Inflammatory Bowel Diseases
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There is substantial evidence that the systemic inflammatory response, mediated both locally and systemically, plays an important pathogenic role in inflammatory bowel disease. The systemic inflammatory response produces protein-energy malnutrition. Anorexia and the resultant semistarvation cause lean tissue loss. Reduction in voluntary motor activity causes further lean tissue loss. Whole body protein synthesis is diminished, while protein catabolism is increased in skeletal muscle and connective tissue. Therefore, both the treatment of inflammatory bowel disease and the prevention of malnutrition must be primary goals for improved long term outcome.

The relative merits of treating Crohn's disease and ulcerative colitis with anti-inflammatory drugs have been well established. However, the severe adverse effects of corticosteroid treatment on growth of pediatric patients are also well documented. An attractive alternative for treatment, therefore, is the search for an enteral nutrition product that has anti-inflammatory properties and prevents malnutrition.

This Workshop discusses the possibilities of using enteral nutrition products which are rich in transforming growth factor B$_2$ (TGF-$\beta_2$), which may contribute to their therapeutic action. There is scientific evidence that treatment with these enteral nutrition products reduces inflammation in the mucosa with histological improvement, and reduces the number of mucosal cells producing proinflammatory cytokines. Of interest also is the effect of enteral nutrition products that are based on protein hydrolysates. Several controlled trials employing fish oil as a source of $\omega$-3 fatty acids to alter cytokine and eicosanoid production in Crohn's disease and ulcerative colitis have been reported. In addition, it appears that in patients with Crohn's disease, fish oil may be effective in preventing relapse.
I would like to thank the Chairmen, Bruce Bistrian and John Walker-Smith, for organizing a workshop which allowed the synergistic effects of enteral nutrition and drugs in inflammatory bowel disease to be discussed. The speakers provided sound background information and highlighted controversial issues. A group of experts who were invited to discuss the speakers’ prepared manuscripts raised many important points which will stimulate the research on treatment of inflammatory bowel disease in the near future.

Finally, I would like to thank Nestlé Clinical Nutrition, USA, and the Nestlé Nutrition Division, Vevey, Switzerland, for providing the logistic support which made this meeting possible.

Professor Ferdinand Haschke M.D.
Vice-President
Nestec Ltd., Vevey, Switzerland
Protein–energy malnutrition is common in inflammatory bowel disease and has a serious impact on morbidity [1]. Recent investigations have suggested that the systemic inflammatory response plays a prominent role in the pathophysiology of inflammatory bowel disease and is the major etiologic factor in the development of protein–energy malnutrition [2]. The definition of a systemic inflammatory response established by the Consensus Conference [3] includes any two of the following: body temperature greater than 38°C or less than 36°C; pulse rate more than 90 beats/min; white blood cell count of more than 12,000/mm² or less than 4000/mm², or bands in excess of 10%; respiratory rate of more than 20 breaths/min; and a partial pressure of carbon dioxide in arterial blood of less than 32 Torr when breathing room air. Lesser degrees of activation of the systemic inflammatory response can be identified by elevations in acute phase protein levels (i.e. C reactive protein), hypoalbuminemia, and enhanced release of proximate cytokines (interleukin-1, tumor necrosis factor) by blood mononuclear cells.

Mechanisms that lead to malnutrition include anorexia [4], reduction in voluntary motor activity [5], anabolic inefficiency [6], and increased protein catabolism [7] (all of which result from activation of the systemic inflammatory response), often in addition to the reduction in oral intake in order to minimize gastrointestinal symptoms.

Nutritional interventions that can serve to limit the development of malnutrition include alternative means of feeding to improve intake (oral supplements, enteral tube feeding, parenteral nutrition), increasing protein intake relative to energy to counter anabolic inefficiency, and modulating the severity of the inflammatory response by changing dietary fat (ω-3 fatty acids, γ linolenic acid, oleic acid).
References


Ulcerative colitis and Crohn’s disease are not new clinical entities. There are several reports of both diseases from the latter half of the 19th century. Retrospective incidence studies have, however, showed an increase in incidence for both diseases, starting in the 1930s, with a consistent increase in Europe and the United States. There is a time lag – the increase in the incidence of ulcerative colitis precedes the increase in Crohn’s disease by 10-20 years. The incidence of Crohn’s disease now seems to have leveled off at an annual incidence of around 6 per 100,000 inhabitants [1], but in the case of ulcerative colitis the incidence figures are more inconsistent and annual incidence rates of up to 20 per 100,000 have been reported from Europe [2]. There appeared to be a north-south gradient in both North America and Europe during the 1980s. Recent studies, especially from Europe, indicate that this gradient is disappearing, as the incidence of inflammatory bowel disease in increasing in the southern part of Europe [2]. Incidence figures from Eastern Europe, on the other hand, suggest that there is a west-east gradient.

There is a strong correlation between the incidence of ulcerative colitis and that of Crohn’s disease. Areas with a high incidence of ulcerative colitis also have a high incidence of Crohn’s disease [3]. There is a familial aggregation in inflammatory bowel disease, and a family history of Crohn’s disease is associated with an increase both for Crohn’s disease and ulcerative colitis and *vice versa* [4]. It has been hypothesized that Jewish ethnicity is associated with an increased risk for both disease entities but incidence data from Israel refute such an association to some extent, as the annual incidence there does not differ from that in other high incidence areas.

Factors that have been associated with ulcerative colitis, Crohn’s disease, or both are listed in Table I. There are very few established risk factors that can explain the temporal trends. Presently, smoking is the only exposure which has consistently been associated with a decreased risk of ulcerative colitis and an increased risk of Crohn’s
disease. Socioeconomic status, physical activity, diet, and oral contraceptives have been proposed, but the results from different studies are inconsistent. Early events such as childhood hygiene and infections have, however, consistently been implicated in studies of both ulcerative colitis and Crohn’s disease [5]. Temporal trends in both diseases could be explained by improvements in hygiene and nutrition: in underdeveloped countries or in other populations with a high perinatal mortality, patients with the potential to develop inflammatory bowel disease would be the first to die from early exposure to infection, which would lead to a low incidence of these diseases 20-40 years later.

TABLE I – Proposed risk factors associated with inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Familial aggregation</th>
<th>Stressful events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Early life exposures</td>
</tr>
<tr>
<td>Smoking</td>
<td>Weaning</td>
</tr>
<tr>
<td>Oral moist snuff</td>
<td>Hygiene</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Infections</td>
</tr>
<tr>
<td>Diet</td>
<td>Dairy products</td>
</tr>
<tr>
<td>Refined sugar</td>
<td>Passive smoking</td>
</tr>
<tr>
<td>Cereals (cornflakes)</td>
<td>“Sheltered child”</td>
</tr>
<tr>
<td>“Fast food”</td>
<td>Infections</td>
</tr>
<tr>
<td>Margarine</td>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Bakers’s yeast</td>
<td>Measles</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Nonspecific virus infections</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

The increase in the incidence of ulcerative colitis and Crohn’s disease during this century is still largely unexplained but exposure to infection early in life is probably of major importance in the etiology of both diseases.

References

Genetic Aspects of Inflammatory Bowel Disease

J. P. HUGOT

A genetic predisposition to inflammatory bowel disease has been suspected since the discovery of ethnic and familial aggregations of the disease [1]. A positive familial history is the most important risk factor known for the development of inflammatory bowel disease [2]; indeed, 6-10% of cases of inflammatory bowel disease are familial. The risk of developing inflammatory bowel disease for a first degree relative of an affected patient is of the order of 1%, corresponding to a 10-fold greater risk than in the general population.

Many candidate genes have been investigated by case-control association studies. The list of such genes is rapidly increasing (Table I). However, further investigations are needed before it can be shown definitively that these candidate genes play an etiologic role in inflammatory bowel disease.

Using a genome-wide approach, three groups have proposed at least eight susceptibility loci for inflammatory bowel disease (Fig. 1). Several of these have to be confirmed (in gray), and the loci mapped on chromosomes 12 and 16 (in black) have now to be identified.

TABLE I – Genes investigated by case-control studies in inflammatory bowel disease.

| HLA genes. |
| TAP genes |
| TNF genes |
| Interleukin 1 gene cluster |
| Interleukin 2 |
| Interleukin 10 |
| Intercellular adhesion molecule 1 (ICAM1) |
| T cell receptor |
| Mucin genes |
| Motilin |
| hMLH1 |
| Vitamin D receptor |
Even in families with inflammatory bowel disease, where a genetic predisposition is now well established, it is possible to show that environmental factors may be important and to demonstrate multifactorial traits in the pathogenesis of the disease [3]. These environmental
factors are still only partially known. Our understanding of the disease mechanisms will require better knowledge of these factors and analysis of their interactions with the predisposing genes.

References


Immunopathogenesis of Inflammatory Bowel Disease: Role of Cytokines and Immune Cell-Enterocyte Interactions

SERGE DIONNE, FRANK M. RUEMMELE AND ERNEST G. SEIDMAN

Crohn’s disease and ulcerative colitis – entities collectively referred to as inflammatory bowel disease – are characterized by chronic relapsing intestinal inflammation. Although the etiology and pathogenesis of these disorders remain unclear, the available evidence suggests that abnormal mucosal immunoregulation is central to the initiation and perpetuation of the inflammation [1].

The current concept of the pathogenesis of inflammatory bowel disease is that multifactorial disease susceptibility genes permissive of the development of the chronic inflammatory lesions act in concert with environmental factors and as yet undefined triggering events or agents. Our understanding of these disorders has benefited enormously from the development of novel animal models and recent advances in cell and molecular biology. Gene knock-out (interleukin (IL)-2, IL-10) and transgenic (HLA-B27) mice only develop inflammatory bowel disease-like lesions in the presence of the host’s normal intestinal flora. Along with clinical evidence that disease recurrence is related to contact with gut luminal contents, this highlights the importance of an abnormal immune response to normal gut microbes in the pathogenesis of these disorders.

In addition to disease susceptibility genes and the gut flora, environmental factors appear to play an important role. These include increased intestinal permeability, probably a result of rather than a primary cause of the intestinal inflammation. Dietary factors such as food antigens and the relative proportion of ω-3 to ω-6 essential fatty acids may induce abnormal immune responses and excessive eicosanoid production, respectively. Mycobacteria and the measles virus are two of many infectious triggering agents that have been proposed, but no particular pathogen has yet been shown to be involved in perpetuating inflammatory bowel disease.
On the other hand, there is evidence that defective immune regulation plays a major role in disease pathogenesis. Crohn’s disease is thought to be characterized primarily by a Th1 cell cytokine profile, whereas ulcerative colitis tends to show a Th2 pattern. In either case, an imbalance in the secretion of pro-inflammatory (interleukin (IL)-1, tumor necrosis factor α (TNFα), IL-8, γ interferon (IFNγ), etc.) and anti-inflammatory cytokines (IL-4, IL-10, etc) is believed to be involved in the pathogenesis of inflammatory bowel disease [2]. It is likely that an abnormal immune response to bacterial activators present in the host flora plays a role in inducing this abnormal response in genetically susceptible individuals.
The immune mediated destruction of the intestinal epithelium in inflammatory bowel disease results in major functional abnormalities, such as the loss of normal absorptive capacities and exaggerated secretion of intestinal fluids and electrolytes, clinically manifesting as malabsorption and diarrhea. In order to understand the pathogenesis of inflammatory bowel disease, it is essential to determine the molecular mechanisms involved in these immune driven disturbances. In zones of acute inflammation, an increased intestinal epithelial cell apoptosis rate has been found, along with hyperproliferation of cells in the crypt compartment. Cytokines such as TNFα and IFNγ have been shown to modulate intracellular signaling pathways, resulting in increased (TNFα) or decreased (IFNγ) proliferation of immature crypt cells. On the other hand, TNFα, as well as FAS ligand (abundantly expressed on cytotoxic lymphocytes), are potent inducers of enterocyte apoptosis. Furthermore, upon stimulation intestinal epithelial cells produce various cytokines, chemokines, and surface molecules which can act as potent attractors for inflammatory cells. It is therefore believed that the intestinal epithelium is not an innocent bystander, passively injured by immune cell mediators. Rather, the intensive interaction between intestinal epithelial cells and immune competent cells is critical to maintain and perpetuate the chronic inflammatory process characteristic for inflammatory bowel disease.

References
Inflammation is a process of major importance in the ability to combat infections and remove and repair tissues damaged by physical and thermal injury. The process is mediated and modulated by a wide range of mediators [1,2]. Pre-eminent among these are the pro-inflammatory cytokines interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-α (TNFα), and reactive oxygen species (ROS). These mediators are, however, closely linked with pathology in a wide range of diseases and conditions which have an inflammatory basis.

Mortality and morbidity, in a diverse range of diseases, have been linked with excessive or untimely oxidant and pro-inflammatory cytokine production. Evidence of oxidative damage has been observed in sepsis, HIV and hepatitis infection, cancer, diabetes mellitus, alcoholic liver disease, and cystic fibrosis. ROS produced during the inflammatory response enhances pro-inflammatory cytokine production by activation of nuclear factor kappa B (NFκB). This interaction is an important part of the upregulation of inflammatory aspects of immune function. Recently polymorphisms within the TNF-α and TNF-β genes have been shown to enhanced the tendency for TNF production and have been linked with increased morbidity and mortality in a wide range of inflammatory diseases and in malaria and sepsis.

Alterations in the intake of fats, antioxidant nutrients, protein, and specific amino acids change many aspects of inflammation by interacting with cytokine and ROS biology. The interaction between ROS and cytokines has the potential to damage the host but is held in check by the antioxidant defenses. Nutrient intake directly and indirectly influences antioxidant defense. Glutathione is a major endogenous antioxidant and is important for lymphocyte replication. Vitamin B-6 and riboflavin participate in the maintenance of glutathione status. Sulfur amino acid deficiency impairs the ability to synthesise glutathione during inflammation and increases neutrophils in lungs of experimental animals. Ascorbic acid and tocopherols exert anti-inflammatory
effects in man and animals. In smokers indices of inflammation are inversely related to the intakes of vitamins C and E.

Studies in healthy subjects, patients, and experimental animals show that unsaturated fats and cholesterol modulate inflammation by interaction with cytokine biology. In general n-6 polyunsaturated fatty acids (PUFA) and cholesterol enhance, and n-3 PUFA, monounsaturated fatty acids, and naturally occurring trans fatty acids suppress, cytokine mediated aspects of inflammation. In addition, n-6 PUFA and cholesterol enhance and n-3 PUFA suppress cytokine production. In smokers indices of inflammation are enhanced if more than 7% of dietary energy is consumed in the form of n-6 PUFA. Fats rich in n-3 PUFA are helpful in various inflammatory diseases. Fats can modulate cytokine biology by various mechanisms closely linked to changes in membrane phospholipid composition. As a result of diet induced change, alterations in prostaglandin, leukotriene, and diacyl glycerol production, protein kinase C activation, and fluidity may occur. However, changes in bulk membrane fluidity are unlikely to underlie the substantial modulatory effects of fats on cytokine biology.

FIGURE 1 – Summary of effects of nutrients on inflammation.

<table>
<thead>
<tr>
<th>Influence on inflammation</th>
<th>Possible mechanism(s)</th>
<th>Effect(s)</th>
</tr>
</thead>
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<tr>
<td>Lipids</td>
<td>Changes in membrane phospholipids</td>
<td>Changes in cytokine and lipid-derived mediator production</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Suppression of oxidant effects and NFκB effects</td>
<td>Altered cytokine production</td>
</tr>
<tr>
<td>Protein/amino acid deficiency</td>
<td>Acute phase proteins/ endogenous antioxidants</td>
<td>Altered cytokine production?</td>
</tr>
</tbody>
</table>

**Conclusion**

Nutrients can modulate the inflammatory aspects of immune function due to their interactions in three main areas where inflammation is initiated and controlled: first, by changing provision of substrate (protein, sulphur amino acids, glutamine) for the synthesis of molecules for components of the executive and control systems; second, by modulating the composition of the membranes of cells involved in the inflammatory process (unsaturated fatty acids and cholesterol); and third, by influencing the interaction between ROS, NFκB activation, and other
aspects of gene expression (sulfur amino acids, vitamins C and E, and vitamin A). A summary of the effects of nutrients on inflammation is given in Fig. 1.

References
The term “inflammatory bowel disease” is applied to bowel diseases of unknown etiology characterized by a chronic and often relapsing inflammation.

Ulcerative Colitis[1]

Ulcerative colitis is a mucosal disease which always affects the rectum and which often also involves a variable contiguous segment of colon. The lesions are continuous, and their upper limit is sharply demarcated from the normal mucosa above. Active lesions consist of edema, erythema, lack of the normal vascular pattern, bleeding, exudation of mucus or pus, and ulceration. They are characterized histologically by the presence of a polymorphonuclear infiltrate confined to the mucosa with crypt abscesses, edema, vascular congestion, branching of the crypts, and mucus depletion from the goblet cells. The colonic symptoms depend in part on the spread of the lesions and on their severity. The main symptoms of active ulcerative colitis are the presence of blood and mucus in stools and frequent bowel movements. Extradigestive symptoms are present in 15% of the patients. Complications include fulminant colitis, significant hemorrhage, toxic megacolon, and colonic cancer. In over 90% of cases chronicity occurs. The risk of having a severe relapse is about 15%. The life expectancy of patients with ulcerative colitis is similar to that of the general population.

Crohn’s Disease[2]

Crohn’s disease may involve any segment of the digestive tract from the mouth to the anus, and often presents with multifocal lesions separated by normal segments. Lesions are most commonly present in the terminal ileum and colon. They may affect any layer of the digestive wall and are often transmural. The main macroscopic lesions are
aphthoid, superficial and deep ulcerations, erythema, edema, pseudopolyps, strictures, and fistulae. Fibrotic lesions thicken the bowel wall, narrow the lumen, and may produce abdominal masses. Non-caseating granulomas are characteristic, but are only seen in 30% of the patients. Symptoms are influenced by the site and type of the inflammatory lesions, but their intensity is poorly correlated with the macroscopic or microscopic features. Osteopenia is present in about half the patients [3]. Complications include intestinal obstruction, perforation, abscess formation, fistulae, intestinal hemorrhages, extraintestinal signs, and an increased risk of carcinoma. Crohn's disease is often naturally a remitting and recurring disease (“relapsing form”). The risk of recurrence is higher in smokers. Surgery is often necessary (in about 50% of cases), and the disease often recurs after surgery [4].

Indeterminate colitis

Most cases of inflammatory bowel disease can be correctly labeled as Crohn’s disease or ulcerative colitis [5]. The term “indeterminate colitis” is used when the diagnosis is difficult.

Pouchitis

Pouchitis is defined as inflammation of the pouch in patients with an ileoanal anastomosis [6]. Symptoms consist of abdominal pain, fever, rectal bleeding, and diarrhea. The disease may be acute or chronic. The etiology is probably a multifactorial event involving genetic, immune, microbial, and toxic mediators.

Microscopic Colitides

“Microscopic colitis” is a clinicopathologic syndrome involving chronic secretory watery diarrhea, a normal macroscopic appearance of the colon, and increased numbers of intraepithelial lymphocytes in the colon on biopsy samples [7]. Microscopic colitides include lymphocytic colitis and collagenous colitis. Both syndromes (but particularly lymphocytic colitis) tend to occur in middle aged women, are often associated with other diseases, and may be induced (or facilitated) by drugs.

References


Diagnostic Criteria for Inflammatory Bowel Disease in Adults

PH. MARTEAU

The inflammatory bowel diseases are diseases of unknown etiology. The diagnosis depends on recognition of the clinical features and sometimes on the family history, when no specific clinical, morphological, or biological signs are present.

When Should Inflammatory Bowel Disease Be Suspected?

Inflammatory bowel disease is usually revealed by gastrointestinal symptoms, including anoperineal lesions. It can also, however, present with extraintestinal symptoms, fever, or weight loss [1]. Other cases of inflammatory bowel disease-in the family and the absence of alternative causes for the symptoms are important arguments in favor of inflammatory bowel disease. The diagnosis of inflammatory intestinal lesions is usually easy in patients who present with “warning symptoms” such as blood in stools, major intestinal transit disturbance, pain, an abdominal mass, high grade fever, or weight loss. It may be more difficult in patients with only moderate symptoms.

Diagnosis Of Inflammatory Bowel Disease In Practice

The diagnosis of inflammatory bowel disease is usually made by: (1) the demonstration of the presence of inflammatory lesions in the gastrointestinal tract; (2) the exclusion of other causes for the lesions (infections, etc), often helped by: (3) the chronicity of the symptoms or lesions, and sometimes by: (4) the family history (about 10% of people with inflammatory bowel disease have a family history of such diseases).

The presence of inflammatory lesions in the gastrointestinal tract can be established by various different techniques. The most important are endoscopy and histological examination of biopsies. The differential diagnosis depends on the site of the lesions and differs between
acute or chronic ileitis or ileocolitis and isolated colitis. The main dif-
ferential diagnoses are infectious enterocolitis, drug related enterocol-
itis, and tumors. Stool examination for pathogens is also often neces-
sary.

The differential diagnosis between inflammatory bowel disease-and
infectious colitis is often difficult in subjects with a first attack of proc-
titis or colitis. Histologic features which seem most helpful in differenti-
tiating inflammatory bowel disease-from infectious colitis are the fol-
lowing: [2, 3]
– basal plasmacytosis
– crypt distortion
– villous mucosa
– mucosal atrophy
– epithelioid granuloma
– Paneth cell metaplasia.

If the clinician and histopathologist cannot make a definite diagno-
sis of inflammatory bowel disease, the term “unclassified colitis” is
used. In this case, the risk of relapse (and thus of inflammatory bowel
disease) is about 50%. The frequency of the main symptoms in patients
with inflammatory bowel disease is shown in Table I.

<table>
<thead>
<tr>
<th>TABLE I – Frequency of the main symptoms in patients with inflammatory bowel disease.</th>
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<tbody>
<tr>
<td>Symptom or sign</td>
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<tr>
<td>Blood in stools</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal mass</td>
</tr>
<tr>
<td>Fistula</td>
</tr>
<tr>
<td>Destructive perineal lesions</td>
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<tr>
<td>Weight loss</td>
</tr>
</tbody>
</table>

The differential diagnosis between ulcerative colitis and Crohn’s dis-
ease may be difficult in some subjects with colitis. Intestinal involve-
ment, anoperineal lesions, the presence of skip lesions, and granu-
lomata are characteristic of Crohn’s disease but may be absent (or undetected) in some patients. Some biological tests have recently been
proposed, for example the serological profile for P-ANCA (perinuclear
antineutrophil cytoplasmic autoantibodies) and ASCA (antibodies to
oligomannosidic epitopes of the yeast Saccharomyces cerevisiae) may
have predictive value [4].

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References


Until the 1970s Crohn’s disease was thought to be uncommon in children, although ulcerative colitis had been recognised in children since the 1920s. The diagnosis of Crohn’s disease is more difficult in children than in adults because systemic manifestations such as growth failure and delayed puberty may dominate the early clinical picture. As a result diagnosis is often delayed. However, the modern approach of fibroptic endoscopy with multiple biopsies, coupled with high quality double contrast radiology adapted to pediatrics, has led to speedy and accurate diagnosis [1].

Three diagnostic categories of chronic inflammatory bowel disease may be recognised: Crohn’s disease, ulcerative colitis, and indeterminate colitis. The latter is a term reserved for those children who have a definite histological diagnosis of colitis but in whom it is not possible, at least at first, to characterise the disorder as either Crohn’s disease or ulcerative colitis.

Crohn’s Disease

A secure diagnosis (definite) may be made by the following [2,3]: (1) The findings of characteristic histology with non-caseating granulomata on endoscopic biopsy; (2) The presence of terminal ileal ulceration on endoscopy and histological ileitis with a characteristic radiological appearance; (3) The presence of characteristic histology after intestinal resection.

A presumptive diagnosis (probable) may be made when radiological investigations show the typical abnormalities found in Crohn’s disease in a child who has clinical features to suggest its presence. Histologically, Crohn’s disease is probable if one or more of the following features are present: (1) focal inflammation; (2) submucosal or transmural in-
flammation; (3) lymphocyte aggregates (without germinal centres); (4) mucus retention in the presence of more than minimal inflammation. If non-caseating granulomas and fissuring ulceration are also present the diagnosis becomes definite.

Ulcerative Colitis

The rapid onset of gastrointestinal symptoms in most children with ulcerative colitis, particularly bloody diarrhea, tends to result in early referral from the general practitioner and prompt investigation. Most children are diagnosed within 6 months of their first symptoms.

A provisional diagnosis of ulcerative colitis in children is usually made on the basis of the typical clinical features, although distinction from Crohn’s colitis is difficult on clinical grounds alone. The diagnostic approach used for Crohn’s disease should be followed [3].

Definite ulcerative colitis is defined histologically by acute inflammation with severe crypt cell distortion and diffuse goblet cell depletion (mucus depletion). Inflammation is diffuse and solely mucosal. Vascularity is increased. Probable ulcerative colitis is indicated by (a) diffuse mucosal inflammation with only mild or moderate crypt distortion, mucosal atrophy or mucus depletion; (b) diffuse acute and chronic inflammation with increased vascularity but little mucus depletion, suggesting a resolving phase.

The possible causes of an inflamed colonic mucosa are listed in Table I. The relation between endoscopic diagnosis and routine laboratory tests in children with chronic gastrointestinal symptoms is given in Table II.

<table>
<thead>
<tr>
<th>Inflamed colonic mucosa</th>
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<tbody>
<tr>
<td>- Inflammatory bowel disease</td>
</tr>
<tr>
<td>- Infective colitis</td>
</tr>
<tr>
<td>- Amoebic colitis</td>
</tr>
<tr>
<td>- Cow’s milk or allergic colitis</td>
</tr>
<tr>
<td>- Autoimmune colitis</td>
</tr>
<tr>
<td>- Chronic granulomatous disease</td>
</tr>
<tr>
<td>- Immunodeficiency</td>
</tr>
<tr>
<td>- “Microscopic colitis”</td>
</tr>
<tr>
<td>- Bechet’s disease</td>
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<tr>
<td>- Hirschprung’s enterocolitis</td>
</tr>
<tr>
<td>- Non-specific colitis with lymphoid nodular hyperplasia</td>
</tr>
<tr>
<td>- Intractable enterocolitis of infancy</td>
</tr>
<tr>
<td>- Metabolic disorders</td>
</tr>
</tbody>
</table>

TABLE I – Differential diagnosis of inflammatory bowel disease in childhood.
TABLE II – Relation between endoscopic diagnosis and routine laboratory tests in children with chronic gastrointestinal symptoms; values are percent.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Crohn’s disease (n = 26)</th>
<th>Ulcerative colitis (n = 13)</th>
<th>Polyps (n = 8)</th>
<th>Normal (n = 37)</th>
<th>Others* (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin &lt;100 g/l</td>
<td>16</td>
<td>30</td>
<td>12</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate &gt;25 mm/h</td>
<td>85</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Albumin &lt;36 g/l</td>
<td>35</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Platelet count &gt;400 10^9/1</td>
<td>88</td>
<td>70</td>
<td>12</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>C-reactive protein &gt;5 mg/l</td>
<td>100</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>All investigations normal</td>
<td>0</td>
<td>8</td>
<td>88</td>
<td>91</td>
<td>28</td>
</tr>
</tbody>
</table>

*Others include tuberculosis, indeterminate colitis, and lymphoid nodular hyperplasia.

References

Nutrition is a potent mechanism for altering the environment of the cells of most organs of the body. It is the epithelium of the gastrointestinal tract, however, that first encounters any variation of nutritional stimuli. The intestinal epithelium therefore serves as a good model in which to study the interactions between nutrients and the expression of genes. Because we know that the phenotype of the cell is a direct result of the expression of its genetic material, alterations in gene expression play a central role in disease pathogenesis. Nutrition as a treatment for disease would become a possibility if nutrients were found to alter gene expression. This is now known to be the case for genes in epithelial cells.

Dietary regulation of gene expression has three main benefits for the epithelial cell.

![FIGURE 1 – Pathway allowing changes in the intestinal lumen to be relayed to the mucosal immune system.](image-url)
First, the epithelium may adapt to changes in the environment of the lumen. This enables the intestine to digest and absorb food more effectively. This form of modulation, although present, does not have as great an influence on the expression of epithelial genes as developmental programming.

The second advantage is the ability of maternal influences to produce changes in genetic expression. For example changes in breast milk could, by changing expression in epithelial genes, enable the mother to have a direct influence the ontogeny of her young.

Third, changes in nutrition may alter the regulation of immunologically active genes in the epithelium. Such genes communicate from the epithelium to the immune system. This pathway allows changes in the intestinal lumen to be relayed to the mucosal immune system (Fig. 1). The epithelium therefore acts as a transduction mechanism in immnosurveillance (Fig. 1b).

Traditionally, immunosurveillance of the gastrointestinal tract has been the function of molecules passing through the epithelium, either between epithelial cells or through specialised M2 cells (Fig. 1a). There is now evidence that class II major histocompatibility complex (MHC) expression and chemokine expression are altered by nutrients, in particular lipids. Changes in the diet cause significant changes in short chain fatty acid concentrations, which are reflected by changes in the fatty acids appearing in the faeces. Butyrate levels in particular vary greatly with changes in diet. Butyrate is known to increase interleukin 8 secretion in cultured enterocytes and acts in synergy with inflammatory stimuli. Sodium butyrate may regulate gene expression by both chromosomal regulation and by stimulating transcription factors binding to gene promotors.

Many diseases of the intestine are immunologically based and it is likely that such mechanisms will play a role in the development of nutritional treatment in the future.

Further reading

Nutrition versus Drug Treatment

KHURSHEED N. JEEJEEBHOOY

Nutritional deficiencies are very common in Crohn’s disease (Table I), and several small studies have shown that total parenteral nutrition is associated with improvement in nutritional status as well as in disease activity [1]. The improvement was ascribed to “bowel rest”. Subsequent studies have shown that it is the nutritional input rather than bowel rest that induces remission [2].

**TABLE I – Causes of malnutrition in inflammatory bowel disease.**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate intake</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Avoidance of unpleasant symptoms</td>
</tr>
<tr>
<td></td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td></td>
<td>Drug treatment</td>
</tr>
<tr>
<td>Increased requirements</td>
<td>Increased metabolic rate</td>
</tr>
<tr>
<td></td>
<td>Growth</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Short bowel</td>
</tr>
<tr>
<td></td>
<td>Bile salt deficiency</td>
</tr>
<tr>
<td></td>
<td>Bacterial overgrowth</td>
</tr>
<tr>
<td>Drugs</td>
<td>Prednisolone (calcium malabsorption)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine (vit A, D, E and K malabsorption)</td>
</tr>
<tr>
<td></td>
<td>Salazopyrine (folate malabsorption)</td>
</tr>
<tr>
<td>Increased losses</td>
<td>Protein losing enteropathy</td>
</tr>
<tr>
<td></td>
<td>Zinc</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Electrolytes</td>
</tr>
</tbody>
</table>

In controlled trials, enteral nutrition with elemental diets was shown to induce a remission similar to prednisone in some studies but not in others, and a meta-analysis indicated that enteral nutrition was not as effective as corticosteroids in inducing a remission. On the other hand an analysis of drug trials in Crohn’s disease shows that there is great variability in the response to treatment, and the response rate with en-
teral diet is more than with published data for placebo response and similar to that with several drugs (Fig. 1). The variability of response depends on disease duration, and previous treatment may alter the response rate.

![FIGURE 1 – Comparison of response of Crohn’s disease to enteral feeding and drug treatment.](image)

Another controversial area is that of the diet formulation and response. Some studies, and a meta-analysis, have shown no difference between polymeric and elemental diets, while others have suggested that the fat content of the diet may influence the outcome.

Conclusions

The following conclusions can be drawn from the various published studies.

1) Nutritional treatment is not likely to induce a remission in patients with colitis.

2) Enteral feeding can induce disease remission in adults and children and promote growth in children. The current evidence showing that disease activity is perhaps the most important cause of growth retardation is supportive evidence that enteral nutrition reduces disease activity.
(3) The efficacy of enteral diets seems to depend upon patient acceptance and the ability to consume them for prolonged periods.

(4) The data showing that total parenteral nutrition can induce disease remission are indirect; its use should be reserved for giving nutritional support in patients in whom enteral feeding is impossible.

(5) It remains to be determined whether it is the elemental nature, nutrient content, or the pharmacological effect of nutrients that is important for the success of this form of treatment.

(6) The use of elimination diets, short chain fatty acids, and fish oils remains experimental.

The data taken as a whole suggest a role for nutritional treatment, but the type of disease and the constituents of the diet need further study.

References
Use of Macro- and Micronutrients for Nutrition Support in Inflammatory Bowel Disease

DAVID H. ALPERS

The appropriate use of nutrition in the management of inflammatory bowel disease is an unresolved issue. There is no disagreement that replacement therapy is indicated when nutrient deficiency is present. Problems arise with the use of macronutrients as either primary or adjunctive treatment for the disease in patients who are not obviously malnourished, with the use of parenteral nutrition when oral intake is adequate (bowel rest), or with the appropriate use of micronutrients for current or future deficiencies.

Assessment

There is no gold standard of nutritional assessment. Many experts agree that unintentional loss of >10% of body weight in 6 months is an indicator of poor outcome, at least in cancer patients. However, in chronic disease this measure can be confounded by errors in recall of weight and by changes in body water (induced, for example, by dehydration or edema). Serum albumin has traditionally been used as a measure of protein nutrition, but inflammatory disorders can decrease the rate of albumin synthesis, increase the rate of degradation, and cause increased transcapillary losses or protein losing enteropathy. The ability to maintain immune competence is also often compromised in chronic illness, but not enough to be helpful in assessment.

Bowel Rest in Crohn’s Disease

When short term remission rates in patients with Crohn’s disease were compared using either total parenteral nutrition (TPN) or enteral nutrition in four separate studies, no difference was found [1]. In general, restrictive diets should be discouraged, and there is no evidence for the value of exclusion diets for patients with Crohn's disease.
Nutrition Support as Adjunctive Treatment

The rationale for using perioperative nutrition support comes from observations in patients with protein–energy malnutrition where wound healing is impaired and immunocompetence is affected. However, the routine use of postoperative TPN in similar patients seen in general surgery increased the rate of postoperative complications by 10% in patients who had not received preoperative TPN [2]. Of course, if the patient is not able to eat or receive enteral feeds preoperatively or postoperatively, parenteral support is indicated. Only in severely malnourished patients undergoing major surgery in the VA TPN Cooperative Study Group did TPN result in fewer non-infectious complications compared with controls [3]. No comparable prospective studies are available for patients with either Crohn’s disease or ulcerative colitis. Uncontrolled studies in patients with inflammatory bowel disease have suggested that the use of TPN preoperatively reduces complication rates and the amount of small bowel resected, but hospital stay might be prolonged.

A retrospective analysis of small bowel fistula patients treated with TPN revealed lower mortality rates, higher spontaneous closure rates, and higher surgical closure rates when compared with historical controls [4]. However, the overall closure rate of about 35% achieved with TPN was not maintained, as half the patients had reopened their fistulas by 3 months.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of patients</th>
<th>Age (years)</th>
<th>Survival (% at 1 year)</th>
<th>Status at 1 year</th>
<th>Complications (No per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>562</td>
<td>36</td>
<td>96</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>Congenital bowel defect</td>
<td>172</td>
<td>5</td>
<td>94</td>
<td>42</td>
<td>47</td>
</tr>
</tbody>
</table>


Home Parenteral Nutrition

Patients with a jejunostomy and less than 100 cm of jejunum, or those who have less than 50 cm of small bowel but an intact colon often
require long term TPN. The availability of home TPN has produced dramatic results in this small group of patients. These results have been documented in the North American Parenteral and Enteral Nutrition Patient Registry, from which the results from 1984–94 are available (Table I). Seventy per cent of patients with Crohn’s disease on home TPN are on full oral diets after 1 year. This result is similar to that found in patients with congenital bowel defects and chronic pancreatitis, and suggests that the remaining bowel can function well.

Recommendations for the Adjunctive Use of Parenteral Nutrition Support in Inflammatory Bowel Disease in Adults
– Bowel rest is not necessary to achieve clinical remission.
– Parenteral therapy is useful in patients who cannot tolerate intestinal feeding and who require nutritional support.
– Home TPN provides an important long term treatment for patients who do not have adequate gut function.

Common Micronutrient Deficiencies in Patients with Inflammatory Bowel Disease
Consideration should be given to the presence of bone mineral, iron, or cobalamin deficiency. Anemia of chronic disease is very common and must be differentiated from iron and cobalamin deficiency. The concomitant use of either enteral nutrition or TPN should not necessarily be considered adequate management for these deficiency states.

References
Enteral Nutrition in Children

ANNE M. GRIFFITHS

Impairment of linear growth is common before the diagnosis of pediatric onset Crohn’s disease as well as during the subsequent years, and height at maturity may be compromised [1]. Of the multiple contributory factors, chronic nutritional inadequacy and direct growth inhibitory effects of cytokines produced by the inflamed intestine are the most important. Therefore the provision of adequate nutrition and a reduction in intestinal inflammation are vital for the management of young patients. The special merits of enteral nutrition in children stem from the potential of liquid diet therapy to facilitate both these aims.

Enteral nutrition is used in the management of pediatric patients with Crohn’s disease not only to improve their energy intake and nutritional status, thereby enhancing growth, but also as primary treatment of active intestinal inflammation.

Meta-analyses of randomized controlled trial data have shown that corticosteroids are more effective than exclusive enteral nutrition in active Crohn’s disease in both adults and children [2]. In the largest pediatric study, 76% of children treated with exclusive nocturnal nasogastric feeding of a semi-elemental formula achieved clinical remission within 4 weeks compared with 90% of those treated with conventional doses of prednisone [3]. No placebo controlled trials of enteral nutrition have been conducted, but the response rates to enteral nutrition in the trials comparing dietary treatment with corticosteroids are clearly superior to placebo response rates in other similar randomized controlled trial settings (Table 1). Moreover, risk/benefit considerations justify a preference for nutritional treatment in growth impaired children, even if the likelihood of remission is greater with corticosteroids.

The mode of action of enteral nutrition as primary treatment remains conjectural. Hypotheses have included alteration in intestinal microbial flora, elimination of dietary antigen uptake, diminution of intestinal synthesis of inflammatory mediators through a reduction in dietary fat, overall nutritional repletion, and provision of important micronutrients to the diseased intestine. The importance of formula
TABLE I – *Enteral nutrition (EN) as primary treatment of active Crohn’s disease: results of randomized controlled trials included in meta-analyses.*

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients in each treatment group</th>
<th>Percent achieving remission</th>
<th>Difference in remission rate</th>
<th>EN-steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EN</td>
<td>Steroids</td>
<td>EN</td>
<td>Steroids</td>
</tr>
<tr>
<td>Enteral nutrition versus corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lochs (<em>Gastroenterology</em> 1991;101:881-8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gonzalez-Huix (<em>Gut</em> 1993;34:778-82)</td>
<td></td>
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<tr>
<td>Gorard (<em>Gut</em> 1993;34:1198-202)</td>
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<tr>
<td>O’Morain (<em>BMJ</em> 1984;288:1859-62)</td>
<td></td>
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<tr>
<td>Seidman (<em>Gastroenterology</em> 1991;100:250A)</td>
<td></td>
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<tr>
<td>Seidman (<em>Gastroenterology</em> 1991;104:A778)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elemental versus non-elemental liquid diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royall (<em>Gut</em> 1994;35:783-7)</td>
<td>19</td>
<td>21</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td>Park (<em>Eur J Gastroenterol Hepatol</em> 1991;3:483-90)</td>
<td>7</td>
<td>7</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>Rigaud (<em>Gut</em> 1991;32:1492-7)</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Raouf (<em>Gut</em> 1991;32:702-7)</td>
<td>13</td>
<td>11</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>Middleton (<em>Ital J Gastroenterol</em> 1991;23:609A)</td>
<td>11</td>
<td>15</td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>
composition is controversial. Data from randomized controlled trials are insufficient at present to establish whether decreased antigenicity related to the protein content or an immunomodulatory effect related to low fat content are important in reduction of intestinal inflammation. These hypotheses are both being explored in ongoing clinical studies.

A major limitation of enteral nutrition has been the tendency of symptoms to recur upon resumption of normal food. Maintenance of nutritionally induced remission is particularly important in pediatric patients if growth is to be facilitated. Two nutritional strategies have been suggested. A recent pediatric prospective controlled trial compared cyclical exclusive enteral nutrition (one month out of four) vs. low dose alternate day prednisone [4]. Although time to first relapse and number of clinical relapses were comparable, children adhering to the nutritional regimen achieved greater gains in height during the 18 month study period. As an alternate strategy, continuation of supplementary enteral nutrition four to five nights per week in addition to a regular ad libitum daytime diet was associated with prolonged clinical remission and improved linear growth in a historical cohort study [5].

References
Remission Induced by a New Specific Oral Polymeric Diet in Children with Crohn’s Disease

J. M. E. Fell, M. Paintin, A. Donnet-Hughes, F. Arnaud-Battandier, T. T. MacDonald and J. A. Walker-Smith

We have previously shown that polymeric diet AL110 (Nestlé) is effective in inducing clinical remission in children with active Crohn’s disease [1]. This remission was associated with evidence of mucosal healing and also with downregulation of local pro-inflammatory cytokines [2,3]. This feed has now been modified as CT3211, which is still casein based and is rich in transforming growth factor β, which may contribute to its therapeutic effect. The composition is given in Table I.

Twenty nine children aged 8.1-17.1 years (median 13.6 years) with active intestinal Crohn’s disease (paediatric Crohn’s disease activity index score (PCDAI) of >10) were treated with CT3211 as their sole source of nutrition for 8 weeks. The volume of feed given during this

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Units</th>
<th>per 100 kcal (100ml)</th>
<th>per 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy</td>
<td>kcal</td>
<td>100</td>
<td>489</td>
</tr>
<tr>
<td>Total fat</td>
<td>g</td>
<td>4.71</td>
<td>23</td>
</tr>
<tr>
<td>Total energy intake – fat</td>
<td>%</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Total protein (casein)</td>
<td>g</td>
<td>3.58</td>
<td>17.5</td>
</tr>
<tr>
<td>Total energy intake – protein</td>
<td>%</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>g</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Total energy – CHO</td>
<td>%</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid component</th>
<th>% by weight</th>
<th>% energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT</td>
<td>26.1</td>
<td>11</td>
</tr>
<tr>
<td>Corn oil</td>
<td>13.9</td>
<td>6</td>
</tr>
<tr>
<td>Milk fat</td>
<td>55.6</td>
<td>23</td>
</tr>
<tr>
<td>Soy lecithin</td>
<td>4.4</td>
<td>2</td>
</tr>
</tbody>
</table>
time was calculated to match their individual daily nutritional requirements. The nutritional treatment was given orally in all cases except one – a child who required nasogastric tube feeding for the first 2 weeks.

Two children failed to respond to treatment and withdrew from the study after 4 weeks. One had colonic Crohn’s disease which subsequently responded to corticosteroids, while the other had an appendiceal abscess which required surgery. This latter complication had probably been present before the start of nutritional treatment.

Of 29 patients recruited, 23 (75%) were in clinical remission at 8 weeks, with a PCDAI of ≤10. Comparing results of the initial assessment with those at 8 weeks, there was a decline in the PCDAI (initial mean score 30 points, mean decline 25 points, \( p <0.00001 \)) and a decline in plasma C reactive protein (initial mean 19 mg/liter, mean decline 13.5 mg/liter, \( p <0.001 \)). At endoscopy there was macroscopic and histological improvement in the colon and terminal ileum in response to treatment. This was associated with a decrease in ileal \( \gamma \)-interferon and interleukin-1 mRNA, and a decrease in colonic interleukin-1 and interleukin-8 mRNA in mucosal biopsies.

**Conclusion**

CT 3211 is an effective oral nutritional treatment for the active intestinal Crohn’s disease of the small and large bowel. It is well tolerated and has minimal side effects. It has been shown to induce clinical remission, with biochemical, endoscopic, macroscopic, and histological response. As further evidence of its efficacy at mucosal level, it induces a decline in the ileal pro-inflammatory cytokines interleukin-1 and \( \gamma \)-interferon, and in colonic interleukin-1 and chemokine IL-8 mRNA.

**References**


Lipid Treatment for Inflammatory Bowel Disease

ANDREA BELLUZZI

Epidemiological observations on the very low incidence of inflammatory bowel disease in Eskimos, who eat large amount of ω-3 fatty acids, together with the known anti-inflammatory effects of these lipids provide the rationale for dietary treatment of patients with inflammatory bowel diseases. Open studies have been undertaken in patients with active ulcerative colitis and significant improvement in symptoms and histological appearance obtained (e.g. [1]).

Lorenz et al. treated 29 patients with Crohn’s disease in different stages of clinical activity and 10 patients with active ulcerative colitis, in a 7 month controlled crossover trial [2]. Encouraging results were obtained in the ulcerative colitis patients, but in the Crohn’s disease group there was no improvement in disease activity score. Hawthorne et al. published the first large placebo controlled study of fish oil treatment in 96 ulcerative colitis patients at different activity stages, treated for 1 year [3]. In patients with active disease a significant steroid sparing effect was shown, but fish oil failed to prevent clinical relapse in patients who were enrolled during remission. Stenson et al. carried out a randomized double-blind placebo controlled crossover trial of fish oil in 24 patients with active ulcerative colitis [4]. They found that during fish oil treatment there was a gain in body weight and an improvement in the histology score. No significant steroid sparing effect was found. Preliminary data suggest that patients with Crohn’s disease may have longer periods of remission when treated with a fish oil enriched diet over a 2 year period. More recently Loeschke et al. presented data on a placebo controlled trial of fish oil in the prevention of relapse of ulcerative colitis [5]. After 3 months, the fish oil group had fewer relapses than the placebo group, but this beneficial effect was lost at the end of the 2 year study. Lorenz-Meyer et al. carried out a large placebo controlled trial in which 204 patients with Crohn’s disease were randomized after acute relapse to receive fish oil, a diet poor in carbohydrate, or placebo for 1 year [6].
In many of the studies side effects such as halitosis, belching and diarrhea were recorded and affected patient compliance.

We recently tested a new ω-3 preparation consisting of 500 mg of enteric coated free fatty acid mixture in a group of patients with Crohn’s disease. This new preparation showed the best incorporation of eicosapentaenoic acid and docosahexaenoic acid into red cell phospholipid membranes, and no side effects were reported. We then performed a 1 year, double-blind, placebo controlled study to investigate the effect of this new preparation on the maintenance of remission in 78 Crohn’s disease patients at high risk of relapse. After 1 year, 23 patients (59%) in the ω-3 group remained in remission, compared with 10 (26%) in the placebo group (Fig. 1).

![Life table analysis: percentage of all randomized patients (39 per group) remaining in clinical remission in an intent-to-treat analysis. From Belluzzi A et al., N Engl J Med 1996;334:1557-616.](figure1)

We carried out another placebo controlled trial of this preparation to determine whether it could prevent lesion recurrence in 50 Crohn’s disease patients who underwent surgical gut resection. Patients were treated for 1 year, starting within 1 month of ileal resection. After
12 months, the overall rate of severe recurrence (score 3-4 on endoscopy or radiological assessment) was 34% (9/26) in the ω-3 group vs. 62% (15/24) in the placebo group.

The therapeutic potential of these lipids in the treatment of inflammatory bowel disease seems to be enhanced by careful attention to the formulation, to the selection of patients, and to the experimental design.

References
Potential Role of Glutamine Administration in Inflammatory Bowel Disease

CAROLYN R. JONAS AND THOMAS R. ZIEGLER

Protein-energy malnutrition and micronutrient depletion are common in patients with Crohn’s disease and ulcerative colitis, which may inhibit gut mucosal regeneration and decrease mucosal antioxidant capacity. The interactions between nutrients and peptide growth factors in intestinal rehabilitation are beginning to be examined in clinically relevant models and in man, with promising results.

Several nutrition-related clinical problems are common in inflammatory bowel disease and are attractive targets for nutrient treatment. These include: (i) chronic diarrhea and malabsorption leading to secondary malnutrition; (ii) short bowel syndrome following small bowel resection, which may require parenteral nutrition; (iii) intestinal barrier dysfunction which may contribute to infection; and (iv) mucosal inflammation with concomitant antioxidant nutrient depletion.

Glutamine as a conditionally essential nutrient

Glutamine is a classical non-essential amino acid. However, studies in animal models and emerging clinical trials strongly suggest that it becomes conditionally essential during catabolic states [1]. Glutamine is a critical substrate in many key metabolic processes, including inter-organ nitrogen transfer, protein synthesis, gluconeogenesis, acid-base homeostasis, and nucleic acid biosynthesis. It is utilized as a major substrate by intestinal mucosal cells and immune cells [1].

One role for muscle breakdown during illness appears to be the provision of glutamine for tissues such as the gut, but this occurs at the expense of a negative nitrogen balance and ultimately decreased muscle mass and function. Glutamine is adequately synthesized to meet metabolic needs during health. However, during illness skeletal muscle exports large amounts of glutamine into the blood (>35% of all amino
acid nitrogen). It is possible that diminished structure and function of certain tissues, such as the intestinal mucosa, during stress may be caused in part by relative glutamine deficiency, as body glutamine utilization exceeds endogenous glutamine production [1].

**Trophic effects of glutamine**

In animals, glutamine added to otherwise complete parenteral nutrition formulations attenuates mucosal small bowel and colonic atrophy, decreases hepatic steatosis, and improves intestinal lymphocyte number and function. Recent *in vitro* studies in gut cell lines suggest that glutamine be trophic to gut cells by both stimulating proliferation and inhibiting apoptosis.

**Effects of glutamine on gut barrier function**

There is evidence that gut barrier function becomes compromised during active inflammatory bowel disease, as shown by increased intestinal permeability of sugar markers and increased rates of endotoxemia. In animal studies there is improved gut barrier function during stress when enteral or parenteral nutrient solutions are supplemented with glutamine [1].

**Effects of glutamine on antioxidant capacity**

Production of free radicals has been implicated in mucosal inflammation and in the acceleration of mucosal cell damage and ulceration during active inflammatory bowel disease [2]. Glutathione (GSH) is one of the body’s major antioxidants. One mechanism for gut trophic effects of glutamine may be upregulation of plasma and tissue GSH levels. Glutamine may serve as a GSH precursor (through interconversion to glutamate) or may alter GSH levels by decreasing tissue requirements of GSH or other antioxidants [3]. In animal models, parenteral glutamine following intestinal ischemia/reperfusion injury markedly increases gut mucosal and circulating GSH concentrations and decreases mucosal levels of lipid peroxidative products.

**Glutamine supplementation in humans**

Several recent clinical studies indicate that both enteral and parenteral glutamine supplementation is beneficial in certain patient groups. Only limited pilot data are available specifically addressing the value of glutamine-enriched nutrition in patients with inflamma-
tory bowel disease. Although glutamine is potentially metabolized to ammonia, glutamate, and other compounds in the body, it is well tolerated clinically, even with large intravenous loads approaching 40% of the administered protein. Diet-controlled and blinded trials in postoperative or bone marrow transplant patients receiving parenteral nutrition have shown that nitrogen balance is significantly improved by supplementation with glutamine. These protein anabolic effects are associated with significantly increased glutamine concentrations in plasma and skeletal muscle, improved rates of protein synthesis, and decreased rates of protein degradation. These results suggest that intravenous glutamine has dynamic protein anabolic effects in catabolic patients. Several investigations also support the concept that glutamine or glutamine dipeptides are trophic to human gut mucosal cells [4].

Parenteral nutrition dependent patients given glutamine supplementation vs. standard glutamine-free parenteral nutrition have significantly increased duodenal villus height and reduced intestinal sugar permeability. Critically ill ICU patients given ALA-glutamine-dipeptide enriched parenteral nutrition postoperatively showed markedly improved D-xylose absorption (194% increase) compared with clinically similar patients receiving glutamine-free parenteral nutrition. L-glutamine rectal suppositories (4 g/d) given to patients with chronic pouchitis after ileal pouch anastomosis appeared to be of clinical benefit. Thus the available limited data suggest that glutamine is a trophic nutrient for human intestinal mucosa and may be of potential benefit for inflammatory bowel disease.

Further work is required to determine the effects of glutamine and diet alone in inflammatory bowel disease, and the molecular mechanisms of action – together with the possible synergistic effect of combining glutamine and growth factors – on human intestinal growth and function.

References
Monoclonal Antibody Therapy in Inflammatory Bowel Disease

ERIC A. VASILIAUSKAS

Recent advances in technology have laid the groundwork for a better understanding of Crohn’s disease and ulcerative colitis, providing insight into mechanisms of disease pathogenesis and potential therapeutic targets. In parallel, pharmaceutical research has forged new and exciting drug treatments that can take advantage of novel treatment strategies, in particular with regard to cytokine-specific drugs. Because responses to cytokine-specific drugs may be related to the nature of the mucosal inflammatory process, substratification of patients within each of these disease entities may allow identification of those most likely to benefit from specific therapeutic interventions.

One such novel approach in inflammatory bowel disease is cytokine-specific monoclonal antibody treatment directed against the pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-\(\alpha\)). This not only offers potential direct patient benefit, but has also increased our understanding of these diseases. TNF-\(\alpha\) has been shown to have the following properties: (1) It stimulates the release of other inflammatory cytokines, prostaglandins, and proteases; (2) It participates in autocrine loops, activating macrophages and enhancing antigen-presenting capability; (3) It increases the permeability of epithelial tight junctions; (4) It enhances the expression of endothelial adhesion molecules involved in recruiting additional inflammatory to migrate to extravascular sites of inflammation (including the mucosa); (5) It inhibits erythropoiesis; (6) It enhances cellular metabolism; (7) It induces acute phase proteins; (8) It induces pyrogenic activity; (9) It mediates granuloma formation.

Thus it has a broad spectrum of biological properties and is upregulated in the inflamed intestinal mucosa of children and adults with inflammatory bowel disease.

Clinical trials have been carried out using chimeric (infliximab) and genetically engineered “humanized” (CDP571) monoclonal antibodies. The findings reported to date from clinical trials with infliximab in the
treatment of Crohn’s disease provide direct evidence that TNF-α inhibition induces clinical response or remission in two thirds of patients with moderately to severely active disease and in two thirds of patients with enterocutaneous fistulae [1-3]. This strengthens the theory that TNF-α may play a central role in the inflammatory process in at least two thirds of the patients with Crohn’s disease. In ulcerative colitis infliximab is well tolerated by patients with severe steroid-refractory disease and may be an effective treatment in selected individuals [4]. Side effects have generally been mild, though two patients developed a lupus-like syndrome. Long term follow up is needed to ensure safety.

Both Crohn’s disease and ulcerative colitis show immunologic and genetic heterogeneity. The specificity of these forms of treatment provides a unique opportunity to evaluate clinical responses in relation to immunologically or genetically determined patient subgroups.

References
Agenda of the 2nd Nestlé Nutrition Workshop: Clinical & Performance Programme

Pasadena, CA, USA - 8-11 November, 1998

“Inflammatory Bowel Diseases”

Chairmen: Prof. Bruce Bistrian, MD, Ph.D.
           Prof. John Walker-Smith, MD, F.R.C.P., F.R.A.C.P.

IBD in perspective
B. BISTRIAN & J. WALKER-SMITH

Epidemiology of IBD
ANDERS EKBORN

Genetics Aspects of IBD
J.-P. HUGOT

Immunological Mechanism
E. SEIDMAN

Nutritional Influence on Inflammation
R.F. GRIMBLE

Clinical & Pathological Aspects of IBD
PH. MARTEAU

Diagnosis Criteria - Adult
PH. MARTEAU

Diagnosis Criteria - Children
J. WALKER-SMITH
Gene Expression & Enteral Feeding
I. SANDERSON

Nutritional Support or Drug Therapy in Adults
K. JEEJEEBHOY

Enteral Feeding vs. Parenteral TPN including Home
D. ALPERS

Enteral Feeding Treatment (children) including Hydrolysed Diet Role
A. GRIFFITHS

Research on CT3211 (Polymeric Diet)
J. FELL

Research Issues of Enteral Feeding in Adults
H. LOCHS

Lipids Treatment in Inflammatory Bowel Disease
A. BELUZZI

Role of Glutamine in IgF1 in Treatment of IBD
TH. ZIEGLER

Monoclonal Antibody Therapy
E. VASILIAUSKAS
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