension and cirrhosis (18). Every effort therefore should be made to manage the patient with Crohn's disease and intestinal resections by oral or enteral approaches before embarking upon the expensive and somewhat risky approach of home total parenteral alimentation.

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Literature Cited

1. Abumrad, N. N., Schneider, A. J., Steel, D., Rogers, L. S. 1981. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. *Am. J. Clin. Nutr.* 34:2551–59
2. Anderson, J. W., Chen, W.-J. L. 1979. Plant fiber. Carbohydrate and lipid metabolism. *Am. J. Clin. Nutr.* 32:346–63
3. Arvanitakis, C. 1979. Abnormalities of jejunal mucosal enzymes in ulcerative colitis and Crohn's disease. *Digestion* 19:259–66
4. Barot, L. R., Rombeau, J. L., Feurer, I. D., Mullen, J. L. 1982. Caloric requirements in patients with inflammatory bowel disease. *Ann. Surg.* 195:214–18
5. Barr, M., Delava, S., Zetterstrom, R. 1975. Studies of the anemia in ulcerative colitis with special reference to the iron metabolism. *Acta Paediatr.* 44:62–72
6. Beeken, W. L. 1975. Remediable defects in Crohn's disease. *Arch. Intern. Med.* 135:686–90

Annu. Rev. Nutr. 1985.5:463-484. Downloaded from www.annualreviews.org by UNIVERSITY OF MIAMI on 01/05/12. For personal use only.

7. Bloch, A. P. 1983. Special needs of the home enteral patient. *Nutr. Support Serv.* 3:8–14
8. Bos, L. P., Nabe, M., Weterman, I. T. 1981. Total parenteral nutrition in Crohn's disease; a clinical evaluation. In *Recent Advances in Crohn's Disease*, ed. A. S. Pena, I. T. Weterman, C. C. Booth, W. Stroben, pp. 499–506. Boston: Martinus Nijhoff
9. Bright-Asare, P., Binder, H. J. 1972. Hydroxy fatty acids (OHFA) stimulate colonic secretion of water and electrolytes. *Gastroenterology* 62:727
10. Brown, H. O., Levine, M. L., Lipkin, M. 1963. Inhibition of intestinal epithelial cell removal and migration induced by starvation. *Am. J. Physiol.* 205:868–72
11. Bury, K. D., Stevens, R. V., Randall, H. T. 1971. Use of a chemically defined, liquid elemental diet for nutritional management of fistulas of the alimentary tract. *Am. J. Surg.* 121:174–83
12. Busk, H. E., Dahlerup, B., Lytzen, T., Binder, V., Gudmandhoyer, E. 1975. The incidence of lactose malabsorption in ulcerative colitis. *Scand. J. Gastroenterol.* 10:263–65
13. Cataldi-Betcher, E. L., Seltzer, M. H., Slocum, B. A., Jones, K. W. 1983. Complications occurring during enteral nutritional support: a prospective study. *J. Parenter. Enter. Nutr.* 7:546–52
14. Chadwick, V. S., Madha, K., Dowling, R. H. 1973. Mechanism for hyperoxaluria in patients with ileal dysfunction. *N. Engl. J. Med.* 289:172–76
15. Compston, J. E., Creamer, B. 1977. Plasma levels and intestinal absorption of 25-hydroxyvitamin D in patients with small bowel resection. *Gut* 18:171–75
16. Compston, J. E., Horton, L. W. L. 1978. Oral 25-hydroxyvitamin D_3 in treatment of osteomalacia associated with ileal resection and cholestyramine therapy. *Gastroenterology* 74:900–2
17. Craig, R. M., Neumann, T., Jeejeebhoy, K. N., Yokoo, H. 1980. Severe hepatocellular reaction resembling alcoholic hepatitis with cirrhosis after massive small bowel resection and prolonged total parenteral nutrition. *Gastroenterology* 79:131–37
18. Dahms, B. B., Halpin, T. C. Jr. 1981. Serial liver biopsies in parenteral nutrition–associated cholestasis of early infancy. *Gastroenterology* 81:136–44
19. Dickinson, R. J., Ashton, M. G., Axon, A. T. R., Smith, R. C., Young, C. K., Hill, G. L. 1980. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 79:1199–1204
20. Dobbins, J. W., Binder, H. J. 1976. Effect of bile salts and fatty acids on the colonic absorption of oxalate. *Gastroenterology* 70:1096–1100
21. Dobbins, J. W., Binder, H. J. 1977. Importance of the colon in enteric hyperoxaluria. *N. Engl. J. Med.* 296: 298–300
22. Driscoll, R. H., Meredith, S. C., Sitrin, M. D., Rosenberg, I. H. 1982. Vitamin D deficiency and bone disease in patients with Crohn's disease. *Gastroenterology* 83:1252–58
23. Dyer, N. H., Child, J. A., Mollin, D. L., Dawson, A. M. 1972. Anemia in Crohn's disease. *Q. J. Med.* 41:419–36
24. Earnest, D. L., Johnson, G., Williams, H. E., Admirand, W. H. 1974. Hyperoxaluria in patients with ileal resection: an abnormality in dietary oxalate absorption. *Gastroenterology* 66:1114–22
25. Eastwood, M. A., McKay, R. M. 1979. An hypothesis for the action of fiber along the gastrointestinal tract. *Am. J. Clin. Nutr.* 32:364–67
26. Elson, C. O., Layden, T. J., Nemchausky, B. A., Rosenberg, I. H. 1980. An evaluation of total parenteral nutrition in the management of inflammatory bowel disease. *Dig. Dis. Sci.* 25:42–48
27. Filipsson, S., Hulten, L., Lindstedt, G. 1978. Malabsorption of fat and vitamin B_{12} before and after intestinal resection for Crohn's disease. *Scand. J. Gastroenterol.* 13:529–36
28. Fischer, J. E., Foster, G. S., Abel, R. M., Abbott, W. M., Ryan, J. A. 1973. Hyperalimentation as primary therapy for inflammatory bowel disease. *Am. J. Surg.* 125:165–75
29. Fleming, C. R., Beart, R. W. Jr., Berkner, S., McGill, D. B., Gaffron, R. 1980. Home parenteral nutrition for management of the severely malnourished adult patient. *Gastroenterology* 79:11–18
30. Fleming, C. R., Huizenga, K. A., McCall, J. T., Gildea, J., Dennis, R. 1981. Zinc nutrition in Crohn's disease. *Dig. Dis. Sci.* 26:865–70
31. Florent, C., L'Hirondel, C., Desmazures, C., Giraudeaux, V., Bernier, J. J. 1981. Evaluation of ulcerative colitis and Crohn's disease activity by measurement of alpha-1-antitrypsin intestinal clearance. *Gastroenterol. Clin. Biol.* 5:193–97
32. Florent, C., L'Hirondel, C., Desmazures, C., Aymes, C., Bernier, J. J. 1981. Intestinal clearance of α_1 antitrypsin. A sensitive method for the detection

Annu. Rev. Nutr. 1985.5:463-484. Downloaded from www.annualreviews.org by UNIVERSITY OF MIAMI on 01/05/12. For personal use only.

of protein-losing enteropathy. *Gastroenterology* 81:777–80
33. Franklin, J. L., Rosenberg, I. H. 1973. Impaired folic acid absorption in inflammatory bowel disease: effects of salicylazosulfapyridine (azulfidine). *Gastroenterology* 64:517–25
34. Gerlach, K., Morowitz, D. A., Kirsner, J. B. 1970. Symptomatic hypomagnesemia complicating regional enteritis. *Gastroenterology* 59:567–74
35. Gerson, C. D., Cohen, N., Janowitz, H. D. 1973. Small intestinal absorptive function in regional enteritis. *Gastroenterology* 64:907–12
36. Gerson, C. D., Fabry, E. M. 1974. Ascorbic acid deficiency and fistula formation in regional enteritis. *Gastroenterology* 67:428–33
37. Greene, H. L., Helinek, G. L., Folk, C. C., Courtney, M., Thompson, S., et al. 1981. Nasogastric tube feeding at home: A method for adjunctive nutritional support of malnourished patients. *Am. J. Clin. Nutr.* 34:1131–38
38. Greenberg, G. R., Jeejeebhoy, K. N. 1981. Total parenteral nutrition in the primary management of Crohn's disease. See Ref. 8, pp. 492–98
39. Halsted, C. H., Gandhi, G., Tamura, T. 1981. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. *N. Engl. J. Med.* 305:1513–17
40. Harries, A. D., Heatley, R. V., Danis, V., Jones, L. A., Fifield, R., et al. 1983. Controlled trial of supplemented oral nutrition in Crohn's disease. *Lancet* 1:887–90
41. Heaton, K. W. 1977. Disturbances of bile acid metabolism in intestinal disease. *Clin. Gastroenterol.* 6:69–89
42. Heaton, K. W., Thornton, J. R., Emmett, P. M. 1979. Treatment of Crohn's disease with an unrefined carbohydrate, fiber-rich diet. *Br. Med. J.* 2:764–66
43. Hellberg, R., Hulten, L., Bjorn-Rasmussen, E. 1982. The nutritional and haematological status before and after primary and subsequent resectional procedures for classical Crohn's disease and Crohn's colitis. *Acta Chir. Scand.* 148: 453–60
44. Heymsfield, S. B., Bethel, R. A., Ansley, J. D., Nixon, D. W., Rudman, D. 1979. Enteral alimentation: an alternative to central venous hyperalimentation. *Ann. Intern. Med.* 90:63–71
45. Howard, L., Ovesen, L., Satya-Murti, S., Chu, R. 1982. Reversible neurological symptoms caused by vitamin E deficiency in a patient with short bowel syndrome. *Am. J. Clin. Nutr.* 36:1243–49
46. Johnson, R. A., Baker, S. S., Fallon, J. T., Maynard, E. P., Ruskin, J. N., et al. 1981. And accidental case of cardiomyopathy and selenium deficiency. *N. Engl. J. Med.* 304:1210–12
47. Jones, D. B., Kerr, G. D., Parker, J. H., Wilson, R. S. E. 1981. Dietary allergy and specific IgE in ulcerative colitis. *J. R. Soc. Med.* 74:292–93
48. Kasper, H., Sommer, H. 1979. Dietary fiber and nutrient intake in Crohn's disease. *Am. J. Clin. Nutr.* 32:1898–1901
49. Kelts, D. G., Grand, R. J., Shen, G., Watkins, J. B., Werlin, S. L., Boehme, C. 1979. Nutritional basis of growth failure in children and adolescents with Crohn's disease. *Gastroenterology* 76: 720–27
50. Kimberg, D. V., Baerg, R. D., Gershon, E., Graudusius, R. T. 1971. Effect of cortisone treatment on the active transport of calcium by the small intestine. *J. Clin. Invest.* 50:1309–21
51. Kirschner, B. S., DeFavaro, M. V., Jensen, W. 1981. Lactose malabsorption in children and adolescents with inflammatory bowel disease. *Gastroenterology* 81:829–32
52. Kirschner, B. S., Klich, J. R., Kalman, S. S., de Favaro, M. V., Rosenberg, I. H. 1981. Reversal of growth retardation in Crohn's disease with therapy emphasizing oral nutritional restitution. *Gastroenterology* 80:10–15
53. Kirsner, J. B., Shorter, R. G. 1982. Recent developments in "nonspecific" inflammatory bowel disease. *N. Engl. J. Med.* 306:775–85, 837–48
54. Klein, G. L., Ament, M. E., Bluestone, R., Norman, A. W., Targoff, C. M., et al. 1980. Bone disease associated with total parenteral nutrition. *Lancet* 2:1041–44
55. Koo, S. I., Turk, D. E. 1977. Effect of zinc deficiency on intestinal transport of triglyceride in the rat. *J. Nutr.* 107:909–19
56. Krawitt, E. L., Beeken, W. L., Janney, C. D. 1976. Calcium absorption in Crohn's disease. *Gastroenterology* 71: 251–54
57. Ladefoged, K., Nicolaidu, P., Jarnum, S. 1980. Calcium, Phosphorus, magnesium, zinc, and nitrogen balance in patients with severe short bowel syndrome. *Am. J. Clin. Nutr.* 33:2137–44
58. Layden, T., Rosenberg, J., Nemchausky, B., Elson, C., Rosenberg, I. 1976. Reversal of growth arrest in adolescents with Crohn's disease after parenteral ali-

Annu. Rev. Nutr. 1985.5:463-484. Downloaded from www.annualreviews.org by UNIVERSITY OF MIAMI on 01/05/12. For personal use only.

mentation. *Gastroenterology* 70:1017–21
59. Lehr, L., Schober, O., Hundeshagen, H., Pichlmayr, R. 1982. Total-body potassium depletion and the need for preoperative nutritional support in Crohn's disease. *Ann. Surg.* 196:709–14
60. Lucey, M. R. 1982. Recurrent pellagra in Crohn's disease. *Lancet* 2:559
61. Lukert, B. P., Stanbury, S. W., Mawer, E. B. 1973. Vitamin D and intestinal transport of calcium: effects of prednisolone. *Endocrinology* 93:718–22
62. MacFadyen, B. V. Jr., Dudrick, S. J. 1974. The management of fistulas in inflammatory bowel disease with parenteral hyperalimentation. In *Int. Congr. Parenteral Nutrition,* ed. C. Romieu, C. Solasscal, H. Joyeux, B. Astruc, pp. 559–69. Univ. Montpellier, France
63. Main, A. N. H., Mills, P. R., Russell, R. I., Bronte-Steward, J., Nelson, L. M., et al. 1983. Vitamin A deficiency in Crohn's disease. *Gut* 24:1169–75
64. Mayberry, J. F., Rhodes, J., Allan, R., Newcombe, R. G., Regan, G. M., et al. 1981. Diet in Crohn's disease. *Dig. Dis. Sci.* 26:444–48
65. McClain, C., Soutor, C., Zieve, L. 1980. Zinc deficiency: a complication of Crohn's disease. *Gastroenterology* 78: 272–79
66. Messing, B., DeOliveira, F. J., Galian, A., Bernier, J. J. 1982. Cholestasis during total parenteral nutrition: Demonstration of facilitating factors and association with gall bladder lithiasis. *Gastroenterol. Clin. Biol.* 6:740–47
67. Mock, D. M., De Lorimier, A. A., Liebman, W. M., Sweetman, L., Baker, H. 1981. Biotin deficiency: An unusual complication of parenteral alimentation. *N. Engl. J. Med.* 304:820–30
68. Mullen, J. L., Hargrove, W. C., Dudrick, S. J., Fitts, W. T., Rosato, E. F. 1978. Ten years experience with intravenous hyperalimentation and inflammatory bowel disease. *Ann. Surg.* 187:523–29
69. Nelson, R. A., Code, C. F., Brown, A. L. Jr. 1962. Absorption of water and electrolytes and mucosal structure, in niacin deficiency. *Gastroenterology* 42: 26–35
70. Newcomer, A. D., McGill, D. B., Thomas, P. J., Hofmann, A. F. 1975. Prospective comparison of indirect methods for detecting lactase deficiency. *N. Engl. J. Med.* 293:1232–35
71. Nyhlin, H., Dyckner, T., Ek, B., Wester, P. O. 1982. Magnesium in Crohn's disease. *Acta Med. Scand. Suppl.* 661: 21–25
72. Ovesen, L., Chu, R., Howard, L. 1983. The influence of dietary fat on jejunostomy output in patients with severe short bowel syndrome. *Am. J. Clin. Nutr.* 38:270–77
73. Payne, D. L., Welsh, J. D., Manion, C. V., Tsegaye, A., Herd, L. D. 1981. Effectiveness of milk products in dietary management of lactose malabsorption. *Am. J. Clin. Nutr.* 34:2711–15
74. Pena, A. S., Truelove, S. C. 1973. Hypolactasia and ulcerative colitis. *Gastroenterology* 64:400–4
75. Penny, W. J., Mayberry, J. F., Aggett, P. J., Gilbert, J. O., Newcombe, R. G., Rhodes, J. 1983. Relationship between trace elements, sugar consumption, and taste in Crohn's disease. *Gut* 24:288–92
76. Pollack, S., Enat, R., Haim, S., Zinder, O., Barzilai, D. 1982. Pellagra as the presenting manifestation of Crohn's disease. *Gastroenterology* 82:948–52
77. Powell-Tuck, J., Garlick, P. J., Lenhard-Jones, J. E., Waterlow, J. C. 1984. Rates of whole-body protein synthesis and breakdown increase with the severity of inflammatory bowel disease. *Gut* 25: 460–64
78. Roe, D. A. 1984. Nutrient and drug interactions. *Nutr. Rev.* 42:141–54
79. Rombeau, J. L., Barot, L. R., Williamson, C. E., Mullen, J. L. 1982. Preoperative total parenteral nutrition and surgical outcome in patients with inflammatory bowel disease. *Am. J. Surg.* 143:134–43
80. Rosensweig, N. S., Herman, R. H., Stifel, F. B., Herman, Y. F. 1969. Regulation of jejunal glycolytic enzymes by oral folic acid. *J. Clin. Invest.* 48:2038–45
81. Roslyn, J. J., Pitt, H. A., Mann, L. L., Ament, M. E., DenBesten, L. 1983. Gall bladder disease in patients on long-term parenteral nutrition. *Gastroenterology* 84:148–54
82. Russell, R. M., Smith, V. C., Multack, R., Krill, A. E., Rosenberg, I. H. 1973. Dark-adaptation testing for diagnosis of subclinical vitamin A deficiency and evaluation of therapy. *Lancet* 2:1161–64
83. Sales, D. J., Rosenberg, I. H. 1983. Total parenteral nutrition in inflammatory bowel disease. *Prog. Gastroenterol.* 4: 299–310
84. Selhub, J., Dhar, G. J., Rosenberg, I. H. 1978. Inhibition of folate enzymes by sulfasalazine. *J. Clin. Invest.* 61:221–24
85. Shike, M., Harrison, J. E., Sturtridge, W. C., Tam, L. S., Bobechko, P. E., et al. 1980. Metabolic bone disease in pa-

tients receiving long-term total parenteral nutrition. *Ann. Intern. Med.* 92:343–50
86. Shike, M., Roulet, M., Kurian, R., Whitwell, J., Stewart, S., Jeejeebhoy, K. N. 1981. Copper metabolism and requirements in total parenteral nutrition. *Gastroenterology* 81:290–97
87. Sitrin, M. D., Meredith, S. C., Rosenberg, I. H. 1978. Vitamin D deficiency and bone disease in gastrointestinal disorders. *Arch. Intern. Med.* 138:886–88
88. Smith, L. H., Fromm, H., Hofmann, A. F. 1972. Acquired hyperoxaluria, nephrolithiasis and intestinal disease. *N. Engl. J. Med.* 286:1371–75
89. Solomons, N. W., Rosenberg, I. H., Sandstead, H. H., Vo-Khactu, K. P. 1977. Zinc deficiency in Crohn's disease. *Digestion* 16:87–95
90. Strobel, C. T., Byrne, W. J., Ament, M. E. 1979. Home parenteral nutrition in children with Crohn's disease: effective management alternative. *Gastroenterology* 77:272–79
91. Sturniolo, G. C., Molokhia, M. M., Shields, R., Turnberg, L. A. 1980. Zinc absorption in Crohn's disease. *Gut* 21:387–91
92. Thomson, A. B. R., Brust, R., Ali, M. A. M., Mant, M. J., Valberg, L. S. 1978. Iron deficiency in inflammatory bowel disease: Diagnostic efficacy of serum ferritin. *Am. J. Dig. Dis.* 23:705–9
93. Thronton, J. R., Emmett, P. M., Heaton, K. W. 1979. Diet and Crohn's disease: characteristics of the pre-illness diet. *Br. Med. J.* 2:762–64
94. Valentin, N., Nielsen, O. V., Olesen, K. H. 1975. Muscle cell electrolytes in ulcerative colitis and Crohn's disease. *Digestion* 13:284–90
95. Waterlow, J. C., Golden, M. H. N., Garlick, P. J. 1978. Protein turnover in man measured with ^{15}N: Comparison of end-products and dose regimens. *Am. J. Physiol.* 235:E165–74
96. Weser, E., Fletcher, J. T., Urban, E. 1979. Short bowel syndrome. *Gastroenterology* 77:572–79
97. Wolman, S. L., Anderson, G. H., Marliss, E. B., Jeejeebhoy, K. N. 1979. Zinc in total parenteral nutrition: requirements and metabolic effects. *Gastroenterology* 76:458–67
98. Woolf, G. M., Miller, C., Kurian, R., Jeejeebhoy, K. N. 1983. Diet for patients with a short bowel: high fat or high carbohydrate: *Gastroenterology* 84:823–28
99. Young, E. A. 1983. Short bowel syndrome: high-fat versus high-carbohydrate diet. *Gastroenterology* 84:872–74

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