

Inflammatory Bowel Disease

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INTRODUCTION

From the earliest clinical descriptions of children with Crohn's disease (CD), it was clear that significant undernutrition is a major feature of the disease. Furthermore, growth retardation, which may have a nutritional component, is a common clinical manifestation. While on occasion undernutrition and short stature may be a feature of chronic ulcerative colitis (UC) in children, these manifestations are less prominent in this disease.

Early reports of nutritional therapy in children with inflammatory bowel disease (IBD) were thus aimed at the restoration of normal nutrition. More recently a body of evidence has shown that in children with CD nutritional therapy has a specific anti-inflammatory action in addition to its ability to restore their nutritional status to normal. Unfortunately there is no such firm evidence in children with UC, yet here also the provision of adequate nutrition still remains important.

The value of nutritional therapy in CD chiefly centers upon the use of exclusive enteral nutrition (EEN) in the treatment of active disease. Enteral nutrition may be defined as the provision of a liquid formula diet by mouth or by tube into the gastrointestinal tract.¹ Bottle feeding of normal infants is excluded from this definition. While it is now clear that oral feeding may be highly effective, research began with liquid formulas administered by intragastric tubes. The technique of tube feeding goes back at least as far as 1872, with a report by Clouston in the *Lancet* on "Forcible Feeding,"² while the work of Elsie Widowsen (1947) drew attention to the adverse effect of malnutrition upon human disease in general.³ The advent of effective parenteral nutrition then made clinicians aware how dramatic the benefits of nutritional rehabilitation from malnutrition could be. The development of a range of complete formula diets of varying compositions, designed for a range of situations, has now made enteral nutrition a highly desirable and practical alternative to parenteral nutrition.

It was Giorgini and colleagues in 1973 who first suggested that treatment of malnutrition could lead to resolution of inflammation in a child with CD.⁴ They described resolution of terminal ileal inflammation on barium follow-through after a period of elemental diet. In adults with CD, Logan and colleagues produced evidence that protein and lymphocyte loss from

the gut decreased during feeding with an elemental diet.⁵ Then in Quebec, Moran and colleagues described four children with CD whose growth failure responded to an elemental diet⁶ and this was confirmed in larger studies.^{7,8} In France, an elemental diet was given to children with CD by continuous nasogastric infusion. This was called constant rate enteral alimentation (CREN), but was a cumbersome technique not popular with the children. They used a complex regimen using oligopeptides, whereas others reported the use of a high-osmolality amino acid-based elemental formula. At St. Bartholomew's Hospital in London a semielemental diet using extensively hydrolyzed milk protein given intragastrically was shown in a small study to be as effective as conventional steroids in the induction of a clinical remission.⁹ Most importantly though this study showed there was no short-term growth while on steroid therapy, whereas enteral nutrition lead to short-term growth acceleration. In subsequent follow-up studies it was shown that this could on occasion be sustained for sometime if the child remained in remission even when back on a normal diet after the period of nutritional therapy.¹⁰ Central to this approach to therapy was the concept of a period of 6 to 8 weeks of enteral nutrition followed by a graded return to a normal diet.

ROLE OF DIET IN ETIOLOGY OF IBD

The etiology of IBD remains one of the greatest challenges in gastroenterology today. The presence of unexplained gut inflammation has inevitably led researchers to try and identify factors in our diet that may trigger, or even cause, IBD. While it appears highly likely that there are several environmental factors involved in the etio-pathogenesis of IBD,^{11,12} the evidence that some of these may be dietary remains tempting.

It was initially suggested that the adoption of an urban lifestyle may lead to an increase in the incidence of IBD, with increases occurring much more rapidly than could be explained by genetic factors alone.^{13,14}

Patients with a recent diagnosis of CD have been shown to consume greater quantities of sucrose than control groups,¹⁵ although this was not confirmed in patients with UC.¹⁶ Whether or not a diet low in fiber leads to an increased risk of CD remains disputed.¹⁷ Many of these studies

have had methodological problems and as a result make it difficult to confirm that dietary differences antedated the development of disease. Reif and colleagues,¹⁸ however, again showed that a high level of sucrose intake (>92 g/d) occurred before symptom onset in patients with both UC and CD (OR: 5.3 and 2.8, respectively), in contrast, fructose and fiber consumption were both negatively associated with a risk for IBD. This carefully controlled study also reported an increase in fat consumption prior to a diagnosis of IBD. These findings were mirrored by Geerling and colleagues¹⁹ who reported an increased risk of developing UC in those with a high consumption of monounsaturated and polyunsaturated (mainly n-6 PUFA) fats as well as Vitamin B6. Overall, these findings suggest no more than that a low residue; highly refined diet is associated with the development of IBD, while a high-fiber diet, rich in fruit and vegetables, may be more protective. Large, prospective epidemiological studies will be necessary to adequately control for the many confounding variables that could affect this type of data.

Conflicting evidence is also available on the role of butyrate in the pathogenesis of UC. Data suggest that butyrate levels decrease in the distal colon,²⁰ with the ability of colonic mucosa to utilize butyrate being reduced even in macroscopically "normal" mucosa of patients with quiescent UC.²¹ However, the response of distal UC and so-called diversion colitis to butyrate enemas has not been striking.^{22,23} Dietary sulfates have been implicated in reducing the ability of colonocytes to utilize butyrate by their conversion to toxic sulfides like H₂S,²⁴ although luminal levels of sulfides do not appear to be significantly higher in patients with UC than in normal controls.²⁵ However, along with a putative role of oxidant injury in the pathogenesis of UC, all these mechanisms appear more likely to be involved as mediators of the injury in UC, rather than primary etiological factors.

It is also of note that researchers have been accumulating evidence over a number of years implicating the food borne pathogen *Mycobacterium avium* subsp. *paratuberculosis* in the pathogenesis of CD. While a detailed discussion of this is beyond the scope of this chapter, the presence of this organism in the food chain and its persistence in milk despite pasteurization, along with the characteristic Th1 immune response it evokes,

continue to hold interest.²⁶ However, well-controlled clinical trials have failed to show any benefit of anti-tuberculous therapy.²⁷ Larger, population-based cohort studies are still needed to better define the importance of this and other specific dietary risk factors.

NUTRITIONAL COMPLICATIONS OF IBD

The chronic and relapsing nature of intestinal inflammation inevitably impacts on a patient's nutritional status. However, their nutritional state is not only determined by the dietary intake, but also by the patient's age, type of disease, disease distribution as well as their disease activity. These factors all contribute to the wide range of nutritional complications seen; from almost none in a child with mild distal UC, to the most severe nutritional consequences of chronically active disease in a child with pan-enteric CD. Nutritional complications are rarer in children with UC, although a severe pancolitis may present with acute weight loss and significant iron-deficiency anemia.

Caloric Deficiency and Growth Failure

The mechanisms surrounding the anorexia and undernutrition seen in IBD are complex and still poorly understood. As well as food avoidance as a result of abdominal pain or diarrhea, the reduction in caloric intake is due to the consequences of the systemic inflammatory response.²⁸ Protein-energy malnutrition may occur as a result of unchecked disease activity, with the associated anorexia being largely mediated by the proinflammatory cytokines IL-1 and TNF. Activity of these cytokines leads to lean tissue loss,²⁹ reduced voluntary motor activity,³⁰ and protein synthesis, with a concomitant increase in protein catabolism.³¹ This state of increased need may not be met during active inflammation, and thus leads to chronic undernutrition. Winter and colleagues elegantly demonstrated the recovery of impaired pancreatic and gastric secretory activity with increasing body mass index (BMI) in severely malnourished (BMI ~ 14) adults with CD.³² Protein intakes up to 1.5 g/kg body weight may be required per day to achieve adequate nutrition, with excessive supplementation perhaps even being counterproductive during the acute inflammatory state.³³ Increased protein oxidation and worsening of the nitrogen balance may result if overfeeding occurs during inflammation.³⁴ Calorie intake in children with CD cannot be accurately determined by using estimates of average requirements (EARs), as four in five children will consume about 120% of EAR (range 100 to 149%) while taking EEN as primary therapy at diagnosis.³⁵ Only the initial BMI was a predictor of subsequent weight gain on EEN, with a median of 11% being achieved over an 8-week course of treatment. Other authors have reported the intake in active disease to be 43 to 82% of recommended values, yet with adequate calorie supplementation, improvements

in linear growth can be achieved.³⁶⁻³⁸ However, simple nutritional restitution may be insufficient to achieve adequate growth, suggesting that other factors are also important in mediating growth retardation.³⁹ An elegant study by Azcue and colleagues⁴⁰ demonstrated an inappropriately maintained resting energy expenditure (REE) in children with moderately active CD when compared to children with anorexia nervosa and similar degrees of malnutrition. This relative increase in energy expenditure, together with the voluntary reduction in intake, further compromises nutritional status and hence optimal growth. Careful animal experiments, which did not look at body composition, suggest that it is the reduced caloric intake that is largely responsible for the weight loss seen in active colitis. However, in this animal study, while able to restore calorie intake and body weight to normal, nutritional supplementation was unable to restore linear growth. At least in this animal model, 30 to 40% of growth impairment is likely to be a direct result of the inflammatory process.⁴¹

Particularly in children with CD, active disease can have a profound and lasting effect on long-term growth,⁴² and this is covered in greater detail later in the chapter. Although it is well documented that up to 90% of children with CD may present with impaired height velocity,⁴³ Hildebrand and colleagues also reported a subnormal growth velocity (< -2 SD) in 24% of prepubertal children with UC, compared to 40% in those with CD.⁴⁴

Osteoporosis

Owing to the fact that this complication is largely a problem of adult life, it is easy to forget that the accumulation of peak bone mass occurs during adolescence and early adult life. The implications of a substantial interruption in this process are only now becoming clearer as better long-term bone density data are becoming available.

Much attention has focused on trying to tease out the relative importance of the factors that lead to reduction in bone mineral density (BMD) in patients with IBD. As the most important determinants of peak bone mass appear to be age and genetic potential, these confound almost all studies in IBD trying to identify possible predictors such as nutritional status, disease duration, activity and distribution, and steroid therapy. However, despite these shortcomings, it appears that up to 40% of adults with established IBD have osteopenia ($T \leq -1.0$; -1 to -2.5 SD from the mean), while around 10% have osteoporosis ($T \leq -2.5$; > 2.5 SD from the mean) when compared to age- and sex-matched controls.⁴⁵ The relative importance of disease activity, nutritional status, and cumulative steroid consumption remains debated. A large adult study did identify chronic steroid exposure as the only significant risk factor for the staggering 40% increased risk in osteoporotic fractures in adults with CD.^{46,47} Furthermore, it appears that BMD is no different to healthy age-matched adult controls within the first 6 months following symptom onset.⁴⁸ Inter-

pretation of BMD in the pediatric IBD population remains a problem in the face of significant pubertal and bone age delay.⁴⁹ However up to 30% of children are still likely to have a significantly reduced BMD,^{49,50} with children with CD tending to be more affected. Overall, therefore, both unchecked inflammation and chronic steroid exposure lead to loss of bone mass.⁵¹

The impact of nutritional status is unclear, as the correlation with BMD may well be confounded by disease activity. Ahmed and colleagues suggest that the growth failure seen in children with CD leads to a reduction in the size/length of their bones, thereby leading to falsely low values of BMD. If adjustments for bone size are made, bone mass in children with active CD appears to be better than previously reported. If bone area is not considered, up to 65% of children with CD would be labeled with moderate to severe osteopenia, while this falls to 22% if appropriate corrections are made.⁵² While aggressive nutritional restitution is likely to minimize the chance of nutritionally dependent bone loss, whether or not supplementation with vitamin D and/or calcium provides added benefits remains to be determined by placebo-controlled studies. Identification of children at greatest risk is important as urinary calcium excretion, plasma 25-OH vitamin D levels, and a baseline bone density scan allow monitoring and subsequent supplementation of documented deficiencies. There is great potential for bone remodeling if children are in good clinical remission. Following presentation with osteoporotic vertebral fractures and in a good nutritional state, a 16-year-old with CD displayed a dramatic recovery of vertebral height within 3 years of largely steroid-free therapy that controlled his disease activity.⁵³

The fact that the consequences of osteoporosis occur so long after the diagnosis of IBD in childhood makes it imperative for pediatricians to be aware of the BMD data now accumulating on adults with IBD. Several larger series are now reporting the clear association with lifetime steroid dose and the increased risk of osteoporotic fractures.⁴⁶ An ideal combination may be enteral nutrition and azathioprine/6-MP in the treatment of children with more severe CD. It is now clear that treatment regimens minimizing steroid therapy, and relying on nutritional therapy or other steroid-sparing agents, do not lead to the reduction in BMD seen in patients receiving corticosteroids. Although the mechanism is still unclear, infliximab has now been shown to increase markers of bone formation.^{54,55} Patients with a lifetime steroid exposure of 12.9 g have a significantly lower BMD than normal controls, while those with <2 g lifetime exposure are comparable to age-matched healthy controls.⁵⁶ However, it is also clear that osteopenia does occur in steroid-naïve patients.⁵⁷ Unchecked inflammatory activity may lead to calcium and vitamin D malabsorption, which in turn increases parathyroid hormone secretion and further bone resorption.⁵⁸ Patients with small-bowel disease

and/or resections are therefore also at risk of long-term osteoporosis.

Micronutrient Deficiencies

Identifying and treating macro- and micronutrient deficiencies are problematic for two main reasons. There is the initial difficulty of finding an accurate and reliable measure for each specific nutrient deficiency, followed by the inherent variability of a disease characterized by a remitting/relapsing course. There is also the impact of medical therapies and surgical interventions on nutrient status, eg, sulfasalazine inhibiting folate absorption and corticosteroids limiting calcium absorption. Clinically relevant micronutrient deficiencies in patients with IBD are unusual, and most are likely to occur when receiving long-term TPN.⁵⁹ Nonetheless, significant subclinical deficiencies in vitamins (B1, B6, C) and certain trace elements (magnesium, copper, and zinc) have been reported.⁶⁰

Vitamin B12 deficiency occurs most often in patients with active terminal ileal CD, or following a resection of this part of the intestine. In addition to the usual consequences of these deficiencies, low serum B12 and folate levels may result in an elevation of homocysteine and hence contribute to a hypercoagulable state,⁶¹ with folate supplementation leading to a reduction in homocysteine levels.⁶² Patients with IBD are also at risk of developing fat-soluble vitamin deficiency. A significant deficiency of both vitamin A and E has been documented in 16% of children with IBD, with moderate to severe disease activity leading to a deficiency in over 40% of children.⁶³ Whether or not this was a consequence of a poor dietary intake or disease activity was not made clear. The range of vitamin deficiencies in patients with long-standing IBD is wide. Two comprehensive studies documented deficiencies in biotin, folate, β -carotene, thiamine, and vitamins A, E, and C in 40 to 90% of adults, despite inactive disease and adequate dietary intakes.^{64,65}

Iron-deficiency anemia is difficult to diagnose in children with CD. Both the anemia of chronic disease and the variability in serum ferritin as part of the acute phase response make clear guidelines impossible. Low values of serum ferritin (<15 μ g/dL) certainly confirm iron deficiency, but this may also be present at much higher values. Combining the more stable serum transferrin receptor (sTfR) with serum ferritin has been of benefit in adults,⁶⁶ while a small pediatric study suggested basic red cell ferritin was a more reliable measure in the presence of inflammation.⁶⁷ Variable absorption and the common gastrointestinal adverse effects of oral iron also make the response to treatment difficult to interpret.⁶⁸ This, together with the potential exacerbation of colitis by the oxidative stress of oral iron supplementation, has led to successful trials of parenteral iron and erythropoietin use.^{69,70}

Trace elements are reduced in up to 50% of patients with active IBD,⁶⁵ with zinc deficiency being the most common.⁷¹ The latter has been implicated in the maintenance of intestinal barrier

function by regulating tight-junction permeability, with supplementation leading to a reduction in gut permeability in both animal models of colitis and adults with active CD.⁷² Authors have shown significantly reduced fractional zinc absorption in adolescents with stable CD compared to normal controls. This appears to be due to unusually high fecal zinc losses.⁷³

Many micronutrients are also antioxidants (Vitamin A, E, C, and selenium), and thus adequate supplementation may help counteract some of the oxidative stress that contributes to ongoing gut inflammation. Both serum selenium and erythrocyte glutathione peroxidase activity have been inversely correlated to plasma TNF- α levels in patients with active CD.⁷⁴

OTHER NUTRITIONAL CONSEQUENCES OF IBD

Patients with long-standing IBD may of course also suffer the nutritional consequences of their therapies. Sulfasalazine is most notable for its impact on folate metabolism by competitively inhibiting dihydropterolate reductase, but folate rarely requires supplementation. Patients with severe ileitis or a significant ileal resection may develop steatorrhea, which in turn binds available free calcium, thus preventing calcium from binding to oxalate. High concentrations of luminal oxalates may lead to hyperoxaluria and renal calculi. A significant decrease in essential fatty acids has been correlated with a BMI <50th centile and active CD,⁷⁵ irrespective of dietary intake.

INDICATIONS FOR NUTRITIONAL TREATMENT

The indications for nutritional intervention differ among the different types of IBD. However, adequate nutritional support is an essential part of the long-term management of any chronic inflammatory disorder. In most cases this involves the provision of nutritional supplements to complement an otherwise inadequate intake and may involve anything from overnight nasogastric feeds to long-term support on home parenteral nutrition. For UC, no exclusively nutritional therapy has been shown to be therapeutically effective. In contrast, over many years patients with active CD have responded well to EEN. There have only been anecdotal reports of patients with indeterminate colitis responding to EEN, although the responders are likely to be those with a more Crohn's-like phenotype.

UC

There have been no studies showing that any form of nutritional intervention, used as sole therapy, can induce a remission in patients with active UC. Two randomized, prospective studies^{76,77} clearly showed there was no role for exclusive total parenteral nutrition and bowel rest in the management of acute UC. Although there

Table 1 Contraindications to Enteral Feeding

- Massive hemorrhage
- Intestinal obstruction
- Bowel perforation
- Toxic dilatation

were some nutritional advantages in the group on TPN, these were outweighed by the complications reported at the time.

Although often not as severe as in patients with CD, malnutrition does occur in children with UC.⁷⁸ However, while exclusively nutritional therapies are of no benefit in treating acute UC, nutritional support plays a vital role in minimizing further morbidity. Up to 10% of children with UC present with weight/height z-scores ≤ -2 ,⁷⁹ and inevitably nutrition is compromised in acute disease, both by a reduced oral intake and by increased losses of both protein and blood from the gut mucosa.⁸⁰ Although the concept of continuing enteral feeds during an episode of acute colitis may raise concerns in some, the evidence clearly suggests that equal nutritional improvement occurs with TPN and total enteral nutrition (TEN) in active colitis.⁸¹ Not only does the latter lead to fewer complications, it is less costly, more physiological, and much simpler to provide. However, there continue to be absolute contraindications to enteral nutrition (Table 1).

Although dietary supplementation plays a role in acute UC, there is no evidence that specific dietary exclusions are of benefit in the long-term. Well-balanced, healthy diets that include normal amounts of dietary fiber are to be encouraged. Short-term studies suggest improved gastrointestinal symptoms on isphaghula husk,⁸² although initial data that suggested diets low in fiber were linked to an increased risk of colon cancer have now been refuted in large epidemiological surveys in women.⁸³

CD

In children with CD there are several reasons for nutritional intervention (Table 2).

Exclusive Enteral Nutrition. EEN is indicated as a first-line therapy in any child with acute CD, provided there are no absolute contraindications to enteral nutrition per se. The issue of whether or not enteral nutrition is as effective as steroid therapy at inducing a remission has been hotly

Table 2 Indications for Nutritional Therapy in Crohn's Disease

- Exclusive enteral nutrition for active disease
- Perioperative parenteral nutrition and bowel rest
- Supplemental enteral nutrition for maintenance of disease remission
- Nutritional support to maintain adequate weight gain
- Dietary supplementation of specific vitamins/minerals

debated for some time. However, what is clear from the pediatric literature over the past 20 years is that an exclusively nutritional therapy can be highly effective at inducing a remission from active disease.⁸⁴⁻⁸⁶ The best results appear to be in those children with newly diagnosed disease,⁸⁷ although the pediatric evidence does remain limited in terms of the number of children reported. Large adult studies,^{88,89} as well as some of the smaller pediatric studies,⁸⁶ suggest disease distribution does not affect the efficacy of the treatment. Colonic disease appears to respond as well as terminal ileal disease, with a similar reduction in inflammatory markers, disease activity, and improved mucosal histology.⁸⁵ More recent retrospective data however suggest that clinical remission with isolated colonic disease may only be about 50%, compared to about 75 to 80% in the presence of any macroscopic ileal involvement.⁹⁰ Although there is only anecdotal evidence on the response of oral and perianal CD to EEN,⁹¹ the authors have made use of EEN as an adjunct in treating severe perianal CD.

Adverse effects to using EEN in CD are very rare. However, we reported a case of refeeding syndrome in a child following her presentation with severe Crohn's colitis. A rapid loss of weight over the preceding 4 weeks, followed by treatment with exclusive polymeric nutrition, led to a dramatic fall in serum phosphate and signs of hypervolemia in the first few days of treatment.⁹² It is important to remain aware of this complication when refeeding previously malnourished children with CD, as adequate supplementation in the first few days can prevent serious complications.

Perioperative Nutritional Support. Preoperative undernutrition has long been known to adversely affect surgical outcome. Although surgical outcome is related to the nutritional state of the patient,⁹³ short-term preoperative use of TPN is insufficient to dramatically improve the nutritional status. Even 7 to 10 days of preoperative parenteral nutrition in malnourished "cancer" patients achieved only a 10% reduction in postoperative complications.⁹⁴ Parenteral nutrition may replace acute nutritional deficits in the immediate perioperative period and may also reduce length of small-bowel resection in adults with CD.^{95,96} Uncontrolled studies in adults with IBD also suggest there is a reduction in postoperative complications following preoperative parenteral nutrition,⁹⁷ yet it appears most effective in patients with severe malnutrition and highly active disease.⁹⁸

Improvements in the medical management of children with IBD are likely to continue reducing the need for surgery, yet recent studies still suggest that almost 60% of adults with CD will require an operation.⁹⁹ Older pediatric data showed that up to 80% of children with CD were needing surgery in the 15 years following diagnosis.¹⁰⁰ Emergency surgery may be unavoidable in a small number of children who present with fulminant colitis; however the majority will require surgery for treatment-resistant disease.

While a child with acute, severe UC will require close monitoring of fluid and electrolytes in the perioperative period, they are less likely to have had a long period of active disease leading to chronic malnutrition.

Despite persistently active, treatment-resistant disease, surgery can often be planned some weeks in advance. In these circumstances, optimizing nutrition over a period of 4 to 6 weeks is likely to result in a much better postoperative course. Provided inflammatory activity and symptoms allow, several weeks of EEN in children with severe CD can lead to nutritional restitution prior to surgery. In isolated cases, the use of TPN for a several weeks may also be justified in preparation for if enteral access is impossible. However, clinicians can be forced to compromise in the face of severe treatment-resistant disease, where disease activity does not allow time for any improvement in nutritional state and surgery should then not be delayed.

Postoperative support for all children, irrespective of the type of abdominal/perianal surgery, should involve institution of enteral feeds as soon as possible. Adult evidence demonstrates no increase in complications when patients are fed enterally within 48 hours of colectomy.¹⁰¹ Very early use of enteral supplements reduces early postoperative complications even in undernourished adults, and leads to a better weight gain, as well as an improvement in physical and mental quality of life.¹⁰² Routine use of postoperative TPN in well-nourished patients should be discouraged as it increases complication rates.¹⁰³ However provision for TPN should still be made if enteral feeding is likely to be delayed for more than 1 to 3 days in any undernourished child who is likely to suffer a long convalescence without achieving full enteral feeds.

NUTRITIONAL TREATMENT OF ACTIVE CD

In severe malnutrition there is clear evidence of a secondary immune dysregulation.¹⁰⁴ Both T-cell numbers and secretory IgA levels are consistently reduced, and there are also defects in bacterial phagocytosis, lysozyme, and interferon production. While today's children with CD are not often severely malnourished, they are certainly well below their expected centile for weight.¹⁰⁵ It is therefore quite clear that this degree of malnutrition does little to attenuate tissue damaging immune responses.

Parenteral Nutrition

The advent of parenteral nutrition in the early 1970s proved useful in managing intractable cases of CD¹⁰⁶ and its use became more widespread as an alternative primary therapy for severe disease.¹⁰⁷ As would later be clearly demonstrated for enteral nutrition,⁴² it was parenteral nutrition that was first shown to reverse growth failure in children and adolescents with active CD.^{37,108} However, as awareness of the septic and thrombotic complications associated with an indwelling line increased, the use of parenteral

nutrition in CD declined. While it still appears to be as effective as elemental nutrition in the short-term treatment of acute disease,¹⁰⁹ its complications, practical difficulties, and expense, limit its use. Furthermore, total parenteral nutrition induces mucosal atrophy and increases bacterial translocation,¹¹⁰ something that is entirely preventable by luminal nutrition.

The combination of intravenous nutritional support and complete bowel rest has not been shown to be more effective in treating active disease than either EEN or TPN with oral feeding.¹¹¹ In a controlled study, 58 to 71% of all groups achieved a clinical remission, indicating that bowel rest per se has no added effect on the disease, but that improved nutrition in any form has clinical benefit. However, there have also been a number of case series suggesting that exclusive parenteral nutrition may be of significant benefit in severe Crohn's colitis,⁹⁵ with at least one study documenting endoscopic healing of mucosal ulcers on exclusive PN.¹¹² Despite this, the preference for nutritional support in most cases remains an enteral feed.

There has been limited success (35%) in achieving fistula closure on exclusive TPN,¹¹³ with any improvement not being sustained once back on a normal diet. In view of other therapies, such as octreotide and anti-TNF α antibody, TPN now has only a very limited role in the management these fistulae.

Children only rarely have bowel resections large enough to require long-term home parenteral nutrition support. However, in adults less than 100 cm of jejunum, or less than 50 cm of small bowel with an intact colon remain, long-term parenteral nutrition is often necessary.¹¹⁴ Yet over 70% of these patients will be on a full oral diet within 12 months of starting home parenteral nutrition.¹¹⁵

Enteral Nutrition

Elemental Diet. An elemental feed is a chemically defined diet whose protein source is amino acids or short-chain peptides, with short-chain carbohydrates and added fat, minerals, and vitamins. The National Aeronautics and Space Administration (NASA) had initially designed elemental diets for astronauts.¹¹⁶ This was with the intention of providing a nutritionally complete diet of which as much as possible would be absorbed. However, while absorption was limited mainly to the upper small bowel, the diet did not prevent the production of stool as had been hoped.

Nutrition was initially used in IBD as an adjunct in malnourished patients with growth failure. Elemental diets were developed and first used as sole therapy for IBD in adults in the 1970s.¹¹⁷ It was then shown that nutrition had a beneficial effect on disease by reducing the increased gut permeability characteristic of CD.⁵ Logan and colleagues studied seven adults with extensive jejunoileal CD. They showed a reduction in both gut protein and gut lymphocyte loss during a period of elemental feeding. This was the first report that an

elemental diet could directly improve gut function, probably by reducing bowel inflammation.

In 1973 Giorghini and colleagues⁴ reported the first successful use of enteral nutrition in treating a child with acute CD. It was then shown that enteral nutrition was effective in treating a series of children with CD. Successful use in combination with drug therapy led on to a further study by the same group, which first showed exclusive CREN to be as effective as steroid therapy at inducing a remission.¹¹⁸ While both these studies had a few patients, they gave the first insights into the possible benefits of nutritional therapy as treatment for childhood CD. In addition to achieving disease remission, nutritional therapy was also found to have beneficial effects on inflammatory masses and fistulae.^{6,118} Simultaneously, both Morin and colleagues⁶ and O'Morain and colleagues,¹¹⁹ documented that an elemental diet improved linear growth in several children with active CD.

A variety of devices, formulas, and regimens were then used to feed patients intragastrically. Continuous feeding^{7,8} and then overnight feeds predominated⁹ for the induction of remission. Supplementation of an elemental diet with glutamine, a gut-specific metabolic fuel, did not further improve efficacy, although the small numbers in this study make conclusions difficult.¹²⁰

Semielemental Diet. Once elemental diets had achieved their first successes, short-chain peptide-containing diets were suggested as a better nitrogen source than amino acids.¹²¹ Silk and colleagues refuted previous evidence that free amino acids were better absorbed than di- and tripeptides. By using an intestinal perfusion technique in adults, he was able to demonstrate better absorption of amino acids from both casein and lactalbumin hydrolysates, than from an equimolar feed of free amino acids. Not only was there a more uniform absorption of amino acids, but the hydrolysates had a beneficial effect on jejunal absorption of water and electrolytes. There followed the first small randomized study of 7 to 8 children in each group, in which overnight nasogastric feeding of a semielemental diet was compared to prednisolone treatment in children with predominant small bowel CD.⁹ A 4–5-chain amino acid-based diet was as effective as steroids at achieving a remission in active CD. It again confirmed the North American finding that there was a clear acceleration in growth in the group not taking steroids.

Polymeric Diet. It therefore appeared that steroids may have a similar efficacy to semielemental feeds in the induction of remission. Several adult studies reported the efficacy of whole-protein diet compared to both that of elemental diets and to steroids. Raouf and colleagues¹²² and others all found polymeric diets to be as effective as an elemental diet at inducing remission.

Polymeric diets were also shown to be as effective as conventional steroid treatment. Gonzalez-Huix and colleagues¹²³ confirmed this in adults, and Ruuska and colleagues⁸⁶ and Beattie and colleagues⁸⁴ in children. Ruuska and colleagues,⁸⁶ in a well-planned but small study ($n = 19$), showed a

polymeric diet to be as effective as steroids in inducing a remission in children with acute CD. A further great advantage in using a polymeric diet then became clear. While almost all children previously required feeding by intragastric tube, whole protein formulas such as AL110 (Nestlé-Clintec), used by Beattie and colleagues⁸⁴ and Nutrison Standard (Nutricia), used by Ruuska and colleagues,⁸⁶ were palatable enough for daily oral consumption. Children rarely required a nasogastric tube to complete their entire nutritional needs. This provided a considerable improvement in the quality of life for children on several weeks of nutritional therapy.

The most recent, and most definitive cohort study to date, by Fell and colleagues,⁸⁵ shows that a whole casein, polymeric diet CT 3211 (now known as Modulen IBD, Nestlé Clinical Nutrition), rich in transforming growth factor β , is well tolerated and achieves a clinical and histologic remission. Twenty-nine consecutive patients were treated with the exclusive enteral diet for an 8-week period. Although over half had mild disease, 12 had moderate to severe disease with a pediatric Crohn's disease activity index (PCDAI) >30 .¹²⁴ A nasogastric tube was only required in one patient for the first 2 weeks of treatment. Only 2 of 29 patients failed to show any clinical response, one with severe colonic disease, the other with an inflammatory mass requiring surgery. Twenty-three of 29 patients achieved a complete remission on PCDAI scoring. The PCDAI fell dramatically within 2 weeks of starting the diet, but continued to fall until 8 weeks of treatment. There was significant macroscopic and histologic improvement after treatment, with mucosal healing occurring in the terminal ileum and colon of 8 and 2 patients, respectively. Serum TNF α and mucosal mRNA for IL-1 β and IL-8 were significantly reduced in both the terminal ileum and the colon after treatment. IFN- γ was significantly reduced and transforming factor beta (TGF- β) was elevated in the terminal ileum alone. There is no direct evidence that the TGF- β in the enteral formula is responsible for the upregulation of mucosal TGF- β . Nonetheless, this study strengthens the findings by Breese and colleagues¹²⁵ that polymeric enteral nutrition alone can achieve an improvement in histology and a complete normalization of some of the mucosal messenger RNA of proinflammatory cytokines involved in tissue damage. Bannerjee and colleagues documented the most rapid reduction in proinflammatory cytokines to date, in children receiving EEN for active CD.¹²⁶ Within 3 days of starting an exclusive polymeric diet, there was a significant reduction in IL-6 and ESR. This, together with improvements in CRP, IGF-1, and PCDAI by Day 7, predated any measures of nutritional restitution (mid-upper arm circumference/triceps skinfold thickness). Further evidence that nutritional therapy in this situation is providing more than an optimal calorie intake.

The lipid composition of some polymeric diets has been held responsible for some of the variability in their efficacy.¹²⁷ High LCT concentrations have been associated with a poorer response in treating active CD, with suggestions that the high linoleic acid concentration may be

responsible,¹²⁸ although high concentrations of MCT in the feed does not effect its short-term efficacy.¹²⁹ However, the only two randomized studies have been unable to show a difference in efficacy between formulas containing either low or high amounts of long-chain triglyceride.¹³⁰ Only one randomized study appeared to show a significant difference in remission rates depending on the fatty acid composition of the polymeric feeds. Gassull and colleagues report a significantly better clinical remission rate in adults after 4 weeks of an exclusive enteral feed rich in n-6 fatty acids, compared to one high in monounsaturated fats (52% vs 20%, respectively).¹²⁷ Why this conflicts with previous evidence¹²³ remains unclear, although the high percentage of synthetic oleate (79% of total fat) in this study may mask beneficial effects previously seen with formulae containing different fatty acid profiles.

There is limited evidence of milk intolerance in adults with active CD. True lactase deficiency is an unusual cause of symptoms in adults with active CD¹³¹; however up to 46% complained of gastrointestinal symptoms related to milk intake. In contrast, exclusive enteral feeding with lactose-free, whole-casein diets has not been associated with intolerance in children with active disease.

Steroids Versus Enteral Nutrition. Contrary to these striking pediatric findings, large adult trials^{81,88,132} as well as meta-analyses of the adult data, have found steroids to be more effective than enteral nutrition at inducing remission in active CD.¹³³ The meta-analysis by Griffiths and colleagues,¹³³ while including both children and adults, excluded most of the smaller pediatric studies. This large review ($n = 413$) reported that steroids were significantly more effective at achieving a remission than enteral diets (OR: 0.35; 95% CI 0.32 to 0.58). Like other analyses, this study also relies on clinical disease activity indices to document clinical remission rates, but these tend to favor steroid therapy by their reliance on a patient's general feeling of well-being. As a result, conclusions from these studies are frequently and inappropriately applied to children, despite there being clear differences between adult and pediatric patients. Most children have had much shorter disease duration and tend to be much more compliant with therapy. Furthermore, no comment is made on the differing adverse effects and abilities of the two treatments to heal gut mucosa, with steroids having been well-documented to have limited effects on gut inflammation.¹³⁴ As yet no analysis has detected a significant difference in efficacy between elemental or polymeric diets.¹³⁵

Despite the several small pediatric studies that suggest a useful role for enteral nutrition in active CD, the view has thus prevailed that enteral nutrition is less effective than steroid therapy. A meta-analysis of pediatric data was performed to maximize the available pediatric data.¹³⁶ Despite limited numbers of truly randomized children, sensitivity analyses allowed the authors to arrive at valid and important conclusions. The summary data clearly showed enteral nutrition to be as effective as steroids in the treatment of children

with active CD. Furthermore, to overturn this finding and demonstrate that steroids were significantly more effective than enteral nutrition would be close to impossible given the outcomes of the pediatric studies reported to date. All these studies principally address efficacy as their primary outcome measure, largely ignoring the very different side effect profiles of each therapy. Corticosteroids have many significant adverse effects, while oral enteral nutrition has almost none. Prospective observational studies have also highlighted that even in the pediatric age group about 30% of children with CD, treated with corticosteroids within 30 days of diagnosis, are corticosteroid dependent at 1 year.¹³⁷

Enteral Nutrition and Crohn's Colitis. There remains the further question of whether enteral nutrition is less effective at treating Crohn's colitis than Crohn's ileitis. Early use of enteral feed was limited to children with predominantly small bowel disease,¹³⁸ with a suggestion that colonic disease was unresponsive to nutritional management.¹³⁹ More recent evidence from Thomas and colleagues,¹⁴⁰ Ruuska and colleagues,⁸⁶ and Fell and colleagues,⁸⁵ however, supports the value of nutritional therapy in large bowel and small bowel disease. The improvement in colonic mucosal cytokine profiles after enteral nutrition⁸⁵ provides hard evidence that there is an effect on colonic disease. Larger studies in adults also confirm that disease location does not appear to influence the response to treatment.^{88,132,133}

However, a more recent retrospective analysis of 60 children treated with EEN suggested disease distribution may be relevant in the response to nutritional therapy. Children with any macroscopic ileal inflammation were significantly more likely to achieve a clinical remission than those children with colonic involvement alone (75% vs 50%).¹⁴¹ Despite this, many individuals with Crohn's colitis continue to respond extremely well, still making EEN the first choice for any child with CD, irrespective of their disease distribution.

Food Reintroduction

There has long been uncertainty as to the best way of reintroducing adults and children onto their "normal" diet after a period of EEN. The evidence for any of these different practices is very limited, with most approaches having been selected by experienced clinicians on the basis of theories prevalent at the time.

The best-described reintroduction program is based on the stepwise introduction foods, starting with the least allergenic.¹⁴² One new food is introduced every 48 hours and if not tolerated, reintroduced at the end of the program. This systematic, but quite laborious program not only allows individual foods to be identified if causing immediate symptoms, but also gives the patients several more weeks on reasonable quantities of enteral nutrition while their normal diet is re-established. The most frequently implicated foods causing discomfort in adults are cereals, dairy products, and yeast,¹⁴² although in children only a very

small minority require exclusion of specific items from their diet. In a 2-year follow-up study of about 100 adults, the relapse rate was only just significantly lower in the group excluding dietary products that caused symptoms compared to those maintaining a normal diet ($p = .048$). However, in a randomized controlled trial of an exclusion diet following a remission induced with an elemental diet, subsequent rechallenge and double-blinded challenges in adults with CD proved that specific dietary exclusions did not persist.¹⁴³ There is thus insufficient evidence to routinely suggest exclusion of specific food items in children with CD.

Other units use less evidence-based, but more practical, reintroduction programs which range from the immediate introduction of a full diet, to a graded introduction over 3 weeks with the "ad libitum" diet increasing by 25% each week, along with the simultaneous reduction in enteral nutrition.

ENTERAL NUTRITION AS MAINTENANCE THERAPY IN CD

There has been much interest in whether dietary modification may prolong a remission in CD.

Initial studies suggested intermittent use of EEN for 1 month in every four could not only reduce steroid requirement and reduce disease activity, but also increase long-term growth rate in children with CD.¹⁴⁴ While this intermittent use of EEN may have had a role in managing patients with otherwise intractable disease and a previous good response to enteral nutrition, repeated and prolonged use of exclusive enteral diets in most adolescents is difficult and mostly unnecessary. Given the availability of other, currently more effective maintenance agents, compliance with supplements of enteral nutrition is likely to be much greater if these can be shown to be effective.

Low-residue diets are not indicated in the maintenance of remission in CD. Unless required as a dietary modification in the presence of fibrosing/stricturing disease, they have not been shown to prevent disease relapse.¹⁴⁵

A retrospective study in which a normal "ad libitum" diet of children with CD was supplemented with an additional 30% of the recommended daily calorie intake as polymeric feed led to the halving of relapse rates within the first 12 months.¹⁴⁶ Small controlled studies also suggest an advantage to simple long-term calorie supplementation per se,¹⁴⁷ although larger, more definitive studies are still awaited. However, it is highly likely that a long-term nutritional supplement, in combination with a well-tolerated immunosuppressant, will provide the optimal maintenance therapy for most children with moderate to severe CD.

Attempts at supplementing diets with specific antiinflammatory agents continue, with fish oils receiving particular attention. Their effects on reducing mucosal eicosanoids (particularly leukotriene B4 and thromboxane A2)¹⁴⁸ have been widely reported. The n-3 fatty acids present in

fish oils may also inhibit interleukin-1 β and TNF production.¹⁴⁹ In addition, they also decrease platelet responsiveness,¹⁵⁰ and thus may act to reduce the multifocal gastrointestinal infarctions that have been reported as early pathogenic steps of CD.¹⁵¹ Several large placebo-controlled, randomized studies have been performed on adults with both CD and UC,^{152,153} but unfortunately much of the data remain conflicting. Although different methodology makes generalizations difficult, several important issues are raised. While low-dose regimens cause no appreciable adverse effects,¹⁵⁴ compliance with high-dose fish oils in adults is poor, making long-term maintenance therapy in children even less attractive. Belluzzi and colleagues¹⁵² found that supplementation with 2.7 g of n-3 fatty acids reduced the relapse rate in adults with CD, while another large study failed to confirm any benefit over placebo in using either >5 g/d of n-3 fatty acids, or maintaining a diet low in carbohydrate (84 g/d).¹⁵³ However, despite no clear-cut clinical benefits, significant changes are reported on a mucosal level. Colonic inflammatory cell infiltrates are reduced and the synthesis of LTB4 and TXA2 downregulated after supplementation with n-3 fatty acids.¹⁵³ It may therefore be that further refining of the composition, formulation, and dose is required before fish-oil supplements become an accepted part of maintenance therapy. A small prospective study in children with CD ($n = 38$) suggests that adjunctive therapy with enteric-coated omega-3 fatty acids and mesalazine (50 mg/kg/d) reduces relapse rates at 12 months compared to mesalazine alone.¹⁵⁵

Other, more specific dietary interventions have been reported to prolong remission in CD. Although none of these has been assessed in larger, placebo-controlled studies, they offer interesting clues to the role dietary modification may play in maintaining disease remission. A small study randomizing patients to a diet low in microparticles¹⁵⁶ suggested significant benefits in disease activity and remission rates after 4 months when compared to 10 patients on a normal diet. Diets low in refined sugars have been not been found to prevent relapse rates in adults with CD.¹⁵⁷ Similarly, the presence of yeast in the diet of patients with CD may potentiate disease relapse, but larger studies are necessary before firm conclusions may be drawn.¹⁵⁸

As the importance of gut microflora in the etiology of IBD is increasingly recognized, so the prospect of modulating it by means of "functional foods" has gained much support. Although discussion is beyond the scope of this chapter, the mechanisms of action and potential implications of this exciting new field are great for patients with chronic intestinal disease driven by enteric flora. It is quite clear that over the next few years we are likely to see larger, placebo-controlled trials of both pro- and prebiotics. Prebiotics are the complex sugars, such as fructo-oligosaccharides and inulin, which pass into the colon undigested where they may be selectively fermented by certain probiotic species.¹⁵⁹ Attempts to maintain

remission in both UC and pouchitis with combined probiotic combinations has proved quite successful,¹⁶⁰ while *Lactobacillus GG* alone may have a role in improving gut barrier function and clinical status in children with CD.¹⁶¹

If long-term nutritional support is required, most children will tolerate a more palatable polymeric formula by mouth. However, some children will require supplementation by tube. While short-term support can be given via a nasogastric tube, longer term needs should be met via a more permanent device. Where nutritional support is needed for several months, placement of a percutaneous endoscopic gastrostomy (PEG) is ideal. Despite initial reservations about possible complications from fistulous tracts formation, PEG placement has now been documented to be uncomplicated in selected adults and children with IBD.¹⁶² In patients receiving corticosteroids adhesion of the gastric to the abdominal wall may be delayed, and thus early “pulling” of the PEG could lead to tract disruption.

THE ROLE OF ENTERAL NUTRITION ON GROWTH AND DEVELOPMENT

Epidemiology of Growth Failure

After the onset of symptoms, but before a diagnosis of CD is made, up to 46% of children will have a reduced height velocity, with only 12% having a normal height velocity up to the time of diagnosis.⁴³ In contrast, only 3 to 10% of children with UC may present with reduced height velocities at diagnosis.⁴⁴ Although much of this data are now over 10 years old, and an accurate diagnosis may now be made more quickly, it is clear that untreated CD has profound implications on a child's growth potential. Motil and colleagues reported in a cross-sectional study of their pediatric IBD patients that 23% had a z-score < -1.64, with 50% of these having a bone age delayed by >1 year over their chronological age. Physicians caring for children with IBD, particularly CD, therefore, have the unique opportunity to try and modify the impact that both disease and therapy has on the growth rate of their patients. Sawczenko and colleagues recently reported that children with the IL6-174 promoter polymorphism are more growth-retarded at diagnosis than those without.¹⁶³ Although levels of CRP were highest in children with this polymorphism, they appeared to be at no increased risk of developing CD than the other polymorphisms compared to 351 healthy controls. The authors speculate that IL-6 mediates growth failure in these children, and that genotyping at an early stage would allow the use of specific growth sparing/focused biological therapies.

A delay in presentation is associated with a significantly greater degree of growth impairment at diagnosis.⁷⁹ The length of this delay appears to correlate with a lower height z-score at diagnosis, and hence with a lower final adult height.¹⁶⁴ A delay in diagnosing the more subtle presenting symptoms of jejunal CD may at least in part

explain the more significant reduction in adult height seen in this particular group of children. Despite management within tertiary centers, 49 to 65% of children with CD have a reduced height velocity in early puberty, with growth velocity remaining less than 4 cm/yr during the first 1 to 2 years of therapy.^{44,165} Hildebrand and colleagues report a mean z-score for height of -0.6, 2 years after diagnosis in 46 consecutive children with CD. Griffiths and colleagues reported that of 67 consecutively diagnosed children with CD followed to maturity, about two-third maintained or increased their z-scores for height.

The outcome of many of these studies reflects management where the mainstay of therapy was often corticosteroids, and so does not include the more recent move to the earlier use of steroid-sparing agents. However, although the most recent follow-up data show that the majority of children diagnosed with CD are closer to their expected adult height, almost 20% will be at least 8 cm below the height expected by mid-parental centile (Sawczenko, 2006 3070/id). Earlier diagnosis and identification of those children at risk of growth failure remain a significant problem for clinicians wanting to optimize growth outcomes.

Etiology of Growth Failure

The growth failure seen in children with IBD is multi-factorial, with inflammation, undernutrition, and steroid therapy being its principal determinants.

Initial evidence suggested that chronic under nutrition was the main factor in the growth failure seen in children with IBD,³⁷ with studies confirming that simple nutritional restitution improved the linear growth of children with CD.^{36,38} Children with active CD have a relative insufficiency of dietary intake when compared with children of the same age,¹⁴⁰ although they may compensate with an increased intake between disease relapses.¹⁶⁵ However, simply increasing the calorie intake, as seen in patients on steroids, does not confer the same benefit on growth as a lower calorie-intake received on EEN.¹⁴⁰ The presence of low levels of insulin-like growth factor-1 (IGF-1) in children with active CD strengthens this association, as the relationship between IGF-1 and malnutrition is now clear.¹⁶⁷ Both IGF-1 and its carrier protein IGF-binding protein-3 are increased significantly by treatment with EEN.^{168,169} Further evidence that inflammation, and not only nutritional factors, plays a role in determining growth can be seen in studies of children undergoing surgery for active IBD. While postoperative catch-up growth is not documented by all authors, several authors show a clear growth-spurt occurring after the removal of an inflamed segment of bowel.¹⁷⁰ Although this is most striking in prepubertal children, the benefit is still substantial if surgery is carried out before the final stages of puberty.¹⁷¹ This response may of course in part be the result of improved post-operative nutrition. However, Varille and colleagues neatly documented that even children

undergoing localized resections for stricturing disease had a significant reduction in REE and increase in nitrogen utilization 4 weeks after surgery, despite maintaining preoperative nutritional and steroid regimens.¹⁷²

There now seems little doubt that ongoing inflammatory activity plays a key role in the inhibition of growth.¹⁷³ Downregulation of proinflammatory cytokines by enteral nutrition may partly improve growth by reducing IL-6, a potent inhibitor of IGF-1.¹⁷⁴ There is a dramatic reduction in CRP, with concomitant increase in IGF-1 and IGFBP-3, within 14 days of commencing EEN.^{84,85} This clearly indicates that enteral nutrition also has a more rapid, direct antiinflammatory action in addition to its longer term nutritional benefits. As has been confirmed in children with rheumatoid arthritis,¹⁷⁵ systemic inflammation, as well as malnutrition, reduces IGF-1. Direct inhibitory effects of proinflammatory cytokines such as TNF α on developing growth plates¹⁷⁶ and a downregulation of IGF-1 by IL-6 are both likely to contribute to growth retardation.¹⁷⁷ The additional suppression of appetite by TNF α ,¹⁷⁸ the failure to downregulate the REE during malnutrition in CD,⁴⁰ and the exacerbation of bowel symptoms by food intake, all add to the final reduction in height velocity.

Enteric losses during active disease can also contribute to the decline in nutritional state. Children with small bowel CD have varying degrees of malabsorption, with some of the hypoalbuminemia occurring as a result of enteric losses.¹⁷⁹ The most important determinant of hypoalbuminemia is the systemic inflammatory response. Although protein loss through an inflamed mucosa does occur, it is usually modest, nonspecific, and occurs in association with loss of globulins. The hypoalbuminemia seen in CD is more frequently associated with the hypergammaglobulinemia occurring as a result of the acute-phase protein synthesis. The latter is principally mediated by IL-6.¹⁸⁰ Furthermore, a sustained protein intake of less than 0.4 g/kg/d¹⁸¹ is necessary to achieve any reduction in serum albumin.

Bile acid malabsorption may not only occur in children with active terminal ileitis, as systemic effects of ileal inflammation may lead to malabsorption in the proximal small bowel.¹⁸² As a result fat malabsorption may occur in some children with CD. In addition, low concentrations of vitamins A, E, and zinc have been shown to correlate more with disease activity than nutritional state,^{63,183} suggesting depletion occurs during the acute inflammation rather than as a result of chronic malabsorption.

Ongoing growth failure in the first years after diagnosis may be due to several factors. Growth velocity can be delayed well beyond nutritional restitution and normalization of inflammatory indices. This, together with the frequent use of high-dose steroids to achieve the initial remission, up to 85% of children in some studies,^{166,184} may arrest normal growth for many months after diagnosis. However, the most recent data suggest that it is neither the disease distribution nor pubertal

stage at diagnosis that determines final adult height,¹⁸⁵ but rather the use of corticosteroids during puberty. Children who were diagnosed with CD during puberty and were treated with corticosteroids were significantly shorter as adults when compared to those who did not receive corticosteroids. In this study, this was the only independent predictor of final adult height.

Nutritional Treatment of Growth Failure

Over 20 years ago several small studies confirmed the central role of nutrition in the long-term management of growth failure in children with IBD. Motil and colleagues^{186,187} concluded that neither low-grade chronic inflammation nor low-dose corticosteroid uses reduced whole-body protein synthesis, and that it was adequate dietary supplementation that led to a significant increase in growth velocity of children with growth failure. This, confirmed by others as nutritional therapies, became more practical for the treatment of acute CD.^{6,36} Sanderson and colleagues were the first to establish the benefit of enteral nutrition over steroid therapy on short-term growth in children with newly diagnosed CD.⁹

MECHANISM OF ENTERAL NUTRITION

Despite the wealth of information that exists about the benefits of enteral nutrition, the mechanisms of action remain largely unclear (Table 3)

The most frequently advanced theory is that the bacterial flora within the gut lumen is modified by enteral nutrition. The clinical evidence of any difference in flora between patients with CD and normal controls remains slim. It was shown in the late 1970s that there are higher bacterial counts within the terminal ileum of patients with active disease.¹⁸⁸ Studies at that time also suggested a reduction in fecal flora after enteral nutrition.¹⁸⁹ It is now clear that increasing severity of systemic disease is associated with an increase in the adherence of fecal bacteria to the enterocytes,¹⁹⁰ and this does not appear to be related to the degree of local mucosal inflammation. The response of acute CD to antibiotic therapy further implicates the bacterial flora in the disease pathogenesis,¹⁹¹ although antibiotics such as the quinolones and metronidazole have other immunomodulatory effects in addition to their antimicrobial actions.¹⁹² The organisms that appear increased in the lumen of patients with CD include *Bacteroides*, *Eubacteria*, and *Peptostreptococcus*.¹⁹³ Elegant work on mice that

develop spontaneous colitis (TCR α -/-) has confirmed that feeding with an elemental diet prevents bowel inflammation.¹⁹⁴ Unlike the mice fed elemental diet, the mice fed regular chow and then develop colitis are colonized by *Bacteroides vulgatus* in >80% of cases. Furthermore, instilling this strain into the rectum of the elementally fed mice led to development of a typical Th-2 type, T-cell induced colitis. Further animal work has shown that elemental diet may reduce progression of granulomatous enteritis by modulating the activation of T cells, the production of NO, and the generation of oxygen free radicals.¹⁹⁴⁻¹⁹⁶

The reduction in antigenic load that accompanies EEN may also contribute, at least in part, to bowel rest. However, a whole-protein diet, and even an ad libitum diet together with some parenteral nutrition, appears to be as effective as an exclusive elemental diet at inducing a remission.^{85,86,111,197} The efficacy of polymeric diets and recent evidence that dietary supplementation with enteral nutrition may prolong a remission,¹⁴⁶ both suggest that reducing luminal antigens may only play a modest role in the efficacy of this therapy.

Whether enteral nutrition per se has either a direct and/or indirect immuno-regulatory effect remains speculative. Degrees of moderate protein malnutrition have been associated with poor immune function. In rodents, protein deprivation leads to impairment of the mucosal immune response, as well as depleting a population of T cells that control oral tolerance.^{198,199} This would suggest that poor nutrition inhibits T cells that downregulate the gut's response to foreign antigens. Enteral feeding may therefore have an indirect effect of on the immune response by restoring an adequate nutritional status.

More recently, the direct influence of luminal content on immune function has been studied. Sanderson and colleagues provided evidence that luminal content can influence epithelial cell gene expression within the gut.²⁰⁰ Short-chain fatty acids, such as butyrate, are bacterial metabolites from unabsorbed carbohydrates. Butyrate induces secretion of insulin growth factor-binding proteins (IGFBPs) by a complex process involving histone deacetylation.²⁰¹ Butyrate has also been shown to potentiate the secretion of IL-8 by intestinal epithelial cells (Caco-2) if these are stimulated with either lipopolysaccharide (LPS) or IL-1 β . LPS was only able to induce IL-8 secretion if these cells were preincubated with butyrate, implying direct effects of the latter on gene regulation.²⁰² Epithelial cell-gene regulation by luminal products thus appears to be able to influence intestinal inflammation through release of such inflammatory cytokines. Upregulation of the chemokine macrophage-inflammatory-protein-2 (MIP-2) increases local neutrophil recruitment.²⁰³

It has also been suggested that the presence, or absence, of individual components of enteral feeds is important in immune regulation. The putative advantage of high TGF- β levels in both AL110 and CT3211 (~24 p.p.m.) is based on the

large body of experimental evidence that this cytokine has the ability to downregulate other proinflammatory cytokines.²⁰⁴ Fell and colleagues⁸⁵ demonstrated mucosal upregulation of TGF- β within the terminal ileum after an 8-week course of TGF- β -rich CT3211. It is still unclear whether this is related to the increased luminal presence of TGF- β or is simply an epi-phenomenon of tissue repair.

It may also be that enteral nutrition plays a direct role in promoting the mechanisms involved in epithelial healing. There are numerous peptides involved in the restoration of a disrupted epithelial barrier. The ulcer-associated cell lineage (UACL)²⁰⁵ secretes cytoprotective peptides that promote epithelial healing. Among them are epidermal growth factor (EGF), TGF- α , human spasmodic peptide (hSP), and the family of trefoil peptides.²⁰⁵ The trefoil peptides in particular have been shown to be vital in protecting against mucosal damage.²⁰⁶ Enteral nutrition may contribute toward the maintenance of mucosal integrity by boosting the proliferation of the UACL.²⁰⁷

While the theory of "bowel rest" has its supporters, others continue to feel it is adequate nutrition alone that could induce remission and growth in these patients.²⁰⁸ Kirschner and colleagues³⁶ demonstrated improved growth in children simply fed an extra 1,000 kcal/d. The same group later confirmed that improved nutrition not only increased linear growth, but also returned previously low levels of IGF-1 to normal in children with active CD.²⁰⁹ Thomas and colleagues¹⁶⁸ confirmed this finding with an elemental feed, which was as effective at increasing IGF-1 as prednisolone, yet better promoted linear growth.

There are likely to be many mechanisms responsible for the clinical efficacy of enteral nutrition. It is clear, however, that the luminal environment is crucial to the expression of mucosal disease. Our ability to regulate specific aspects of this environment by nutritional or other means remains a great challenge. The multitude of variables that may be important in achieving a disease remission makes identification of single factors extremely difficult. Current attention is focused on modifying enteral formulas in line with the recent evidence on dietary fats, while continuing to ensure their clinical efficacy and tolerability.

Mucosal Healing

Attention has focused on the ability of treatments to achieve mucosal healing.²¹⁰ Breese and colleagues¹²⁵ gave an initial indication that enteral nutrition was able to downregulate intestinal mucosal inflammation. Enteral nutrition was as effective as cyclosporin and steroids in reducing the percentage of IL-2 secreting cells in the terminal ileum after treatment, while it appeared more effective than steroids at reducing the percentage of IFN- γ secreting cells. Furthermore, it was only the enterally fed group that showed significant histologic improvement.

Despite being only a small study, Breese and colleagues raised two important issues. First, that

Table 3 Exclusive Enteral Nutrition

- Alteration in bacterial flora
- Reduction in antigenic load
- Whole body nutritional restitution
- Provision of enterocyte nutrition
- Direct immunoregulatory effect
- Increased concentrations of Transforming Factor β
- Low lipid and fiber content

Table 4 Data Showing mRNA Transcripts (10^3)/ μ g Total RNA from Biopsies Taken before and after Treatment with CT3211 and Normal Controls

	Terminal Ileum			Colon		
	Control	Pre-treatment	Post-treatment	Control	Pre-treatment	Post-treatment
IL-1 β	15**	350	16*	0.54**	130	18*
IFN- γ	1**	8.6	1.1*	1.1**	3.5	1.2
IL-8	50	660	150	4.8**	1500	130*
IL-10	1.5	1.7	1.3	3.7**	1.9	1.2
TGF- β	16	4.2	34*	11	15	15

Adapted from reference 85.
 *Significant change ($p < .05$) with treatment assessed by *t*-test.
 **Significant difference between pre-treatment (diseased) and control values assessed by Mann-Whitney U-test.

enteral nutrition may be able to heal mucosa, second, that mucosal cytokine analysis following treatment did not necessarily correlate with either clinical or histologic indices of remission.

The mucosal cytokine responses of a much larger cohort of children were reported by Fell and colleagues.⁸⁵ While clear clinical and histologic remission was achieved in over 70% of children, cytokine profiles also dramatically improved with a polymeric diet alone. The dramatic downregulation of the potent proinflammatory cytokines IL-1 β , IFN- γ , and IL-8 is the most concrete evidence to date that enteral nutrition acts at the mucosal level (Table 4).

The issue of whether clinical, endoscopic, histologic, or immunologic remission should be the gold standard remains a matter of personal practice.²¹⁰ If we are to believe that the presence of chronic inflammation predisposes to long-term complications and malignancy,²¹¹ it may be a state of immunologic remission at the mucosal level that should be achieved in children with a lifetime of CD ahead of them.

BODY COMPOSITION, ENERGY EXPENDITURE, AND PROTEIN METABOLISM

It has become clear that both in adults and children, active gut inflammation is associated with alterations in body composition. While substrate metabolism during active CD resembles that during starvation, it is more a consequence of malnutrition and may be easily reversed by treatment with EEN.^{40,212} BMI, lean body mass (LBM), and fat mass are all decreased in children with IBD, and this may be related to poor calorie intake.^{186,213} A higher BMI and LBMs were both positively correlated with increased BMD, factors that again stress the importance of adequate nutrition in maximizing long-term BMD.

EEN provides a simple but effective treatment for children with CD. Not only does it appear to influence disease activity directly, it also appears to have clear benefits on growth and nutrition.

Early evidence suggested that REE was increased in patients with inactive CD.²¹⁴ It now appears, however, that if the REE is calculated per unit of LBM, it is the same in active CD as it is in normal controls.⁴⁰ The REE/LBM was found to

be significantly lower in children with anorexia nervosa than in normal controls. When comparing these malnourished noninflammatory disease-controls with children with active CD, the authors showed that the appropriate physiological response to starvation is lost during active inflammation. Thus this inappropriately elevated REE further contributes to weight loss. On treatment with elemental feed, their absolute REE did increase to above normal levels, but per unit of LBM only remained within the normal range. This study also showed that an elemental diet was significantly better than steroids at accruing lean body tissue and was again better at achieving linear growth.

Despite the documented increase in energy intake by children on steroids compared to those on an elemental diet,¹⁶⁸ the latter group have a significantly greater rise in their median height velocity standard deviation score (SDS) after 4 weeks on an elemental diet. Adequate calorie intake alone in the presence of steroid therapy (124% of RDA) is thus unable to achieve optimal growth. The short-term growth suppressant effects of prednisolone²¹⁵ probably override any advantage conferred by the improved calorie intake. IGF-1 levels appeared greater after steroid treatment than after enteral nutrition, yet a significant increase in IGF-1 was only associated with greater height velocity after an elemental diet.¹⁶⁸

The rate of protein turnover in seven children with chronically active CD receiving steroids was considered to be similar to that of normal adolescent controls,¹⁸⁶ although their nitrogen balance was found to increase 4-fold during nutritional supplementation. Another small study compared the effect of steroids ($n = 6$) and elemental feed ($n = 6$) after the first 7 days of treatment in acute CD.²¹⁶ Labeled L-leucine studies showed an equal increase in protein turnover after 7 days of treatment, whereas in the steroid treated group this was at the expense of total body protein stores. Clinical improvement was similar in each group. In a more recent study by Thomas and colleagues,²¹⁷ rates of protein turnover were also elevated in active CD. Labeled L-leucine studies and mass spectrometry analysis showed an equal reduction in protein turnover to normal levels, both by steroids ($n = 4$) and by elemental feed ($n = 6$). This study only assessed protein turnover after several weeks of treatment,

and only after effective recovery and nutritional restitution were almost complete.

Royall and colleagues²¹⁸ published evidence in 30 adults with active CD that proportionate increases in body fat, protein, and water occurred after 21 days of elemental nutrition. In this study, a sustained remission was only achieved in patients who showed a gain in total body nitrogen.

Further evidence that optimizing nutrition may contribute to a clinical remission arises from the study by Slonim and colleagues.²¹⁹ The combination of a protein-rich diet (> 2 g/d) and subcutaneous growth hormone (GH) led to a significant reduction in CDAI within 4 months, in a small group of adults with moderate to severe CD. Increased uptake of amino acids²²⁰ and improved intestinal and muscle protein synthesis are mechanisms that are likely to be important in mediating this effect.²²¹ Direct effects of GH on IGF-1 are not felt to be as significant, as no correlation was found between IGF-1 levels and clinical response.

FUTURE DIRECTIONS

From the above discussion it is abundantly clear that nutrition still has a major role to play in the management of children with IBD, and in particular those with CD. While EEN is clearly effective in many children with active CD, it remains difficult for some children and their families to complete prolonged courses. Work is continuing to assess whether long-term supplementation of a normal diet prolongs remission.

Palatable whole-protein formulae are being modified to include higher percentages of n-3 fatty acids, while the addition of probiotics to feeds is also already underway.

Work also continues on isolating the specific factors within formulas that may directly act on mucosal inflammation. Upregulation of mucosal TGF- β may be a direct result of higher levels of TGF- β within a formula (Modulen IBD, Nestle), while further characterization of the gut microflora in children with IBD may allow specific supplementation with specific prebiotics, substrates that selectively stimulate the growth of certain favorable probiotic species.

CONCLUSIONS

Despite the ever-increasing choice of therapies available to children with IBD, the role of nutrition remains central to their optimal management. The impact of bowel inflammation on growth and development cannot be underestimated. As final adult height is determined during the pubertal growth spurt, it is crucial to minimize the impact that both the disease and its therapies may have on a child's growth potential.

Advances in identifying children at particular risk of growth failure may, in the future, allow specific interventions to maximize growth.

We strongly suggest that EEN remains the best primary therapy for the treatment of all

children presenting with a new diagnosis of CD, apart from those with severe perianal disease. Thereafter the challenge is to maintain a lasting remission, particularly during puberty. This is likely to be best achieved with early use of immunosuppressants such as azathioprine/6-mercaptopurine, hoping to minimize steroid use. Continued vigilance of undernutrition and appropriate use of dietary supplementation remain essential to an optimal outcome.

The consequences of developing a chronic inflammatory disease during childhood will be felt long after a child is handed over to our adult physician colleagues. Increased risks of osteoporotic fractures, high rates of surgery, and a reduced final height are only some of the areas where nutritional therapy is vitally important. The ability of therapies to achieve healing of the gut mucosa is of utmost importance in children who have a lifetime ahead of them. Although dietary therapies do not yet play a significant therapeutic role in maintenance therapy for IBD, it is likely that evidence about potential disease-modifying dietary supplements will continue to appear. It is important that as more potent immunologic agents become available to treat these diseases, we do not forget the therapeutic role of nutrition in CD its absence of adverse effects, and its proven impact on growth and gut mucosa.

While newer therapies may require less commitment from families and medical teams, their unknown long-term safety profile still makes enteral nutrition an excellent choice for children with CD for many years to come.

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