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OMEGA-3 FATTY ACIDS & INFLAMMATORY BOWEL DISEASE

An Interactive Qualifying Project Report

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Degree of Bachelor of Science

By

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ABSTRACT

This project investigates research surrounding the potential of the anti-inflammatory omega-3 fatty acids to serve as a treatment for inflammatory bowel disease (IBD). A literature review of clinical studies of omega-3 fatty acids and IBD was conducted. It was concluded that insufficient evidence currently exists to prove that omega-3 fatty acids would significantly benefit all IBD patients. However, modifying the diet to increase omega-3 fatty acids is recommended. Educational brochures for patients and gastroenterologists were prepared for this purpose.

ACKNOWLEDGEMENTS

Many people helped me to survive and thrive during the two-year undertaking of this project. Primarily, thank you Professor O'Connor, for allowing me to design a project that was uniquely my own, helping me through all of the *many* stumbling blocks I had along the way, and being so patient during this long, long project. This project would have been much less valuable if it weren't for all of the people with IBD who openly shared their experiences, perceptions, and frustrations. Thank you, Mom, for looking over the earlier drafts and making suggestions on the brochures. Thank you, Dr. Penny Kris-Etherton, for encouraging me in the early stages and serving as inspiration. Thanks to Dr. Jean-Marie Houghton for critiquing my brochures and also Dr. Robert B. Zurier for critiquing drafts. Thank you, Dr. Phillip Calder, for making it possible for me to attend ISSFAL '04. Finally, thanks to my fiancé, Ethan Ray, for helping me to keep things in perspective and being tirelessly supportive of all of my ambitions.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AA	arachidonic acid
AHRQ	Agency for Healthcare Research and Quality
ALA	alpha linolenic acid
CCFA	Crohn's and Colitis Foundation of America
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FFA	free fatty acids
GLA	gamma linolenic acid
IBD	inflammatory bowel disease
IL	interleukin
IQP	Interactive Qualifying Project
ISSFAL	International Society for the Study of Fatty Acids and Lipids
LA	linoleic acid
N-3	omega-3
N-6	omega-6
NCCAM	National Center for the Study of Complementary and Alternative Medicine
NIDDK	National Institute of Diabetes & Digestive & Kidney Diseases
PSU	The Pennsylvania State University
PUFA	polyunsaturated fatty acid
Th	Helper T
UC	ulcerative colitis
UMMS	University of Massachusetts Medical School
WPI	Worcester Polytechnic Institute

CHAPTER 1

INTRODUCTION

"Let food be thy medicine and medicine be thy food."[1] This quote by Hippocrates is cited often by groups advocating nutritional remedies for disease. However, rejecting common modern (allopathic) methods entirely can result in less than optimal medical care.

In chronic diseases, especially, the issue of ideal medical intervention is hotly debated. The principle that bearers of chronic disease may take handfuls of pills per day is accepted by many. Indeed, advances in pharmacology have led to medicines that have made symptoms more bearable.

On the other side of the fence are those that will avoid synthetic treatments at all costs in favor of herbalism, acupuncture, or other treatments under the broad umbrella of holistic medicine. With the recent finding that almost all prescription pain relievers used long-term to treat the aches of arthritis increase the risk of heart attacks,[2] many people are left nervous about filling such prescriptions. Natural medicine (which does not include synthetic drugs) is increasing in popularity, and many people are looking for ways to modify their diets and lifestyles to optimize their quality of life.

This project attempts to draw an evidence-based conclusion on the role of a specific natural approach—modification of dietary fat—in treating chronic disease. The conclusion is

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[1] James T. Ehler, "Food Reference Website," http://www.foodreference.com/html/qmedicine.html (accessed 2 January 2005).

[2] S. R. Maxwell and D. J. Webb, "COX-2 Selective Inhibitors--Important Lessons Learned," *Lancet*. 365, no. 9458 (5 February 2005): 449-51.

then applied in the creation of educational materials needed to communicate the project's findings. The purpose of this IQP is to ask what role, if any, modification of dietary fat holds in the therapy for one particular the chronic disease—inflammatory bowel disease (IBD).

This chapter orients the reader to the project subject, goals, potential practical results, and serves as introduction to IBD. It contains a description of IBD, its symptoms, and the social implications of the illness for people who experience it. Following this overview is a discussion of *who* gets IBD. Once the reader is oriented to the nature of IBD, this introduction gives an overview of the current approaches (medication and surgery) to treating IBD. Following this discussion of the current paradigms, the reader is exposed briefly to "dietary intervention" as an alternative that may offer improved treatment of IBD. After the idea of dietary intervention is introduced, the procedure and goals of the project are outlined. At the conclusion of this chapter, a short preview of each of the succeeding chapters is presented.

1.1. Overview

Inflammatory bowel disease is the collective term for two related illnesses: ulcerative colitis (UC) and Crohn's disease (CD). Both diseases result in chronic inflammation of the digestive tract. Inflammation is a general term for redness, swelling, and heat associated with a type of immune response. An example of inflammation is the puffy tenderness of a paper cut. In people with IBD, inflammation occurs in the tissues of the digestive organs.

The difference between UC and CD is the depth of the tissue affected and location of disease within the digestive tract.[3] UC occurs only in the large intestine (the last part of the digestive tract) and affects only the very inner lining of tissue. CD can occur anywhere in the

[3] James F. Marion, Peter H. Rubin, and Daniel H. Present, "Differential Diagnosis of Chronic Ulcerative Colitis and Crohn's Disease" in *Inflammatory Bowel Disease (5th Ed.)*, Joseph B. Kirsner, ed., (Philadelphia: W. B. Saunders, 2000), 315.

digestive tract and often affects the entire depth of tissue. The symptoms and treatment of UC and CD often overlap, so they are often referred to collectively as IBD.

The symptoms of IBD are chronic and life altering. It is first important to explain that IBD comes and goes. The active state of IBD is called a "flare" or "flare-up," and IBD in its non-active state is said to be "in remission." During a flare of IBD, the intestinal inflammation causes cramping, abdominal pain, and diarrhea. Additionally, people with IBD may notice blood and mucus in their stools. The blood results from tissue ulcerations that are similar to scrapes. The mucus is produced by the body in response to this irritation. Sometimes, the inflammation is severe enough to result in fever.

CD, because it can affect the entire thickness of the tissue, carries additional complications. Strictures, which are swelling in the intestines, narrow the lumen (tube) and may restrict the passage of fecal matter.[4] Malabsorption of important vitamins and nutrients may also occur, resulting in weight loss and poor growth in children with IBD.[5] Additionally, the cramping, pain, and diarrhea, often result in less eating by the patient—resulting in further concern for adequate nutrient intake.[6]

As may be expected, these physical symptoms result in a wide array of social and emotional concerns for people with IBD. There is a stigma surrounding issues associated with the digestive process. It is considered impolite to allude to defecation in conversation and even more of a social faux pas to pass gas in public. People with IBD often experience a world that does not understand their urgent need to use bathroom facilities. They may feel

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[4] Robert H. Riddell , "Pathology of Idiopathic Inflammatory Bowel Disease" in *Inflammatory Bowel Disease (5th Ed.)*, Joseph B. Kirsner, ed., (Philadelphia: W. B. Saunders, 2000), 436.
[5] Sidney F. Phillips, "Pathophysiology of Symptoms and Clinical Features of Inflammatory Bowel Disease" in *Inflammatory Bowel Disease (5th Ed.)*, Joseph B. Kirsner, ed., (Philadelphia: W. B. Saunders, 2000), 359-360.
[6] Ibid.

isolated and uncomfortable discussing their needs and concerns. People with IBD sometimes worry about body image and acceptance by the opposite sex.

There is the additional issue of losing control in more than one sense. Patients may feel that their own bodies have turned against them. They do not know when they will experience the symptoms of the disease and cannot make them go away. They lose control of a very intimate bodily process. Chronic medical conditions—in general—are difficult emotionally, and a patient who is diagnosed with IBD may experience a range of emotions such as denial, hostility, despair, sadness, and grief, as well as adaptive coping responses to the ups and downs of chronic illness.[7]

1.2. People Affected

IBD is a global problem. The disease strikes rich and poor, men and women, and all ethnicities.[8,9] The causes are not completely understood. The Crohn's and Colitis Foundation of America (CCFA), a national organization that coordinates much research on IBD, extrapolates from epidemiological studies and estimates that one million Americans suffer from IBD.[10] Inflammatory bowel disease affects men and women in almost equal numbers. Jews of Ashkenazic (European) descent have the highest incidence of IBD in Western Europe and the United States, and their incidence remains high even in low incidence areas.[11] Globally, IBD is most prevalent in Europe and North America.[12]

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[7] H. M. Spiro, "Six Physicians with Inflammatory Bowel Disease," *Journal of Clinical Gastroenterology* 12 (1990): 309.
[8] Vibeke Binder "Epidemiology of IBD During the Twentieth Century: An Integrated View." *Best Practice and Research Clinical Gastroenterology*. 18 no. 3 (June 2004): 463-479.
[9] F. Farrokhyar, E. T. Swarbrick, and E. J. Irvine. "A Critical Review of Epidemiological Studies in Inflammatory Bowel Disease." *Scandinavian Journal of Gastroenterology* 36 no. 1 (Jan 2001): 2-15.
[10] Crohn's and Colitis Foundation of America. "Facts About the Epidemiology of Inflammatory Bowel Diseases (IBD)" http://www.ccfa.org/about/press/epidemiologyfacts (Accessed 28 December 2004.)
[11] Miles C. Allison, Amar P. Dhillon, Wyn G. Lewis, Roy E. Pounder. *Inflammatory Bowel Disease* (London, UK: Mosby, 1998), 8.
[12] Ibid., 5.

In North America, IBD is more prevalent in the white community than among blacks or Asians.[13] Black Americans have a higher incidence than Africans, and Asian Americans have a higher incidence than Asians living in Asia.[14] The rate among the people living in Japan is rising, bringing that population closer to the levels found in America and northern Europe than the rest of Asia.[15] These observations point to an effect of urbanization on the prevalence of IBD.

This disease often occurs at a very vulnerable age, during the teenage years, when the self-image is being formed and independence established. Most cases are diagnosed between the ages of 15 and 30.[16] Another peak in incidence occurs between 50 and 65.[17] These peaks may suggest hormonal involvement in the development of IBD because the teenage years and twenties are a time of sexual maturation and child-bearing (for women), and the age of 50-65 may be a time of decreasing sex hormones.

1.3. Medical Treatment

The current arsenal used to treat people with IBD consists of 5-aminosalycilates, corticosteroids, immunosuppressives, biologics, and surgery. An important point to keep in mind is that these treatments are palliative; that is, they are meant to reduce the symptoms of IBD, not cure it. Gastroenterologists (the specialists who treat IBD) try different medications in different combinations to achieve the best possible control of the illness's symptoms by reducing flares and retaining remission. All of these medications carry side effects for the patient ranging from allergic reactions and emotional instability to a compromised immune

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[13] Ibid.
[14] Ibid.
[15] R. Shoda, K. Matsueda, Y Shigeru, N. Umeda, N. "Epidemiologic Analysis of Crohn's Disease in Japan: Increased Dietary Intake of N-6 Polyunsaturated Fatty Acids and Animal Protein Relates to the Increased Incidence of Crohn Disease in Japan." *American Journal of Clinical Nutrition* 63 (1996): 741-745.
[16] S. H. Stein, and R. P. Rood, *Inflammatory Bowel Disease: A Guide for Patients and Their Families (2nd Ed.)* (Philadelphia: Lippincott Williams and Wilkins, 1999), 25.
[17] Ibid.

system and increased risk of osteoporosis (see Section 2.5.1.) Moreover, many patients do not want to feel dependent on daily medication, especially if the medication does not cause an immediate noticeable improvement of their symptoms. Medications for IBD are also very costly, and this in itself raises problems.

1.4. Dietary Intervention as a Possible Therapy

There is another approach with the potential for treating IBD. This is a dietary approach, which involves modification of lipid intake, specifically polyunsaturated fat. Fatty acids have been receiving a lot of media attention for their role in heart disease. The American Heart Association advocates a diet with less saturated fatty acids (the type in animal products and coconut oil) and more unsaturated fatty acids (from olive and vegetable oils, and fish) to prevent heart disease. However, little attention has been paid to the role of polyunsaturated fatty acids (PUFAs) in regulating immune function and their role in preventing immune disorders.

There are two classes of PUFAs: omega-6 (n-6) and omega-3 (n-3). Both types of PUFAs must be present in all diets because humans do not have the ability to make these essential fatty acids. Sources of n-6 include all refined vegetable oils: corn, safflower, sunflower, peanut, cottonseed, and soybean. N-6 PUFAs are also found in high concentration in the fat of animals fed a diet of corn and grains (as is common in modern agriculture). N-3 PUFAs are found mainly in fish and flax seed, although canola, walnut, and green plants also provide small quantities of n-3 PUFAs.

PUFAs regulate the inflammatory response by serving as the starting materials for certain chemicals (eicosanoids) of the immune system. The chemicals built from n-6 PUFAs are pro-inflammatory, while n-3 PUFAs are precursors for anti-inflammatory chemicals. It is

helpful to think of the role of PUFAs like two people on opposite sides of a balance. N-6 PUFAs are on the inflammatory side, and n-3 PUFAs are on the anti-inflammatory side. In the Western diet, the weight on the n-6 side is 10-20 times more than the weight on the n-3 side.[18] Although it is not known exactly what the ideal ratio of n-6 to n-3 PUFAs is, it is estimated to be 1 or 2:1.[19] In conclusion, the ratio of pro-inflammatory n-6 PUFAs to anti-inflammatory n-3 PUFAs is very high in Western diets, which may pose problems for immune system regulation.

Adjusting this ratio to a more favorable inflammatory balance may offer potential for treating inflammatory illnesses—including IBD. Increasing n-3 PUFA intake and decreasing n-6 PUFA intake may decrease the level of inflammation occurring in these illnesses. Decreasing inflammation (and the resulting symptoms of illness) might allow for better control of such illnesses and decreased dependence on medication for people with IBD.

1.5. Project Goals

As stated in Worcester Polytechnic Institute's *Undergraduate Catalog*, the purpose of the Interactive Qualifying Project (IQP) is to challenge students to relate social needs or concerns to specific issues raised by scientific and technological developments. This project is attempting to investigate and to improve awareness of another possible approach—beyond the technologies currently used to treat IBD. The treatment of IBD is of great social concern because IBD causes much suffering to many people.

The primary goal of this project is to investigate the potential of modifying the ratio of n-6 to n-3 PUFAs in the diet as a treatment for IBD. Upon completion of this

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[18] Penny M. Kris-Etherton, D. S. Taylor, S. Yu-Poth, P. Huth, K. Moriarty, V. Fishell, R. L. Hargrove, G. Zhao, T. D. Etherton, "Polyunsaturated Fatty Acids in the Food Chain in the United States," *American Journal of Clinical Nutrition* 71, (1 Suppl.) (2000):179S-188S.

[19] Artemis P. Simopoulos, "The Importance of the Ratio of Omega-6/Omega-3 Essential Fatty Acids," *Biomedicine and Pharmacotherapy* 56 (2002): 365-379.

investigation, the results are presented for use by various groups having the most potential interest in this information. These groups include people with IBD, the Crohn's and Colitis Foundation of America (CCFA), the International Society for the Study of Fatty Acids and Lipids (ISSFAL), and the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) (see Section 3.1.4.). People with IBD are presented with recommendations based on an analysis of the current research pertaining to the role of PUFAs in treating IBD; others of the aforementioned groups may be interested in future directions for research in this area. The project goals as they relate to each group are discussed below.

1.5.1. Recommendations for Patients Based on Current Research

People with IBD and gastrointestinal specialists (gastroenterologists) are the primary audience for the results of this project. Based on the analysis performed in this project, recommendations are made to these audiences on PUFA consumption. Appropriate materials are provided to communicate the project's findings to people with IBD and gastroenterologists.

1.5.2. Recommendations for Further Research

Dietary intervention is not a currently accepted method for treating IBD. This is perhaps because the current pool of research seems weak and conflicting. After analyzing the potential of n-3 PUFAs based on completed research, the project includes a discussion of research in progress and proposes future research designs based on what is currently known. The agencies that have an interest in funding research in the field of IBD are discussed in Section 3.1.4.

1.6. Methodology of the Project: Design and Research

The design of the project was based on conversations held with IBD patients and a consultation with a nutritional researcher. The IBD patients who spoke with the author were relatively misinformed concerning the role of diet in the inflammation relevant to their disease; they also stated that their gastroenterologists had not advised them to modify the fatty acid composition of their diets. The nutritional researcher, Dr. Kris-Etherton of the Pennsylvania State University, who has published guidelines for the role of PUFAs in preventing cardiovascular disease for the American Heart Association, was consulted to insure the validity of the author's idea that similar guidelines could be established for IBD.

To ensure that the project's ideas were novel, CCFA was contacted, and patient materials in the form of brochures and booklets for patients and their families were obtained. One brochure was titled "Diet and IBD" and contained no useful information pertaining to PUFAs. The books included *Managing Your Child's Crohn's Disease or Ulcerative Colitis*[20] and *The New People...Not Patients.*[21] (The fourteen educational brochures may be downloaded from the CCFA's website: http://www.ccfa.org/research/info/brochuresintro.)

The foundation of this project is a literature review that included the reading of pertinent medical texts, reviews, and primary research on IBD and PUFAs. Online searches of public databases of research papers—i.e., PubMed and ScienceDirect—allowed compilation of applicable journal articles. The articles (when not available directly from the

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[20] K. Benkov and H. Winter, *Managing Your Child's Crohn's Disease or Ulcerative Colitis* (New York: Crohn's and Colitis Foundation of America, Inc., Mastermedia, 1996).
[21] Penny B. Steiner-Grossman, P. Banks, and D. Present, *The New People...Not Patients : A Source Book for Living With Inflammatory Bowel Disease* (New York: Crohn's & Colitis Foundation of America, Inc., Kendall Hunt Publishing Company, 1997).

public databases) were obtained from the Lamar Soutter (University of Massachusetts Medical Center) and Paterno (the Pennsylvania State University) libraries.

This project is divided into chapters focusing on background, methods, discussion, and conclusions. Chapter 2 provides background information on Inflammatory Bowel Disease and PUFAs. It first explains the function of the digestive and immune systems and how they are involved in IBD. The pathogenetic theories of IBD are then presented followed by an epidemiological analysis of IBD. Finally each common medical/surgical treatment strategy is examined for its mode of action, side effects, and prescribed preparations. This chapter continues with a discussion of issues facing medical/surgical treatment of IBD. The background information on PUFAs includes a complete description of what PUFAs are and their biological role, and the issues presented in changing PUFA consumption in Westernized cultures.

Chapter 3 describes the methodology of the project. It explains how the project was performed, discusses research sources that were utilized, and the methods used.

Chapter 4, the discussion section, analyzes clinical studies of PUFAs in treating IBD. This section looks at both the results of the studies and at how the design of the studies may have influenced their results.

Chapter 5 concludes the project by providing recommendations for patients and gastroenterologists and discusses possible directions for future research to be funded by the aforementioned groups.

CHAPTER 2

BACKGROUND

This chapter presents background material on IBD. This background material begins with the bodily systems involved in IBD and then defines IBD. The discussion continues to the pathogenesis, epidemiology, and medical treatment of IBD and the challenges associated with current medical treatment strategies. This portion of the background chapter is designed to inform the reader of the current state of IBD treatment in order to lay a foundation for the succeeding discussion on an innovative potential method of treatment.

Following the IBD-oriented portion of the background chapter is a primer on polyunsaturated fatty acids. This information begins with an explanation of what a polyunsaturated fatty acid is and then discusses types, functions within the body, and dietary sources of polyunsaturated fatty acids. At the conclusion of the chapter is information on the design of clinical studies and how factors in design influence the evaluation of study outcomes.

2.1. Bodily Systems Involved in Inflammatory Bowel Disease

Two bodily systems are involved in IBD. These systems are the digestive and immune systems. It is necessary to understand the functions of both systems in order to understand IBD. The following sections give a general overview of the functions and terminology of the digestive and immune systems.

2.1.1. The Digestive System

The gastrointestinal tract[22] is a series of hollow, tubular structures running from the mouth to the anus. It includes the esophagus, stomach, small intestine, and large intestine (**Figure 2.1**). As food travels through this system, it is broken down and absorbed by the lining cells of the intestine and transported into the bloodstream. Digestion transforms fats into fatty acids and glycerol, proteins into amino acids, and carbohydrates into simple sugars. All of these are sources of energy for the body.

IBD often occurs in both the small intestine and large intestine. The intestines are where absorption of food occurs. Three parts of the small intestine—the duodenum, the jejunum, and the ileum—perform some of the absorptive function.

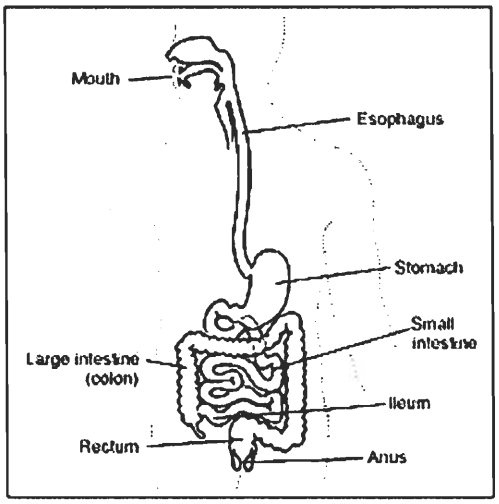

Figure 2.1. The Digestive System. From the National Institute of Digestive and Kidney Diseases. *Crohn's Disease*. http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/ (accessed January 2003).

As food passes through the intestines, each part performs its specific function. Food is churned in the duodenum, and stomach acids are neutralized. Bile is fed to the duodenum from the gall bladder to help absorb fats. Most digestion takes place in the jejunum. All the basic nutrients, including vitamins, minerals, water, and electrolytes such as calcium and salt,

[22] Elaine N. Marieb, *Anatomy & Physiology* (San Francisco: Benjamin Cummings, 2002), 738-789.

are absorbed through the walls of the small intestine into the bloodstream. At the ileum, vitamin B12 is the final nutrient to be absorbed. The food remnants then pass through the ileocecal valve into the colon. The colon's main function is to reabsorb water from the waste material, store the solid waste, and eliminate it through the voluntary muscles at the anus.

The cells making up the gastrointestinal tract are specially designed for the function of moving food and absorbing nutrients. Like any hollow organ, the inside of the gut is the mucosa, which consists of a layer of epithelial cells (the epithelium) and supporting loose connective tissue (the lamina propia) immediately beneath the epithelium. Deeper connective tissue supporting the mucosa is called the submucosa. There is a thin layer of smooth muscle, the muscularis mucosae, at the boundary between the mucosa and submucosa. The mucosa is adapted to its function (differentiated) at each point along the gastrointestinal tract. Tissue specialization and surface shape are correlated with the different processes occuring along the tract.

2.1.2. The Immune System

The immune system[23] is responsible for manufacturing cells that recognize and destroy antigens (foreign things) that invade the body. The immune system offers protection from infectious agents that exist in the environment (bacteria, viruses, fungi, parasites) and from other noxious insults. These cells of the immune system (leukocytes) include lymphocytes, monocytes, granulocytes, mast cells, and macrophages.

Lymphocytes have the most prevalent role in the immune response. They include B lymphocytes, natural killer cells, and T lymphocytes—so called because they mature in the thymus gland. T lymphocytes are further divided into helper T cells and cytotoxic T cells by the presence of markers on the cell surface. The cells of the immune system are found

[23] Ibid., 660.

circulating in the bloodstream, organized into lymphoid organs such as the thymus, spleen and lymph nodes, or dispersed in other locations around the body.

Communication within the immune system is brought about by direct cell-to-cell contact and by the production of chemical messengers. Chief among these chemical messengers are proteins called cytokines that can act to regulate the activity of the cell that produced the cytokine and/or the activity of other cells. Each cytokine can have multiple activities on different cell types. Cytokines act by binding to specific receptors on the cell surface and thereby induce changes in growth, development, or activity of the target cell.[24]

Helper T lymphocytes are subdivided functionally according to the pattern of cytokines they produce. Type-1 helper T lymphocytes (Th1 cells) produce interleukin (IL)-2 and interferon-γ which activate macrophages, natural killer cells, and cytotoxic T lymphocytes. Interactions with bacteria, viruses, and fungi tend to induce Th1 activity. Type-2 helper T lymphocytes (Th2 cells) produce IL-4, IL-5, and IL-10, which suppress the cell-mediated immunity of Th1 cells. An imbalance or deregulation between the Th1 and Th2-type responses is a characteristic of many human diseases.[25]

Tumor necrosis factor (TNF)-α, IL-1, and IL-6 are among the most important cytokines produced by monocytes and macrophages. These cytokines activate neutrophils, monocytes, and macrophages to initiate bacterial and tumor cell killing, increase adhesion molecule expression on the surface of neutrophils and endothelial cells, stimulate T and B lymphocyte proliferation, up-regulate major histocompatibility antigens (these are involved

[24] Ibid., 683.
[25] T. R. Mossmann, S. Sad, "The Expanding Universe of T-Cell Subsets: Th1, Th2, and More," *Immunology Today* 17 (1996): 138-146.

in the presentation of antigen to T lymphocytes), and initiate the production of other cytokines.[26] Thus, TNF, IL-1, and IL-6 are mediators of immunity.

In addition, these cytokines mediate the systemic effects of inflammation such as fever, weight loss, and acute-phase protein synthesis in the liver.[27] Production of appropriate amounts of TNF, IL-1, and IL-6 is beneficial in response to infection, but inappropriate or overproduction can be dangerous. These cytokines, especially TNF-α, are implicated in causing some of the pathological responses which occur in inflammatory conditions.[28]

2.2. Definition of Inflammatory Bowel Disease

This section provides the definition of IBD that this project uses. As mentioned above, the generally accepted view is that IBD is the collective term for UC and CD—two conditions that result when the immune system is deregulated in the digestive tract.

2.2.1. Roles of the Immune System and Digestive Tract

IBD is the result of abnormal control of the immune system's response to environmental triggers. These triggers may include the bacteria that occur naturally in a person's gastrointestinal tract.

In the healthy intestine, invading bacteria are recognized as antigens and responded to by stimulation of the immune response, while those bacteria that are normally present are left alone. The healthy intestine is tolerant of its bacterial inhabitants.

In contrast, immunologic evidence indicates that in the intestines of those with IBD, some of this tolerance is lost. Inflammatory signals turn on the immune system in response to the normal bacteria, and the inflammation, for some reason, does not clear up. The

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[26] Charles A Janeway, Paul Travers, Mark Walport, and Mark J. Shlomchik. *Immunobiology: the Immune System in Health and Disease.* 6th Ed. (New York: Garland Science Publishing, 2005), 53.
[27] Ibid.
[28] Ernest H. S. Choy and Gabriel S. Panayi, "Cytokine Pathways and Joint Inflammation in Rheumatoid Arthritis," *New England Journal of Medicine* 344 (2001): 907-916.

resulting imbalance of immune-regulating chemicals causes an inappropriate inflammatory response and the symptoms of IBD.

This deregulated immune response is evidenced by a high density of immune cells called polymorphonuclear cells (also known as granulocytes) within the inflamed gut epithelium (inner lining) which include neutrophils and monocytes—which mature into macrophages.[29] There is also an abundance of lymphocytes (B and T cells).[30] Succinctly, all of the immune cells are present, and all of them are actively spewing out chemical messages to each other.

The granulocytes are recruited through the epithelium into the mucosa and together with the resulting macrophages release reactive oxygen species.[31] Also, these cells produce IL-1, IL-6, and TNF which lead to tissue damage. There is also increased vascular endothelial and mucosal permeability (the junctions of the cells become "leaky" allowing immune cells to migrate to the area).[32] In both UC and CD, there is an increased amount of antibodies (produced by the mature B cells).[33] T cells increase release of interferon-γ, IL-12, and IL-18 from immune cells, and this release feeds back into the activation of Th cells through a feedback loop of inflammatory cascades.[34] The scene has been described as an "alteration of local immunological homeostasis."[35] This seems an understatement of the immunological chaos occurring in the gut tissue of patients with IBD.

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[29] Allison et al., 15.
[30] Ibid.
[31] Ibid.
[32] Ibid.
[33] Ibid.
[34] Allsion et al., 18; Daniel K. Podolsky, "The Current Future Understanding of Inflammatory Bowel Disease," *Best Practices and Research in Clinical Gastroenterology* 16 (2002): 936.
[35] Allsion et al., 15.

2.2.2. Crohn's Disease vs. Ulcerative Colitis

The major difference between the two subtypes of IBD is that UC normally affects only the large bowel, and CD can occur anywhere from mouth to anus.[36] In UC, the inflammation is limited to the inner lining of the large intestine (colon or bowel) and rectum.[37] The inflammation usually begins in the rectum and lower (sigmoid) intestine and spreads upward, sometimes affecting the entire colon. UC rarely affects the small intestine except for the lower section, the ileum. The inflammation causes the colon to empty frequently, resulting in diarrhea. As cells on the surface of the lining of the colon die and slough off, ulcers (tiny open sores) form, causing pus, mucus, and bleeding. Endoscopic examination also shows a shortened colon, loss of the characteristic intestinal pouches (haustral loss) and granulation (formation of small, red prominences) of the mucosa (inner layer.) These features are shown in **Figure 2.2**.

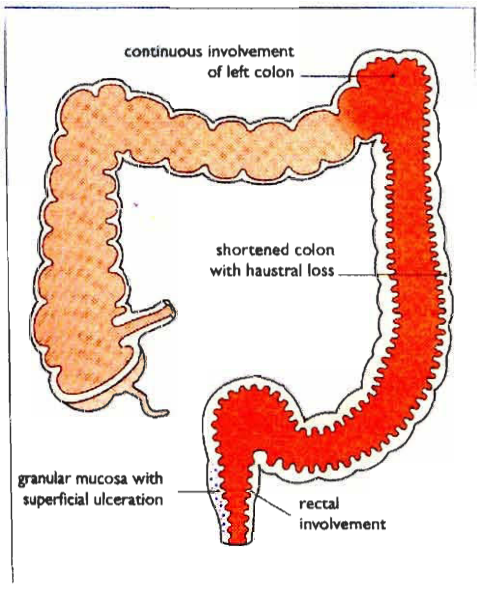

Figure 2.2. Characteristic Pathological Changes in Ulcerative Colitis. From Miles C. Allison et al., *Inflammatory Bowel Disease* (London: Mosby International,1998), 13.

[36] Miles C Allison, Amar P. Dhillon, Wyn G. Lewis, Roy E. Pounder, *Inflammatory Bowel Disease* (London: Mosby, 1998), 11.
[37] Ibid.

The most common symptoms of UC are abdominal pain and bloody diarrhea. Patients also may suffer fatigue, weight loss, loss of appetite, rectal bleeding, and loss of body fluids and nutrients. Severe bleeding can lead to anemia. Sometimes patients also have skin lesions, joint pain, inflammation of the eyes, or liver disorders. It is uncertain how problems outside the bowel are linked with UC, but the above-mentioned complications may occur because the immune system triggers inflammation in other parts of the body.

Total colitis involves the entire colon, while distal colitis involves only the terminating portion and rectum. Greater involvement results in greater severity of symptoms. Also, severe complications can occur in UC, such as toxin megacolon, in which the colon swells and must be removed. Ulcerations can perforate the colon. Patients with severe UC are at a higher risk for colon cancer. These complications are shown in **Figure 2.3**.

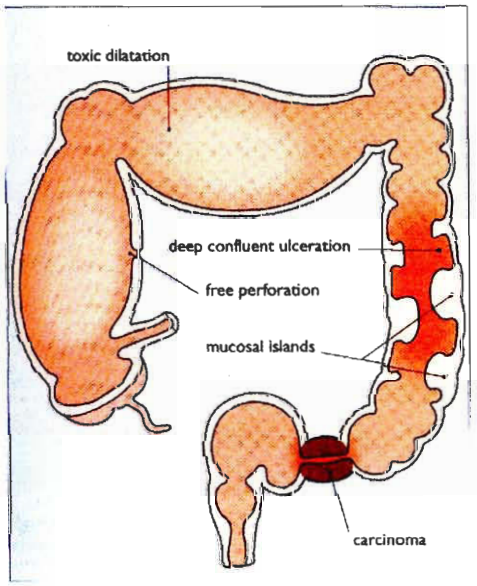

Figure 2.3. Local Complications in Ulcerative Colitis. From Miles C Allison et al., *Inflammatory Bowel Disease* (London: Mosby International, 1998), 13.

In CD, the inflammation extends through the entire thickness of the organ lining and is usually not confined to the large intestine. The disease also affects discontinuous segments

of the gastrointestinal tract. The connection between the large and small intestines—the ileocaecum—is often involved (**Figure 2.4**.)

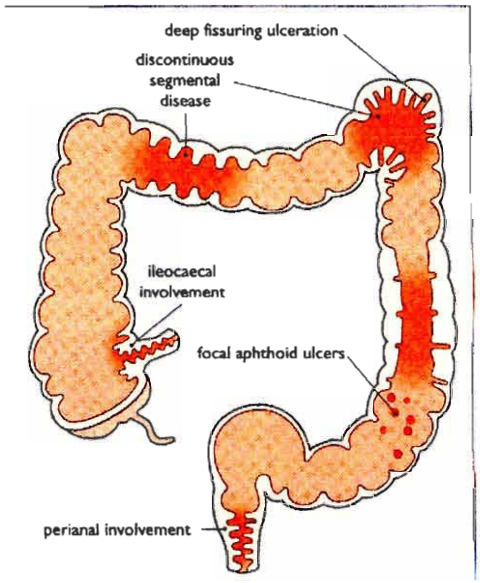

Figure 2.4. Characteristic Pathological Changes in Crohn's Disease (Only the large intestine is shown but Crohn's disease occurs anywhere in the digestive tract.) From Miles C. Allison et al., *Inflammatory Bowel Disease* (London: Mosby International, 1998), 13.

In addition to the symptoms of UC, a patient with CD may experience complications such as fistulas (abnormal connections between the bowel and other organs), strictures (swelling of the intestines so intense that it blocks the passage of fecal matter), and abscesses. These local complications of CD are illustrated in **Figure 2.5.**

Differential diagnosis of these two forms of IBD is sometimes difficult because of the overlapping signs and symptoms. Most gastroenterologists will use endoscopic methods (i.e., a colonoscopy) with review of biopsies (tissue samples) to directly examine the inside of the intestinal tract to determine which label to use.[38] Occassionally, diagnosis of UC or CD is not made for months or years after diagnosis of IBD.[39] Some cases remain diagnosed

[38] Allison et al., 3, 11.
[39] Allison et al., 12.

as "indeterminant colitis," or become classified as Crohn's colitis which shares characteristics of both UC and CD.

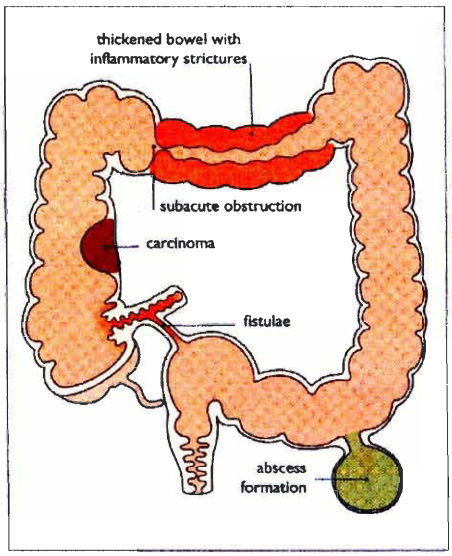

Figure 2.5. Local Complications in Crohn's Disease. From Miles C. Allison et al., *Inflammatory Bowel Disease* (London: Mosby International, 1998), 13.

2.3. Pathogenesis of Inflammatory Bowel Disease

The causes of IBD are not completely understood. Numerous mechanisms have been described: infectious agents, mucus abnormalities, abnormal local immune response, and autoantibodies.[40] However, none of these theories have been confirmed, and the etiology of IBD remains uncertain.

IBD appears to be multifactoral, with genetic and environmental factors cooperating in its development. Studies with twins have been performed to study the respective role of environmental and genetic factors.[41,42,43] Monozygotic twins (from the same egg) are

[40] J. P. Hugot, H. Zouali, S. Lesage, G. Thomas, "Etiology of the inflammatory bowel diseases," *International Journal of Colorectal Disease* 14 (1999): 2-9.
[41] C. Tysk, E. Lindberg, G. Jarnerot, B. Gloderus-Myrhed, "Ulcerative Colitis and Chrohn's Disease in an Unselected Population of Monzygotic and Dizygotic Twins. A Study of Heritability and the Influence of Smoking," *Gut* 29 (1998): 990-996.

genetically identical. In the case of genetic determinants only, the concordance rate of the disease would be 100% in monozygotic twins. This is not the case either in CD, which has a concordance rate of 20-44% or UC, which has a concordance rate of 6-16%.[44] This is strong evidence that not only genetic factors, but also environmental factors, play a role in IBD.

Bacteria also seem to be involved in the pathogenesis of IBD. Experimental colitis cannot be reproduced in animals raised in germ-free environments.[45] Moreover, the bacterial population in the intestines of people with IBD is altered.[46] However, rather than being a cause of the disease, it seems more likely that intestinal bacteria play a secondary role in exacerbating intestinal inflammation. That is to say, the bacteria would not be an issue except for the fact that the immune system is already out of control and develops abnormal responses to gut flora (bacterial inhabitants). This abnormal response to nonpathogenic bodies is analogous to an allergic response.

2.4. Epidemiology of Inflammatory Bowel Disease

This section discusses the groups of people likely to develop IBD based on location, ethnicity, and age. The main epidemiological observations are that IBD most often develops during the teenage years and early twenties and is most common in industrialized regions of the world.

2.4.1. Regional Variation

IBD appears to be an affliction primarily affecting those living in Westernized, or industrialized societies. CD and UC are rarely diagnosed in less developed countries. This

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[42] N. P. Thompson, R. Driscoll, R. E. Pounder, A. J. Wakefield, "Genetics vs. Environment in Inflammatory Bowel Disease: Results of a British Twin Study," *British Medical Journal* 312 (1996): 95-96.
[43] M. Orholm, V. Binder, T. I. A. Sorensen, K. O. Kyvik, "Inflammatory Bowel Disease in a Danish Twin Register," *Gut* 39 (Suppl. 3) (1996): A187
[44] Hugot et al.
[45] Allison et al., 22.
[46] Ibid.

may be because of environmental reasons or because IBD—although it exists—is simply not diagnosed in less developed countries.

IBD is most prevalent in the United States, Canada, the United Kingdom, Scandinavia, and Western Europe (**Figure 2.6**). Within those countries, rates are about five times higher in the Jewish population than in the general population.[47] There is likely a susceptibility gene that increases the tendency of Ashkenazy Jew to develop IBD.

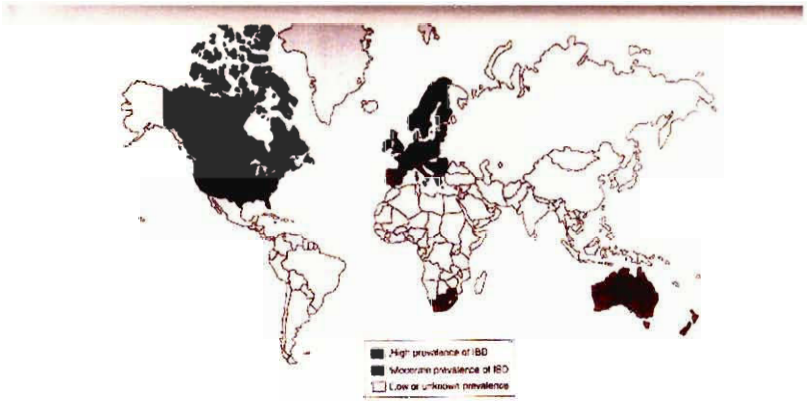

Figure 2.6. Regional Variation of Inflammatory Bowel Disease. S. H. Stein and R. P. Rood, *Inflammatory Bowel Disease: A Guide for Patients and Their Families* (2nd Ed.) (Philadelphia: Lippincott Williams and Wilkins, 1999).

Most non-industrialized areas of the world have low incidence of IBD. Asians have little IBD, except in Japan, where the rates have been rising steadily since the country began to industrialize after World War II.[48] IBD is rare among Africans living in Africa, although African Americans do experience IBD at an incidence equal to Caucasians in the U.S.[49]

So-called migrant studies of IBD incidence are also very telling. CD is rare in Hong Kong Chinese and more common among Chinese migrants in Vancouver.[50] After emigrating

[47] Kirsner, 597.
[48] Shoda et al., 741-745.
[49] Crohn's and Colitis Foundation of America. "Facts About Inflammatory Bowel Diseases" http://www.ccfa.org/about/press/ibdfacts. (Accessed February 10, 2005.)
[50] Allison et al., 9.

from the West Indies to Europe, Sikhs and Hindus are at an increased risk of CD.[51] Finally, Asians moving to the UK have increased UC.[52]

These statistics continue to provide possible evidence that a "Western diet," which is high in animal fats, protein, and refined oils and relatively low in fruits, vegetables, and fiber, and a typical "Western lifestyle"—characterized by its sedentary nature—may play some part in the development of IBD. However, diet alone cannot be considered a "cause," since studies have not found that those within the population at large whose intake of protein and animal fat is higher than normal have an increased incidence of IBD.[53]

2.4.2. Age Variation

IBD is most often diagnosed in the teens and twenties. There is another peak in occurrence around 50 years of age (**Figure 2.7.**)[54] So IBD often strikes when people are at a tender, identity-forming stage during the young adult period. This prevalence is likely due to the hormonal changes associated with increased hormones during sexual maturation and then later with declining sex hormones.

2.5. Medical/Surgical Treatment of Inflammatory Bowel Disease

The quantity and sophistication of medications used to treat the symptoms of IBD grow greater as research progresses. However, there is no medication as of yet that can cure either UC or CD. Although not all the associated mechanisms of inflammation are understood, currently available medications seek to influence the inflammatory cascade, decreasing the damage caused by severe and chronic inflammation.

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[51] Ibid.
[52] Ibid.
[53] K. D. Cashman and F. Shanahan, "Is Nutrition an Aetiological Factor for Inflammatory Bowel Disease?" *European Journal of Gastroenterology and Hepatology* 15 (2003): 607-613.
[54] Stein and Rood, 25.

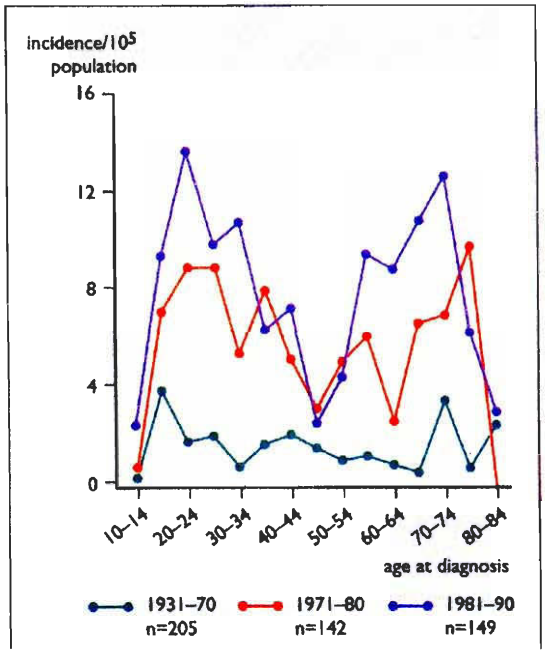

Figure 2.7. Age Specific Rates for Inflammatory Bowel Disease. From Miles C. Allison et al., *Inflammatory Bowel Disease* (Mosby International London, UK 1998), 9.

When medical treatment fails to control flares of IBD, surgery may become necessary. For UC, surgery, although radical, is curative. Once the diseased colon (large intestine) is removed there is no more colitis because there is nowhere left for it to occur. But the surgical removal of the colon is also life changing. In the case of CD, surgery to remove parts of the digestive tract is only corrective of an immediate problem or severe and persistent symptoms that do not respond to medical management because CD tends to recur after surgery. This section includes a discussion of common medications and surgery.

2.5.1. Medications for Inflammatory Bowel Disease

Medical management begins with the attempt to reduce the symptoms that cause a person to seek medical care—the initial flare of disease—and to bring on a remission. After this is accomplished, the goal becomes maintenance either of total remission or of disease activity at a low enough level to permit reasonably good quality of life. Maintenance therapy

is a mainstay of treatment for IBD. In maintenance therapy, medicines are administered over a long period of time to prevent recurrence of the disease. A study conducted in Norway found that administration of 5-aminosalicylic acid (the most common maintenance therapy) in UC reduced relapse rates to about half over a 1-year period and resulted in only a modest therapeutic gain in CD.[55] Subsequent flares also need to be treated medically, if possible, before an individual turns to surgery that is either corrective (for CD) or curative (for UC).

The same group of drugs is used for treatment of flares and maintenance therapy, but the drugs are used in different doses and for different durations. There is also variation from physician to physician—based on professional preference.

Combinations of drugs are often used, and it is sometimes difficult to assign the benefits to a particular one. The situation is such that medical management of individuals who live with IBD becomes more art than science, involving a basic understanding of the therapeutic benefits of each drug in combination with an intuitive sense of what benefits are actually occurring in a particular patient. This information can be derived only from close physical examination and from attentive listening and observation by the specialist.

Four groups of drugs are generally used to treat IBD: 5-aminosalicylate compounds, corticosteroids, immunosuppressives, and antibiotics. There is an additional new category of treatment using monoclonal antibodies, which are genetically engineered copies of immune system proteins. However, these new compounds are not yet commonly used and will not be discussed within the scope of this project. The four main types of treatment are discussed below followed by a short discussion of surgical treatment of IBD.

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[55] B. Moum "Medical Treatment: Does it Influence the Natural Course of Inflammatory Bowel Disease?" *European Journal of Internal Medicine* 11 (2000): 197-203.

2.5.1.1. 5-Aminosalicylates

The active ingredient in a host of compounds used to treat inflammatory bowel disease is 5-aminosalicylic acid (5-ASA). One compound, sulfasalazine, is used very frequently to mediate the inflammatory response. Sulfasalazine produces a number of side effects that run from mild to severe, including headache, nausea, and vomiting.[56]

Sulfasalazine is a combination of two molecules, 5-ASA and the antibiotic sulfapyradine. The active ingredient is 5-ASA, and sulfapyradine causes the side-effects. In the 1990s, non-sulfa-based 5-ASA compounds—Rowasa, Pentasa, Dipentam, and Asacol—came into general use for treating IBD.[57]

Despite its side effects, sulfasalazine is still often the first medication used in treatment of ulcerative colitis or Crohn's disease, mostly because it is so inexpensive in comparison with the newer compounds.[58] This is a standard drug used for both maintenance and treatment of flare-ups. The newer forms are also available as rectal suppositories and enemas that allow the medication to be administered locally.

2.5.1.2. Corticosteroids

Corticosteroids are powerful drugs that reduce inflammation and seem to have an immunosuppressive action as well.[59] Steroids can be administered topically by enema for ulcerative proctitis (colitis confined to the rectum) and for left-sided colitis. They can also be administered orally—and in cases where patients cannot tolerate oral feeding—intravenously or intramuscularly.[60]

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[56] Penny Steiner-Grossman, Peter A. Banks, and Daniel H. Present. *The New People...Not Patients: A Source Book for Living with Inflammatory Bowel Disease* (New York: Crohn's and Colitis Foundation of America, 1997), 39.
[57] Ibid., 39-40.
[58] Ibid.
[59] Grossman et al., 40-41.
[60] Ibid., 41.

Steroids are used to treat moderate-to-severe symptoms during flare-ups. They are not effective as maintenance therapy.[61] They are often combined with 5-ASA drugs because steroids are able to enhance the effectiveness of 5-ASA.[62] Prednisone and prednisolone are the most commonly used corticosteroids for treatment of inflammatory bowel disease. These are synthetic formulations of the hormone cortisol, which is produced by the adrenal gland.[63] Other corticosteroids used to treat ulcerative or Crohn's disease include betamethasone, hydrocortisone, budesonide, and adrenocorticotropic hormone (ACTH).

Corticosteroids can produce a number of side effects.[64] The lesser of these are a general puffiness and "mooning" of the face, acne and other skin disruptions, insomnia, tremors, night sweats, and mood disturbance. Dangerous side effects include an increase in blood pressure and severe emotional disturbances, such as psychosis and depression. Blood glucose can become elevated and potassium reduced. Long term steroid use can lead to cataracts or glaucoma. Some individuals who are on steroid therapy also suffer from osteoporosis, a loss of bone mass.

A rare disorder called aseptic necrosis of the hip, sometimes referred to as avascular necrosis of the femoral head, can also occur.[65] In addition, while steroid treatment helps improve appetite in those who may have experienced severe weight loss and malnutrition during their flare-ups, continued use of the drugs means an ongoing increase in appetite and can lead to enormous weight gain, which has its own dangers.

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[61] Ibid., 40.
[62] Ibid.
[63] Ibid., 41.
[64] Ibid., 41-42.
[65] Ibid., 42.

2.5.1.3. Immunosuppressives

Immunosuppressive drugs are powerful compounds that override the body's natural immune defenses.[66] They are most known for their use in preventing rejection of organ transplants, but since the 1960s, gastroenterologists have also used immunosuppressives to "turn off" the inappropriate inflammatory response in the bowel.[67]

The two most common immunosuppressives are 6-mercaptopurine (trade name, Purinethol) and azathioprine (trade name, Imuran). They work by inhibiting T-helper lymphocyte cells, which as discussed previously (Section 2.1.2), play a large role in the inflammatory process. These drugs are often used early in the treatment of a severe flare-up, either in conjunction with the 5-ASA compounds or after a short course of steroids. They are also used to treat fistulas, and even as maintenance therapy.[68]

It often takes three to six months for the benefits of immunosuppressives to begin appearing. During this time, individuals taking them are required to have regular blood tests to make sure that a steep reduction in white blood cells does not occur, which would create a risk for severe infection.[69] Individuals who cannot tolerate these medications develop fever and rash, nausea and vomiting, hepatitis or pancreatitis.[70] During therapy, patients may also be more susceptible to illness due to a weaker immune system.

2.5.1.4. Antibiotics

Evidence is pointing increasingly to bacteria as an important element in CD. Research is being conducted into finding the bacterial agents that trigger inflammatory response. In addition, for those with CD of the terminal ileum and damage to the ileocecal valve, bacteria

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[66] Ibid.
[67] Ibid.
[68] Ibid., 42-43.
[69] Ibid., 43.
[70] Ibid.

from the colon commonly back up into the ileum. This causes a condition known as bacterial overgrowth, in which bacteria flourish in the small intestine, where they are not normally present.[71] Bacterial overgrowth causes problems with nutrient absorption, as well as bloating, gas, and diarrhea.

For this reason antibiotic treatment is increasingly common in CD. Broad-spectrum antibiotics such as ciprofloxacin (Cipro), clarithromycin (Biaxin), and Ampicillin are often used in a short course of treatment in an effort to reduce the bacterial overgrowth and calm the infection.[72] Scientists have recently attached Cipro to a budesonide-controlled capsule that releases the medication in the ileum.

The most commonly used antibiotic is metronidazole (Flagyl). The drug often induces remission, but does not maintain it. Flagyl also helps heal fistulas. Side effects include metallic taste, loss of appetite, yeast infections, and numbness of the hands and feet.[73]

2.5.1.4. Biological Therapy

A relatively new class of therapeutics for IBD directly targets individual players in the inflammatory cascade. The first agent was Infliximab (Remicade), an antibody to TNF. Infliximab is administered through an intravenous infusion where it travels through the blood to specifically bind and inactivate TNF systemically. Infliximab also signals programmed cell death—a non-inflammatory means of cell death—in T cells.[74] Soluble TNF receptors have also been created. Entanercept (Enbrel) is one example of a soluble TNF receptor which "captures" TNF.

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[71] Ibid., 44.
[72] Ibid., 43-44.
[73] Ibid., 44.
[74] Theodore M. Bayless and Stephen B. Hanauer, *Advanced Therapy of Inflammatory Bowel Disease* (London: B. C. Decker, 2001): 285.

All of these biological therapies require an infusion ranging from twice a week (etanercept, or Enbrel) to one injection every 8 weeks (infliximab, or Remicade.)[75]

These potent drugs are not used immediately when patients present with IBD because of their side effects and questionable safety in long-term use. Opportunistic or latent infections, such as tuberculosis, may emerge following immune suppression, and malignancies may also result.[76]

2.5.2. Surgical Procedures for Inflammatory Bowel Disease

Surgery for ulcerative colitis involves total removal of the colon. This procedure, known as a proctocolectomy (**Figure 2.8**) is a curative procedure, since ulcerative colitis is confined to the large intestine.[77] Once it has been removed, the disease will not reappear.

Unlike surgery for ulcerative colitis, surgery for Crohn's disease is not curative; it is only corrective of an immediate complication. Between two-thirds and three-quarters of individuals who suffer from Crohn's disease will undergo surgery at some point.[78] There is a 20 percent chance that the inflammation will recur near the surgery.[79]

The most common surgery for individuals with CD is partial intestinal resection with reanastomosis (reconnection).[80] This is performed to remove areas of the bowel significantly damaged by disease and can be done anywhere in the small or large intestine. Surgery is performed to remove either a partial or total obstruction.[81] The diseased portion of the bowel is removed and the two ends of healthy bowel are sewn together.

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[75] Ibid.
[76] Ibid.
[77] Steiner-Grossman et al., 57.
[78] J. Zonderman and R. S. Vender, *Understanding Crohn Disease and Ulcerative Colitis* (Jackson, MS: University Press of Mississippi, 2000), 72.
[79] Steiner-Grossman et al., 66.
[80] Steiner-Grossman et al., 57.
[81] Ibid.

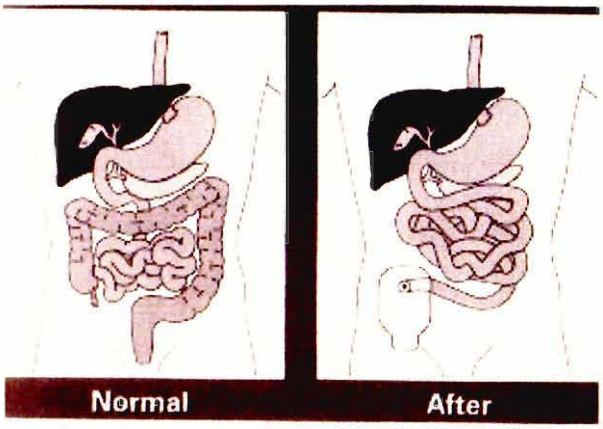

Figure 2.8. Proctocolectomy and Permanent Ileostomy. S. H. Stein and R. P. Rood, *Inflammatory Bowel Disease: A Guide for Patients and Their Families* (2nd Ed.) (Philadelphia: Lippincott Williams and Wilkins, 1999), 157.

2.6. Problems of Medical/Surgical Treatment of Inflammatory Bowel Disease

There are several problems that the current medical methods of treating IBD face. Firstly, patients indicate dissatisfaction with their treatment and are seeking alternative therapies. Secondly, medical treatment does not seem to alter the natural course of IBD. Thirdly, there is great cost associated with current medical treatment strategies.

2.6.1 Use of Non-Prescribed Therapies Indicates Patient Dissatisfaction

Alternative (non-conventional) medicine is becoming increasingly popular among people with IBD. In one international study, 51% of 289 IBD patients used some form of alternative medicine.[82] Notably, 68% of the patients at one of the study's centers (Los Angeles) used a form of alternative medicine.[83] The study found that patients were likely to use alternative medicine if they were not satisfied with conventional therapy, viewed hospitals as dangerous places, thought that alternative medicine practitioners should have a role in hospitals, or felt that their medical situation was hopeless.[84]

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[82] P. Rawsthorne, F. Shanahan, N. C. Cronin, P. A. Anton, R. Lofberg, L. Bohman, and C. N. Bernstein, "An International Survey of the Use and Attitudes Regarding Alternative Medicine by Patients with Inflammatory Bowel Disease," *The American Journal of Gastroenterology* 94 (1999): 1298-1303.
[83] Ibid.
[84] Ibid.

In a study conducted the University of Calgary, Canada, the same percentage of use (51%) of alternative medicine was found in the 2 years prior to the study.[85] Vitamins and herbal products were the most commonly reported therapies. The side effects and lack of effectiveness of standard therapies were the most commonly cited reasons for seeking complementary medicine.[86]

Another study at the University of Calgary aimed to develop models of the influences on the decision-making process IBD patients used in deciding to use alternative medicine.[87] The authors reported that patients "actively sought credible information about complementary therapies that would be responsive to their personal context but none of the participants felt that their physicians could provide such information."[88] A common finding of the studies is that patients are discontent with the current limits of the medical approach to treating IBD. This suggests that new avenues of treatment should be investigated.[89]

2.6.2 Lack of Cure

Current medications cannot cure inflammatory bowel disease. Removing the entire colon does remove symptoms of ulcerative colitis in that it leaves no place for the disease to occur. However it does not seem that organ removal is a "cure," and this surgery is not an option to be taken lightly because of the lifestyle changes associated with it (i.e. wearing an ostomy, or bag, to hold fecal contents).

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[85] R. J. Hilsden, C. M. Scott, and M. J. Verhoef, "Complementary Medicine Use by Patients with Inflammatory Bowel Disease," The *American Journal of Gastroenterology* 93 (1998): 697-701.
[86] Ibid.
[87] C. M. Scott, M. J. Verhoef, R. J. Hilsden, "Inflammatory Bowel Disease Patients' Decisions to Use Complementary Therapies: Links to Existing Models of Care," *Complementary Therapies in Medicine*, 11 (2003): 22-27.
[88] Ibid., 25.
[89] Of note to this project, no studies have yet been conducted concerning patients decisions to increase n-3 PUFAs.

2.6.3 Cost of Medical Therapies

Current medical therapy is expensive. As with any chronic disease, IBD requires extensive long-term medical care. The CCFA cites a 1990 study which found the medical costs of IBD in the U.S. totaled $1.4-$1.8 billion annually.[90] Surgery and inpatient care were estimated to account for roughly one-half of this amount.[91] The disability costs of illness (lost labor productivity) were estimated to be $0.4-$0.8 billion, making the total estimated annual cost of IBD $1.8-$2.6 billion.[92] This figure is likely to be much higher in 2005 due to increased prevalence and monetary inflation.

2.7. Polyunsaturated Fatty Acids

Fat is a basic component of the diet. Americans get 35-45% of their calories from fat.[93] This chapter of the project provides the background information on fatty acids needed to understand their potential role in immune system modification.

2.7.1. Types of Fatty Acids

Fatty acids are basically chains of carbon bound to hydrogen with a carboxylic acid group at one end. Fatty acids are grouped into three familiar categories: saturated, monounsaturated, and polyunsaturated. These designations refer to the types of bonds that hold their carbon atoms together. Fatty acids, in addition to having common names, are often represented by a naming system that lists the number of barons followed by a colon and the number of total double bonds between these carbons. For example, oleic acid, which is 18 carbons long and has one double bond, would be expressed as 18:1.

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[90] Crohn's and Colitis Foundation of America. "Facts About Inflammatory Bowel Diseases" http://www.ccfa.org/about/press/ibdfacts. (Accessed February 10, 2005.) Unable to find the study referenced by the website.
[91] Ibid.
[92] Ibid.
[93] M. I. Gurr, J. L. Harwood, and K. N. Frayn, *Lipid Biochemistry* 5th Ed. (Oxford: Blackwell, 2002), 134.

Saturated fatty acids have single bonds between all the carbon atoms. In this configuration, a fatty acid has all the hydrogen atoms it can accommodate, so it is said to be "saturated with hydrogen"—hence the term saturated fatty acid. A "saturated fat" is one that contains a significant amount of saturated fatty acids. Most saturated fats are solid or semisolid at room temperature.

Monounsaturated fatty acids have one double bond in the fatty acid chain. Olive oil and canola oil contain high amounts of monounsaturated fatty acids, so they are classified as "monounsaturated oils." Monounsaturated oils are liquid at room temperature but become cloudy or semisolid when refrigerated. The double bond in a monounsaturated fatty acid causes it to have a "kinked" shaped.

Polyunsaturated fatty acids (PUFAs) are fatty acids that have two or more double bonds. Oils that contain a high percentage of PUFAs include corn, safflower, sunflower, peanut, cottonseed, soybean, fish, walnut, and flaxseed oil. All polyunsaturated oils are liquid at room temperature and remain liquid in the refrigerator. The more double bonds on the carbon chain, the more "unsaturated" the oil, and the colder temperatures it can withstand without hardening. The most highly unsaturated oils are flaxseed and fish oils.

PUFAs are also known as essential fatty acids because they must be consumed in the diet. Humans do not have the enzymes needed to convert other fatty acids into PUFAs but do need PUFAs to live.

2.7.2. Types of Polyunsaturated Fatty Acids

PUFAs can be further subdivided into omega-3 (n-3) and omega-6 (n-6). N-3 fatty acids have their first double bond between the third and fourth carbon atoms and are

therefore called n-3's; the n-6 fatty acids have their first double bond between the sixth and seventh carbon atoms and, hence they are called n-6's.

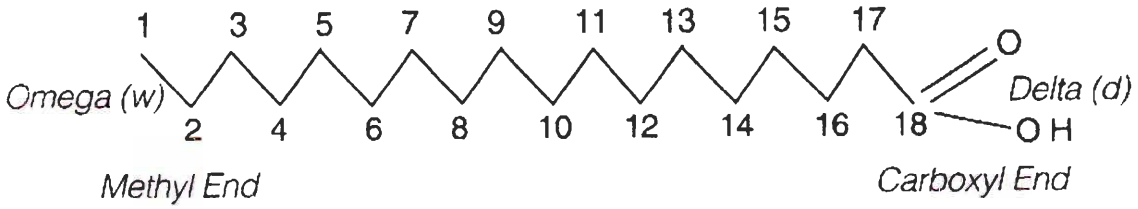

Figure 2.9. Omega Numbering System for Fatty Acids. From Udo Erasmus, *Fats that Heal Fats that Kill* (Bunaby, BC, Canada: Alive Publishing, 1993), 17.

The shortest fatty acid in the n-6 family is the 18-carbon linoleic acid (LA, 18:2). The corresponding 18-carbon fatty acid in the n-3 family is alpha-linolenic acid (ALA, 18:3). The two fatty acids are shown in **Figure 2.10**.

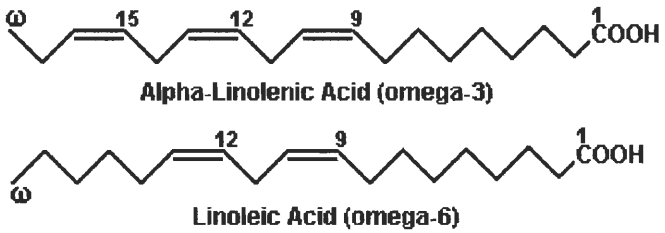

Figure 2.10. Chemical Structures of Alpha-Linolenic Acid and Linoleic Acid. From ScientificPsychic.com, *Fats, Oils, Fatty Acids, Triglycerides - Chemical Structure* (Accessed 28 March 2005).

When LA and ALA interact with certain enzymes, they go through two transformations: they become desaturated by losing hydrogen and increasing the number of double bonds, and they become longer by adding carbon atoms.[94] When they change in this

[94] The enzymes are known as desaturases and elongases. LA and ALA compete for the same enzymes.

manner, they are given new names. LA becomes gamma-linolenic (GLA), and then arachidonic acid (AA). ALA becomes eicosapentaenoic acid (EPA) and then docosahexaenoic acid (DHA). (For a more detailed schematic of the fatty acid synthesis pathways, see *APPENDIX A.*)

Each molecule of dietary fat contains 3 fatty acids attached to a glycerol backbone, like the branches of the letter 'E.' This molecule is called a triacylglycerol (**Figure 2.11**). Fatty acids are bonded to the glycerol backbone through ester bonds.

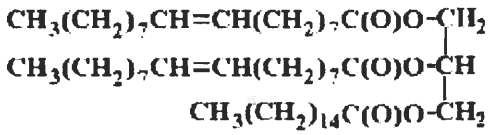

Figure 2.11. Representative Triacylglycerol Structure. From ScientificPsychic.com, *Fats, Oils, Fatty Acids, Triglycerides - Chemical Structure* (Accessed 28 March 2005).

In their "free" form, these fatty acids are long chains consisting of carbon and hydrogen and end with an acidic group (-COOH). Fatty acids can also be present as methyl and ethyl esters.[95] Rather than being bonded to a molecule of glycerol, they are bonded to a methyl (one carbon) or ethyl (two carbons) group.

2.7.3. Eicosanoids: A Link between Polyunsaturated Fatty Acids, Inflammation, and Immunity

A key bodily role of PUFAs is that they are converted into hormone-like substances called eicosanoids. Eiocosanoids have a very short life, act locally, and influence many biological processes including hemostasis and inflammation.[96] The parent fatty acids for the eicosanoids are AA (20:4) from the n-6 PUFAs and EPA (20:5) from the n-3 PUFAs. The

[95] An ester bond is a chemical bond formed between carbon and an oxygen of the fatty acid.
[96] A. Gil, "Polyunsaturated Fatty Acids and Inflammatory Diseases," *Biomedicine and Pharmacotherapy* 56 (2002): 388-396.

functions of eicosanoids from these two families tend to be opposite. In other words, those from the n-6 type oppose the functions of those of the n-3 type.

Eicosanoids are involved in every aspect of day-to-day health. Among other functions, they influence blood pressure, boost or repress the immune system, alter pain perception, and make the body more or less prone to allergies and inflammation. It is possible to alter the body's production of eicosanoids by changing the oils in the diet because the eicosanoids produced from n-3 fatty acids can have different and sometimes opposite effects from eicosanoids produced from n-6 fatty acids. If the diet is high in n-6 oils, for example, the body produces more proinflammatory eicosanoids, increasing the risk of asthma, allergies, arthritis, psoriasis, colitis, and other inflammatory diseases.

PUFAs are cut or "cleaved" from the phospholipids of cell membranes by the action of the enzymes phospholipases, most commonly phospholipase A2. This process of lipases releasing PUFAs from phospholipids is called enzymatic cleavage, and it occurs in response to specific cytokines, growth factors, or other stimuli. Enzymatic cleavage breaks the ester bond that holds the fatty acid in the membrane. In this way the amount of free fatty acids (FFAs) in a cell is regulated by the activity of phospholipase A2.

When FFAs are available, the activity of the enzyme cyclooxygenase creates prostacyclins of the 2 and 3 series, and prostaglandins and thromboxanes of the 3 and 4 series from AA and EPA, respectively.

Prostaglandin (PG) E2 (series 2—from AA) has a number of proinflammatory effects including inducing fever and erythema (redness of the skin), increasing vascular permeability and vasodilation (which allows migration of immune cells), and enhancing pain and edema

(swelling) caused by other agents.[97] (See *APPENDIX A* for a graphical representation of the above section.)

2.7.4. Dietary Sources of Polyunsaturated Fatty Acids

PUFAs originate in the food chain starting with plants. Only plants contain the enzyme needed to add the additional double bonds that create PUFAs. When animals eat these PUFA-containing plants, they concentrate the fatty acids in their tissues. Generally speaking, green plants and flax seed are high in n-3 PUFAs. Animals that consume diets based around green plants, such as algae-eating fish are also high in n-3's. Canola and walnut oil are also considered good sources of n-3 PUFAs. Other vegetable oils—such as corn, safflower, and soybean—are highly n-6 dominant. It follows that animals that are primarily grass fed have a much higher n-3 concentration than those that are fed corn or other grain-based diets.

The richest sources of EPA and DHA (the immunomodulatory n-3 PUFAs) are oily fish. Salmon, mackerel, herring, and anchovies are high in n-3 PUFAs. (*APPENDIX D* is a table of dietary sources of n-3 PUFAs per 100 g of food and includes an extensive listing of different seafoods and oils. *APPENDIX E* is the amount of EPA + DHA in a more select listing of seafood sources.)

2.8. Factors in Clinical Study Design

Although experimentation can be performed in cells, animals, and tissue samples, research involving human subjects is needed to translate scientific evidence into medical practice. This project's conclusions are based on a literature review of clinical research. Examination of clinical research provides a better understanding of medical practices.

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[97] Gurr et al., 82.

Clinical experiments provide the strongest research-based arguments for or against a particular medical treatment. Patients are put into one group receiving treatment and another group which serves as a control and does not receive the treatment being examined (they might be "treated" with a placebo instead or receive no treatment at all). The design of such studies attempts to control for factors such as age, gender, medication, and severity of disease. Such experiments are the best current source of evidence for practical application in the human population.

The strongest clinical experiments are those that are double blind studies. In a double blind study, patients receive either the active treatment or are "treated" with an identical placebo which contains no active ingredients. The identity of the treatment—whether active or placebo—is concealed from both the patient and the person administering the treatment; it is the gold standard of clinical research because it introduces the least bias to the results.

However, there are many challenges in comparing the different clinical studies of IBD due to the many factors that differ between them. These factors include the method of delivery of n-3 PUFAs, the dose delivered, the types of patients included, and the outcomes measured. Often the numbers of patients included in the studies are small, so the results are not significant by statistical measures. One commonality among the studies is the use of gelatin-coated fish oil capsules. These capsules are a convenient and easily measured means of incorporating n-3 PUFAs into the diets of study participants.

Another common type of clinical study design is a crossover study. A crossover study compares the results of both the treatment and the placebo on the same group of patients. In these studies patients participate as both the treatment group and placebo control for the experiment. For example, in an experiment testing n-3 PUFAs versus a placebo, half

of the participants would receive n-3 capsules and half would receive the placebo for a given period of time. A "washout" period would follow during which there would be no treatment. Following the washout period the groups would switch and receive the other treatment (n-3 PUFAs or placebo). These studies are useful because they lessen the effect of subject variability on results.

CHAPTER 3

PROCEDURE

This chapter explains how this project was conducted. The major topics of this chapter are the methods of project execution and the resources utilized. The "Project Method" section discusses the tasks used to acquire background information on the topic of IBD and dietary intervention designed to treat it. The second section, "Resources Utilized," discusses the many sources of information that were used and how they affected the outcome of this project.

3.1. Project Method

Major tasks involved with this project included designing the project, researching background material, conducting a literature review, and presenting the results of this review in the form of recommendations for gastroenterologists and their patients.

3.1.1. Project Design

The project design was based on conversations held with IBD patients and a consultation with a nutritional researcher. These discussions provided an understanding of what information might be of use to people with IBD.

The IBD patients who spoke with the author were relatively uninformed concerning the possible role of diet in IBD. They stated that their gastroenterologists had not advised them to modify the fatty acid composition of their diets. These patients were from varied

backgrounds, some being college and family acquaintances of the author, and others drawn from a local IBD support group sponsored by the CCFA.

The nutritional researcher, Dr. Penny Kris-Etherton of the Pennsylvania State University, who has worked with the American Heart Association to develop guidelines for the role of PUFAs in preventing cardiovascular disease, was consulted concerning the validity of the idea that similar guidelines might be made for preventing and treating IBD following the outcomes of this study.

To ensure that the project's goals were novel, the CCFA was contacted in order to obtain its books and materials. These books and materials are widely distributed to people with IBD with the intent of improving patient knowledge and optimizing treatment. The CCFA books were purchased through their website (www.ccfa.org). These books included *The New People...Not Patients: A Source Book for Living with Inflammatory Bowel Disease*[98], *Managing Your Child's Crohn's Disease or Ulcerative Colitis*[99], and *Crohn's Disease and Ulcerative Colitis: An Essential Guide for the Newly Diagnosed*[100].

The CCFA also distributes fourteen brochures with the following titles: *About Crohn's Disease; About Ulcerative Colitis; Medications; Maintenance Therapy; Diet and Nutrition; Emotional Factors; Complications; Understanding Colorectal Cancer; Surgery; Sexuality; Women's Issues; A Parent's Guide; A Teacher's Guide;* and *A Guide for Children and Teenagers.*

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[98] Penny B. Steiner-Grossman, P Banks, and D. Present, *The New People...Not Patients: A Source Book for Living With Inflammatory Bowel Disease* (New York: Crohn's & Colitis Foundation of America, Inc., Kendall Hunt Publishing Company, 1997).

[99] K. Benkov, H. Winter *Managing Your Child's Crohn's Disease or Ulcerative Colitis* (Published by Crohn's and Colitis Foundation of America. New York: Mastermedia, 1996).

[100] J. Sklar, *Crohn's Disease and Ulcerative Colitis: An Essential Guide for the Newly Diagnosed* (New York: Marlowe & Company, 2002).

The brochure entitled *Diet and Nutrition* asserts, "You may be surprised to learn that there is no evidence that dietary factors cause or contribute to these inflammatory bowel diseases." The purpose of this brochure is to "provide dietary guidelines for patients and their families." The brochure focuses mainly on low-residue diets (minimal fiber to allow the bowel to rest) and the avoidance of spicy foods and dairy products (which aggravate the symptoms of some people). (This brochure is included as *APPENDIX B.*)

On the last page of this brochure, there is a sentence that states: "Fish or flaxseed oils, in the diet or as supplements, have helped fight the inflammation in IBD." If this is true, then it is confusing why no other portion of the pamphlet hinted that patients might use food in this way. On page 5, there is a section that poses the question "Do any specific foods worsen the inflammation of IBD?" and the answer is "No…." Based on these passages, it seems that the CCFA's message about the role of diet in preventing and treating the inflammation of IBD was confusing and contradictory. One of the goals of the project then became the development of clear recommendations concerning the use of n-3 PUFAs that would be submitted to the CCFA in hopes that these recommendations would reach patients' hands.

The three books distributed through the CCFA contain short sections—often one paragraph—that hint that further research might show evidence for fish oil in treating IBD. The focus remains on low-residue diets and eating from all the food groups to avoid vitamin and mineral deficiencies. Causing alarm from a nutritional perspective is that the "Standard American Diet" with its high amount of animal fat and protein, refined vegetable oils, and processed grains is also the typical model of the low-residue diet used to treat IBD. It is this same diet that is associated with increased incidence of IBD. The continued assertion that

Americans with IBD did not need to redefine the role of diet in promoting and resolving the inflammation of IBD offered further encouragement for pursuing this project.

These aforementioned findings allowed for the design of a project that was novel in nature and had the potential to change well-established ideas.

3.1.2. Background Research

Background material was collected through readings of medical and educational texts. The main areas that needed to be researched to allow understanding of the project were the digestive and immune systems, inflammatory bowel disease, and fatty acids. Without understanding all these different areas the journal articles being analyzed would have made little sense, and the resulting analysis would have been compromised.

3.1.3. Literature Review

The project was conducted primarily as an applied literature review. Resources were gathered that would allow an informed analysis to be made pertaining to the potential of dietary interventions in treating IBD.

After months of gathering articles, new information emerged through an email from Dr. Kris-Etherton, which directed the author to a group of newly published "evidence reports" by the Agency for Healthcare Research and Quality. The "evidence report" that included an analysis of clinical studies of IBD and n-3 PUFAs (full title: *Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis*) was downloaded from the Internet and incorporated into the project—drastically changing the design of the project.[101] This "evidence report" had in

[101] C. H. MacLean et al., *Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease,*

fact accomplished one goal of this project, which was to assemble the body of clinical research pertaining to IBD and n-3 PUFAs and then make an evidenced based conclusion on their potential.

Instead, the project shifted to analysis of medical opinions, the "evidence report," and the individual studies' strengths and flaws. Analysis of the Agency for Healthcare Research and Quality "evidence report" became a valuable starting point for the rest of project's conclusions.

3.1.4. Presentation of Results

The analysis of the research evidence is presented in the results section (Section 4.2). Additionally, an in-progress study was discovered during the course of the project, and it is also discussed. This critical analysis of the research is presented in Chapter 4.

This scientific analysis was used in the task of creating both a brochure for gastroenterologists and a brochure for patients detailing recommendations based on the current state of research (*APPENDIX C*). Moreover, the analysis was used to decide if further research is warranted. These results are of potential interest to the Crohn's and Colitis Foundation of America, the International Society for the Study of Fatty Acids and Lipids, and the National Institute of Diabetes & Digestive & Kidney Diseases, and the National Center for Complementary and Alternative Medicine. These groups are discussed below, and their contact information is included (among others) in *APPENDIX F*.

Systemic Lupus Erythematosus, and Osteoporosis, Evidence Report/Technology Assessment. No. 89 (Prepared by Southern California/RAND Evidence-based Practice Center, under Contract No. 290-02-0003), AHRQ Publication No. 04-E012-2, Rockville, MD: Agency for Healthcare Research and Quality. March 2004. webpage: http://www.ahrq.gov/clinic/evrptfiles.htm.

3.1.4.1. Crohn's and Colitis Foundation of America

The nonprofit organization, the Crohn's and Colitis Foundation of America (CCFA)—a national organization dedicated completely to IBD—is a target group for the results of this project. The CCFA has a major role in influencing the path of IBD research and increasing patient knowledge. The CCFA recently published its *Research Priorities*, and the role of diet was not among them.[102] If the CCFA were to identify the role of diet as a research priority, it might devote funds and educational materials to developing knowledge in this area. As discussed previously, the current CCFA position as stated in its brochures and books is that nutrition plays no role in the pathogenesis of IBD, and its position on the role of nutrition in the treatment of IBD is conflicting.

3.1.4.2 National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health, conducts and supports clinical research on the diseases of internal medicine and related subspecialty fields as well as many basic science disciplines.

The Institute's Division of Intramural Research encompasses centers studying a broad spectrum of metabolic diseases such as diabetes, inborn errors of metabolism, endocrine disorders, mineral metabolism, digestive diseases, nutrition, urology and renal disease, and hematology. Basic research studies include: biochemistry; nutrition; pathology; histochemistry; chemistry; physical, chemical, and molecular biology; pharmacology; and toxicology.

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[102] Crohn's and Colitis Foundation of America, "Challenges in IBD Research: Updating the Scientific Agendas 2002," http://www.ccfa.org/media/pdf/laychallenges.pdf.

In an NIDDK report, it was stated that "A long range plan in IBD research has guided NIDDK on a path that has led to an approximate six-fold growth of the IBD research grant portfolio from 1989 to the present."[103] IBD is an area focus of three of the Institute's Digestive Disease Research Centers.

3.1.4.3 International Society for the Study of Fatty Acids and Lipids

The International Society for the Study of Fatty Acids and Lipids (ISSFAL) is an international society of scientists, health professionals, administrators, educators and communicators from more than 40 countries with an interest in the health effects of dietary fats. The purpose of this Society is to increase the public's understanding of the role of dietary fatty acids and lipids in health and disease through research and education. The most recent ISSFAL annual conference was held in Brighton, England, June 27 to July 1, 2004. The author attended this conference as a student delegate in order to communicate and further develop the ideas presented in this project. The next conference is in the summer of 2006 in Cairns, Australia, and it is planned that the project's results will be further developed—and presented—at that time.

3.1.4.4. National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) is dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training complementary and alternative medicine researchers, and disseminating authoritative information to the public and professionals. It was established in

[103] National Institutes of Diabetes and Digestive and Kidney Diseases. "NIDDK Recent Advances and Emerging Opportunities" 2001, 69. http://permanent.access.gpo.gov/websites/www.niddk.nih.gov/federal/advances/digestive.pdf

1998 and has a budget of $123,116,000 appropriated by congress for use in fiscal year 2005.[104]

3.2. Resources Utilized

The nature of this project allowed much of it to be conducted using a combination of online resources and libraries. The main online resources were PubMed (www.pubmed.com) and ScienceDirect (www.sciencedirect.com). Additionally, the Worcester Polytechnic Institute (WPI) Gordon Library, the Pennsylvania State University (PSU) Paterno Library, and the University of Massachusetts Medical School (UMMS) Lamar Soutter Library were utilized for providing access to books and journals used in this project.

Online resources provided searchable public databases of research papers. The two used in the literature review central to this project were PubMed and ScienceDirect. These searchable databases provided the material necessary for the compilation of applicable journal articles. Some articles were available for direct download from the internet via the WPI, PSU, and UMMS subscription services to various journals. When the articles were not available for direct download—which was often true of both older and just-published articles—they were obtained from library journal shelves and archives. Two libraries served this purpose: the UMMS Lamar Soutter and the PSU Paterno libraries. In rare circumstances, articles were purchased online.

The WPI Gordon Library provided the textbooks needed to write the non-IBD-related portion of the background. The library contains many scientific and engineering texts and served as a good source of material explaining immune and digestive function. *Lipid*

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[104] National Center for Complementary and Alternative Medicine, "NCCAM Facts-at-a-Glance." http://nccam.nih.gov/about/ataglance/index.htm (12 December 2004).

Biochemistry,[105] supplemented with biology and biochemistry textbook readings, provided the foundation needed to explain background information on polyunsaturated fatty acids.

The PSU Paterno library served as a source of many of the journal articles pertaining to fatty acids. PSU is renowned for its nutrition department and is well-resourced in this area.[106]

The UMMS Lamar Soutter Library provided the medical texts needed to explain inflammatory bowel disease. This library contains many books related to digestive diseases. A wide variety of books were read prior to writing the background. The greatest amount of focus was in reading *Inflammatory Bowel Disease.*[107]

[105] M. I. Gurr, J. L. Harwood, and K. N. Frayn, *Lipid Biochemistry* 5th Ed. (Oxford: Blackwell, 2002).
[106] The Paterno library was used while the author was at PSU to participate in a summer research project (summer of 2003).
[107] Stephen B. Hanuer, "Medical Therapy for Ulcerative Colitis" Chapter in *Inflammatory Bowel Disease* 5th Edition. Edited by Joseph B. Kirsner. (Saunders, Philadelphia: 2000), 512-542.

CHAPTER 4

ANALYSIS OF OMEGA-3 FATTY ACIDS STUDIES

Epidemiological observations were one of the first lines of evidence of the importance of dietary intake of n-3 PUFAs. Greenland Eskimos—who eat a large amount of fish and fish-eating animals—have a very low incidence of inflammatory bowel disease.[108]

However, this epidemiological evidence has yet to translate to medical application. This chapter begins with the medical opinion of n-3 PUFAs, then examines a federal agency-funded "evidence report," and continues in an analysis of the studies to date. Following this discussion of the "state of the art" research on n-3 PUFAs and IBD, an in-progress study is presented.

At the conclusion of this chapter the analyses are used to formulate an opinion on the state of the research and future directions. Additionally, recommendations are made in Chapter 5 pertaining to practical (for gastroenterologists and patients) and research applications of the contents of this chapter.

4.1. Medical Opinion

Gastroenterologists would be the primary influence in the use of n-3 PUFAs by people with IBD, and this section begins by developing an understanding of the current medical view of the role of fatty acids in IBD. The sources for identifying a general medical opinion were a collection of books read by physicians and physicians in training.

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[108] H. O. Bang, J. Dyerberg, and N. Hjorne, "The Composition of Food Consumed by Greenland Eskimos," *Acta Medica Scandinavica* 200 (1976): 69-73.

Surprisingly, the entirety of the texts contained in sections on omega-3 fatty acids within several voluminous tomes on inflammatory bowel disease could be reprinted on one side of one sheet of paper. A good example is this statement:

> Despite the ability to alter phospholipid profiles and trends in favor of benefit, the degree of inhibition of proinflammatory mediators has been modest, and clinical benefits have failed to overcome patient intolerance to fishy odors. The development of an enteric-coated fish oil preparation, recently effective in preventing Crohn's disease relapse, may offer an alternative option for therapy in UC.[109]

Medical experts seem to acknowledge that a potential exists for the use of fatty acids in treating IBD, but this potential has not been translated into clinical evidence warranting the recommendation of fish oil supplementation. There are also compliance issues caused by the preparations (fish oil capsules) used in clinical studies. The general opinion seems to be that fish oil is an unproven therapy, and even if does offer modest gains, patients are not likely to comply due to the side effects of treatment. This opinion is in line with the statements of the CCFA and general patient perceptions—as discussed earlier in this project.

4.2. Agency for Healthcare and Research Quality Evidence Report

Prior to undertaking—and during a large portion of the beginning of this project—the author was unaware that there exists an "expert review" on omega-3 fatty acid research. This review is a statistical analysis of the evidence presented in human studies of n-3 fatty acids and IBD (as well as many other conditions). It was conducted by the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. This report entitled, "Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid

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[109] Stephen B. Hanuer, "Medical Therapy for Ulcerative Colitis," Chapter in *Inflammatory Bowel Disease* 5th Ed., Joseph B. Kirsner, ed. (Saunders, Philadelphia: 2000), 541.

Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis," is publicly available on the internet.[110]

Dr. Kris-Etherton of the Pennsylvania State University directed the author to this source through a personal email. Unfortunately, a very specific internet search would be required to find it, and its more than 200 pages of contents would not likely be useful to an untrained reader; it was not prepared in the language of a lay audience. In fact, *Appendix A* is a figure from the report. It is informative, but it requires knowledge of the field of eicosanoid research.

The results presented in this "evidence report" are statistically-based. The weaknesses of each study design were put forward. Then statistical comparisons were made between the studies where possible. In the case of studies on n-3 PUFAs and IBD, comparisons among studies are very difficult because of varying doses of fish oil, compounding factors (e.g., medication, random occurrence of flares), and different end-point measurements used by the studies (induction of remission, histological scores, and reduction of medication).

The AHRQ evidence report has the strength that it was professionally performed and very complete in its inclusion of studies. Thirteen clinical studies of IBD and n-3 PUFAs were included for analysis by a field of medical and scientific experts who can be assumed to have no self-serving interests. The findings of this report do little to point to future directions. This project's analysis begins on the grounds of AHRQ's position on the state of

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[110] H. M. MacLean et al. *Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis*. Evidence Report/Technology Assessment. No. 89 (Prepared by Southern California/RAND Evidence-based Practice Center, under Contract No. 290-02-0003). Agency for Healthcare Quality Research, Publication No. 04-E012-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2004. Downloaded from http://www.ahrq.gov/clinic/evrptfiles.htm.

n-3 research in IBD and then is further developed with the author's own findings and suggestions.

The final conclusion of AHRQ's "evidence report" is that research has not shown that n-3 PUFAs are an effective treatment for IBD.[111] This conclusion was drawn because some of the studies show positive effects, but other studies show no effect—or even a statistically insignificant negative effect.[112] AHRQ concludes that there is not enough correlation and control of variables among the studies to make an evidenced claim for the use of fish oil in treating IBD.[113]

This lack of statistically sound evidence is likely to be the reason that, although the current understanding is that the n-3 PUFAs have an immunoregulatory role, medical textbooks and patient literature on IBD and nutrition devote few words to the subject. However, there is further investigation that can be performed to explain the apparent contradictions in these studies' findings.

4.3. Effect of Form of Intake of Omega-3 Fatty Acids in Clinical Experiments

Many professionals, including those involved in AHRQ's report, believe that the form of administration (intake) of the fatty acids is very important to the success of n-3 treatment.[114] A standard fish oil capsule is made of gelatin and encloses about 1 gram of fatty acids. These fatty acids are in the triacylglycerol form (Section 2.7) and include 180 mg of EPA and 120 mg of DHA. The remaining 700 mg of fatty acids are a mixture of non-therapeutic fats naturally present in fish oil.

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[111] Ibid., 56, 61.
[112] Ibid., 61.
[113] Ibid.
[114] Ibid., 57.

As a bottle of these capsules is opened, a very fishy smell can be detected, but the taste of fish is almost undetectable in the mouth. The experience is not at all comparable to taking the oil directly by mouth—which used to be very popular when cod liver oil was swallowed by the spoonful to prevent rickets. Still, some people may be prone to "fishy burps" or other gastrointestinal effects—especially if larger quantities are taken. A further concern relevant to research is that it is difficult to conceal the identity of treatment from subjects receiving fish oil in a trial. The subjects know their treatment as soon as they open the bottle due to the smell of fish (unless the placebo were also made to smell like fish).

Enteric coating is a solution to the problems of side effects and taste. The capsules can be coated with a material that not only conceals the smell but also delays the release of the fish oil until it has moved past the stomach into the duodenum.[115] This prevents fishy burps and may also have the advantage of delivering the oil more directly. Fat absorption also takes place in the duodenum, so there is no reason that the oil must be available in the stomach; it can be released from the capsule and absorbed in the duodenum.

Enteric-coated capsules seem to be generally well tolerated (personal observation). Several samples smelled like brown sugar and tasted sweet and faintly of lemons (personal observation). The enteric coating completely conceals the identity of the contents which is essential in a double blind study (Section 2.8.) Enteric-coated fish oil capsules are identical in size and content to the standard gelatin variety and thus at least equally effective in administering a dose of fish oil. They have also become widely available as manufacturers have become aware of consumer preference.

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[115] Enteric coating is a process of coating capsules with pH-sensitive polymers of cellulose esters such as cellulose acetate phthalate and cellulose acetate trimellitate. In gastric fluid, the polymers are protonated and therefore insoluble. In the high pH of the small intestine, the polymers are ionized and become soluble. Source: Hong Xia Guo, "Compression Behaviour and Enteric Coated Film Properties of Cellulose Esters." Academic Dissertation. University of Helsinki, Finland. (2002), 12.

It is unfortunate that none of the thirteen studies of ulcerative colitis and fish oil included in AHRQ's review made use of enteric-coated capsules. The success of a trial using enteric-coated capsules in Crohn's disease deserves further attention and is examined in the next section.[116]

4.4. The Belluzzi Study of Omega-3 Fatty Acids and Inflammatory Bowel Disease

The clinical study performed by Belluzzi et al., published in 1996, is a clear example of the importance of design in a successful clinical trial.[117] This study is notable on many accounts—especially in its design—and this section attempts to discuss what the study has contributed to evidence that n-3 PUFAs can be therapeutic in IBD. It is often cited because of its unique design and because it is one of few studies that resulted in statistically significant results showing effectiveness of n-3 PUFAs in treating IBD.

4.4.1. Design Features

The design of the Belluzzi study seems instrumental in its successful outcome. There are several notable features of this Italian study:

- *Only CD patients were used.* This point makes the outcomes easier to evaluate because only the Crohn's subtype of IBD was investigated.
- *The n-3 PUFAs were administered in the free fatty acid (FFA; not as a triacyclglycerol) form.* The FFA form does not require the action of phospholipases to make the n-3's available for use by the body.
- *The capsules were enteric coated.* This decreased side effects.
- *A carefully-designed placebo was used* (rather than olive oil which may be anti-inflammatory). Olive oil is rich in phenolic (antioxidant) compounds and could possibly reduce free radicals and thereby decrease inflammation.

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[116] The enteric-coated capsules used—and the study itself—were referred to in the quote in Section 4.1.
[117] Andrea Belluzzi, C. Brignola, M. Campieri, A. Pera, S. Boschi, and M. Miglioni, "Effect of an Enteric-Coated Fish Oil Preparation on Relapses in Crohn's Disease," *New England Journal of Medicine* 334 (1996): 1557-1616.

- *The study period was 12 months.* This relatively long period allowed incorporation of the n-3 PUFAs into membranes and shifted the balance of immunomodulatory chemicals (eicosanoids and cytokines) to a less inflammatory profile.
- *The dosage of n-3 PUFAs (2.7 g total: 1.8 g EPA and 0.9 g DHA) was divided among three daily doses (0.6 g EPA and 0.3 g DHA)*, which might have helped absorption.
- *The dropout rate was very low (5 of 78).* With 73 people remaining in the study, it was easier to perform statistical analysis.

4.4.2. Results

Belluzzi found that this treatment significantly prevented flares of CD. Among the 39 patients in the n-3 PUFA group, 11 (28%) had relapses during the study period of 12 months, while 27 of 39 patients (69%) in the placebo group had relapses (the probability that this result is due to chance alone is less than 0.1 %).[118] After completion of the one-year study, 23 patients (59%) in the n-3 FA group remained in remission, as compared with 10 (26%) in the placebo group (the probability that this result is due to chance alone equals 0.3 %).[119] The authors state that logistic-regression analysis indicated that only n-3 FAs and not sex, age, previous surgery, duration of disease, or smoking status affected the likelihood of relapse (**Figure 4.1**.)

The levels of the main fatty acids in the patients were also measured at the beginning and end of the study. The changes in the levels of fatty acids in the patients who remained in remission at the end of the study indicated that n-3 PUFAs replaced n-6 PUFAs (arachidonic acid) in the phospolipid membranes of cells. This endpoint measurement illustrates the effectiveness of the design (dose, preparation, and duration) of the Belluzzi study.

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[118] Ibid., 1558.
[119] Ibid., 1559.

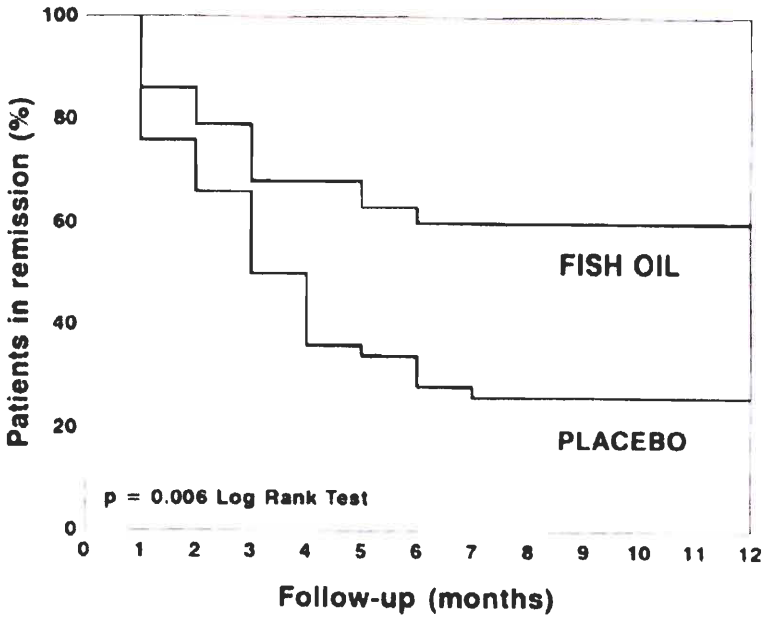

Figure 4.1. Percentage of Patients Remaining in Clinical Remission During the Treatment Period. Andrea Belluzzi, C. Brignola, M. Campieri, A. Pera, S. Boschi, and M. Miglioni, "Effect of an Enteric-Coated Fish Oil Preparation on Relapses in Crohn's Disease," *New England Journal of Medicine* 334 (1996): 1559.

4.5. Issues in Clinical Study Design and Their Effects on Results

The Belluzzi study discussed above underlines the importance of study design. The reasons for discrepancies among the other studies could reside in the different study designs. Also important is the selection of formulation (capsules) and dosage—which if not chosen properly—could lead to a very high incidence of side effects. The following sections discuss possible laws in study designs that can lead to results that do not show the true potential of n-3 PUFAs in treating IBD.

4.5.1. A Short Washout Period in a Crossover Design

In studies using the crossover design (Section 2.8), a short washout period may yield misleading results. An early prospective, controlled, and double blind study treated 39

patients with IBD, of which 29 had CD in different stages of clinical activity, in a 7 months controlled crossover trial.[120] Patients were randomized to receive either 3.2 grams daily of n-3 PUFAs or olive oil as a placebo. There was a one-month washout period between the two treatments. At the end of the study, the Clinical Disease Activity Index (CDAI, a measure of 8 indications of disease severity) of the CD patients was unchanged by n-3 PUFAs supplementation.

The short washout period may not have allowed for a complete displacement of the extra n-3 PUFAs from the cell membranes. It has been demonstrated that the biological effect of n-3 PUFAs, i.e. inhibition of cytokine production, lasts for more than 10 weeks after suspension of n-3 PUFAs.[121] Additionally, the study made of use of an olive oil placebo (discussed below).

4.5.2. Poor Choice of Placebo

Olive oil, due to its high content of polyphenols (antioxidant compounds in plants), may exert important beneficial effects. The effects include soaking up free radicals (which have a role in promoting inflammation)[122] and inhibition of eicosanoid formation[123] (see Section 2.7.3). These properties may interfere with the validity of the final endpoint comparison in studies.

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[120] R. Lorenz, P. C. Weber, P. Szimnau, W. Heldwein, T. Strasser, K. Loeschke, "Supplementation with N-3 Fatty Acids from Fish Oil in Chronic Inflammatory Bowel Disease—a Randomized, Placebo-Controlled, Double-Blind Crossover Trial," *Journal of Internal Medicine* 225 (1989): 225-232.

[121] S. Endres, R. Ghorbani, V. E. Kelly, K. Georgilis, G. Lonnemann, J. W. M. Van der Meer, J. G. Cannon, T. S. Rogers, M. S. Klempner, P. C. Weber, "The Effect of Dietary Supplementation with N-3 Fatty Acids on the Synthesis of Interleukin-1 and Tumor Necrosis Factor by Mononuclear Cells," *New England Journal of Medicine* 320 (1989): 265-270.

[122] I. T. Budiarso, "Fish oil versus olive oil," *Lancet* 336 (1990): 1313-1314.

[123] A. Petroni, M. Blasevich, M. Salami, N. Papini, G. F. Montedore, and C. Galli, "Inhibition of Platelet Aggregation and Eicosanoid Production by Phenolic Components of Olive Oil," *Thrombosis Research.* 78 (1995): 151-60.

4.5.3. Poor Absorption of Formulation

Choosing the most "bio-available" form of treatment is important in any study. For example, calcium citrate is more easily absorbed than calcium carbonate,[124] so less of the mineral must be administered to obtain the same effective dose. This seems to also be true of n-3 PUFAs.

A study was conducted to compare the human absorption of fish oil PUFAs as ethyl esters, triacylglycerols, or FFAs.[125] Absorption of the dose into cell membranes was, respectively, 20 to 21%, 57 to 68%, and greater than or equal to 95%. The superior absorption of the free fatty acid may be due to not requiring enzymatic cleavage by lipases (see Section 2.7.3.). Availability of lipases could be a limiting factor in the absorbance of the other preparations, specifically ethyl esters or triacylglycerol derivatives.

The Belluzzi group used this finding—that different chemical formulations have different bioavailability—to test possible preparations to be used in the group's experiments.[126] They carried out a study of patient tolerance in a group of CD patients with a new mixture of n-3 PUFAs. The capsules contained 500 mg of oil comprised of 40% EPA and 20% DHA as FFAs, and the capsules had different enteric coatings. Traditional n-3 PUFAs (from fish body oils) are in the form of triacylglycerols and are contained by uncoated gelatin capsules. The special concentrated n-3 PUFA capsules used by the study were provided by Tillotts Pharma AG, Ziefen, Switzerland, and are known by the trade name Purepa®.

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[124] K. Sakhaee, T. Bhuket, B. Adams-Huet, D. S. Rao, "Meta-Analysis of Calcium Bioavailability: a Comparison of Calcium Citrate with Calcium Carbonate," *American Journal of Therapeutics* 6 (1999): 313-21.
[125] L. D. Lawson and B. G. Hughes, "Human Absorption of Fish Oil Fatty Acids as Triacylglycerols, Free Acids, or Ethyl Esters," *Biochemical and Biophysical Research Communications* 152 (1988): 328-335. (abstract)
[126] A. Belluzzi, C. Brignola, M. Campieri, E. Camporesi, P. Gionchetti, F. Rizzello, C. Belloli, G. De Simone, S. Boschi , and M. Miglioli, "Effects of a New Fish Oil Derivative on Fatty Acid Phospholipids-Membrane Pattern in a Group of Crohn's Disease Patients," *Digestive Diseases and Sciences* 39 (1994): 2589-2594.

The patients were randomized into five groups of ten patients each and supplemented with four different Purepa® preparations and a triacylglycerol control:

(A) Purepa® without enteric coating

(B) Purepa® with cellulose acetate trimellitate coating (CAT; pH 5.5)

(C) Purepa® with 60 minute time release with CAT coating

(D) Purepa® with cellulose acetate phthalate coating (CAP; pH 6.9)

(E) triacylglycerol fish oil preparation (EPA 18%, DHA 12%)

The incorporation of n-3 FAs into phospholipids in plasma, as well as in red cell membranes, was evaluated (**Table 4.1**).

Table 4.1. Percentage of Arachidonic, Eicosapentaenoic, and Docosahexaenoic Acids Incorporated into Red Blood Cells (**A**), and Plasma Phospholipids Membranes (**B**) Before and After Six Weeks of Treatment in Five Different Groups of Crohn's Disease Patients. Adapted from A. Belluzzi, C. Brignola, M. Campieri, E. Camporesi, P. Gionchetti, F. Rizzello, C. Belloli, G. De Simone, S. Boschi, and M. Miglioli, "Effects of a New Fish Oil Derivative on Fatty Acid Phospholipids-Membrane Pattern in a Group of Crohn's Disease Patients," *Digestive Diseases and Sciences* 39 (1994): 2592.

(A)

Fatty acids (%)	Group A		Group B		Group C		Group D		Group E	
Change (After-Before)	Before	After	Before	After	Before	After	Before	After	Before	After
Arachidonic	17.5	15.5	18.0	16.0	17.8	13.2	18.1	17.7	18.1	17.0
Change	-2.0		-2.0		-4.6		-0.4		-1.1	
Eicosapentaenoic	0.2	2.4	0.3	2.8	0.2	4.4	0.4	1.1	0.4	1.4
Change	+2.2		+2.5		+4.2		+0.7		+1.0	
Docosahexaenoic	3.5	5.0	3.4	4.9	3.7	6.3	3.2	4.0	3.2	4.2
Change	+1.5		+1.5		+2.6		+0.8		+1.0	

B)

Fatty acids (%)	Group A		Group B		Group C		Group D		Group E	
Change (After-Before)	Before	After	Before	After	Before	After	Before	After	Before	After
Arachidonic	7.9	6.1	9.1	7.8	8.5	6.1	8.8	6.5	8.4	6.8
Change	-0.2		-1.2		-2.4		-2.3		-1.6	
Eicosapentaenoic	0.4	4.8	0.5	4.2	0.5	8.5	0.6	2.8	0.55	3.2
Change	+4.4		+3.7		+8		+2.2		+2.65	
Docosahexaenoic	2.3	4.1	1.9	4.0	2.4	5.3	2.8	3.6	2.0	3.7
Change	+1.8		+2.1		+2.9		+1.8		+1.7	

The Belluzzi group found that the absorption rate of n-3 fatty acids is highest when they are administered as free fatty acids in enteric-coated preparation (Group C). Belluzzi et al. estimated that the dose needed to achieve the incorporation into the phospholipid membranes is one-third of the dose used previously.[127] As a result of the lower dose, it would be expected that the frequency of side effects would be reduced, compliance would be increased, and long-term treatment would become more feasible in many patients.

4.5.4. Poor Patient Compliance

In many of the studies in which high doses of fish oil were used, poor patient compliance was registered. The lack of compliance was likely caused by the unpleasant taste of fish and many large pills to swallow—and by minor side effects such as halitosis, belching, and diarrhea.

These side effects were probably due to the high daily intake of fish oil preparations necessary for obtaining a satisfactory intestinal absorbance and incorporation of n-3 PUFAs into membranes. The side effects from the Belluzzi study are shown in **Table 4.2**. Group C was the only group to report no side effects; it was also the group experiencing the highest incorporation of n-3 PUFAs into membranes. The enteric coating effectively prevented the upper gastrointestinal side effects that are commonly associated with high doses of fish oil.

In conclusion, the role of the composition of the formulation in lowering the incidence of side effects—along with the selection of patients and experimental design—seems to change the probability that a clinical study will show evidence of a therapeutic potential of n-3 PUFAs in the therapy of IBD.

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[127] Ibid., 2592.

Table 4.2. Side Effects Registered in 50 Patients with Crohn's Disease Treated with 5 Different Types of Fish Oil Preparations. Adapted from A. Belluzzi, C. Brignola, M. Campieri, E. Camporesi, P. Gionchetti, F. Rizzello, C. Belloli, G. De Simone, S. Boschi, M. Miglioli, "Effects of a New Fish Oil Derivative on Fatty Acid Phospholipids-Membrane Pattern in a Group of Crohn's Disease Patients," *Digestive Diseases and Sciences* 39 (1994): 2589-2594.

	Side Effects of Different Preparations				
	Group A	Group B	Group C	Group D	Group E
Total Patient Number	10	10	10	10	10
Upper Gastrointestinal (belching, flatulence, halitosis)	5	0	0	0	6
Lower Gastrointestinal (increased bowel motions)	0	5	0	7	2
No Side Effects	5	5	10	3	2

4.6. Phase III Study in Progress: Epanova™ in Crohn's Disease

Based on the success of the Belluzzi study, Tillotts Pharma AG[128] (maker of the Purepa capsules used in that study) initiated a much larger study of n-3 FAs in Crohn's disease in January of 2003.[129] Tillotts has termed this a Phase III trial, recruiting 720 patients each from North America and from Europe. In Phase III clinical trials, the study drug or treatment is given to large groups of people to confirm its effectiveness, monitor its side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.[130]

Tillotts is calling these trials "Epanova™ in Crohn's Disease" (EPIC). EPIC 1 is the trial in Europe while EPIC 2 is being performed in the U.S. and Canada. William Sandborn of the Mayo Medical School is serving as the primary investigator and has stated that "Currently there is no treatment that combines proven efficacy in Crohn's disease with an

[128] Tillotts is also the manufacturer of Asacol (Section 2.5.1.1.)
[129] Tillotts Pharma AG "Epic-Studies," http://www.epanova.com/epic_studies/general_information.php. (Accessed 10 December 2004).
[130] Tillotts Pharma AG "About Epanova," http://www.epanova.com/about_epanova/product_information.php. (Accessed 10 December 2004).

absence of serious side effects....If the outcome is positive, the resulting risk/benefit profile of Epanova™ is likely to be of interest to Crohn's patients and their gastroenterologists."[131]

4.6.1. Details of the Epanova™ in Crohn's Disease Trials

Each EPIC study employed 720 patients with Crohn's disease in order to evaluate the safety and efficacy of Epanova™. Responses will be based on the Crohn's Disease Activity Index (CDAI), a widely used measure of reporting the severity of the disease. The Belluzzi study used nine 500 mg hard capsules per day, while the EPIC trials use four 1 g soft capsules per day. Less capsules might be better for compliance, but the larger capsules may be more difficult to swallow for some people (based on interviews). The source of DHA and EPA is FFAs in plankton from the Southern Pacific (which makes it suitable for use by vegetarians). The EPA and DHA are concentrated in a "12-stage process," the details of which are not publicly available. Gel capsules are filled with these purified n-3 PUFAs and given their enteric coating.

The 1440 total patients from EPIC I and II—with mildly to moderately active Crohn's disease—were brought into remission with a course of steroids, either prednisolone or budesonide (Section 2.5.1.2.), and then randomized to receive either Epanova™ or placebo for a year. Patients who are brought into remission with steroids have a high likelihood of experiencing a flare when steroids are withdrawn. Looking at a "high flare risk" group enhances the ability to see an effect with the Epanova™ treatment. Therefore, maintenance of remission (prevention of a flare) becomes an easily measured outcome of the study.

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[131] Tillotts Pharma AG. "Tillotts Pharma AG Initiates Two Epanova in Crohn's Disease (EPIC) Phase III Trials." Ziefen, Switzerland,10 October 2002, www.epanova.com/press_releases/021010_Ziefen.php.

4.6.1.1. EPIC 1

EPIC 1 was conducted in eight, mainly European countries (Belgium, Czech Republic, France, Germany, Israel, Italy, Lithuania, and the UK), involving approximately 40 trial centers. Patients who were already in remission were randomized to receive either Epanova™ or placebo capsules for one year.

4.6.1.2. EPIC 2

EPIC 2 was conducted in the US and Canada and involved 30 centers. The 10 sites in the U.S. were hospitals in Atlanta, GA; Chicago (2), IL; Urbana, IL; Louisville, KY; Rochester, NY; Chapel Hill, NC; Lincoln, NE; Great Neck, NY; and Cleveland, OH. As in EPIC I, these patients received either Epanova™ or placebo capsules for one year.

4.6.2. Awaiting the Results of the Epanova™ in Crohn's Disease Trials

According to ClinicalTrials.gov (a service of the National Institutes of Health), the trials were set to be completed on January of 2005.[132] Once the data are processed, the findings will be released to the public. The date of publication is currently scheduled to be December 2005.[133]

The results of the EPIC studies may provide more conclusive evidence on the role of n-3 PUFAs in IBD than studies that have been published to date. Technically, the process of testing should be repeated in ulcerative colitis patients. Intuitively, if n-3 PUFAs are found efficacious in the Crohn's subtype of IBD, n-3 PUFAs as a treatment in ulcerative colitis

[132] National Institutes of Health. "An Efficacy and Safety Study of Omega-3 Free Fatty Acids (Epanova™) for the Maintenance of Symptomatic Remission in Subjects with Crohn's Disease," http://clinicaltrials.gov/ct/show/NCT00074542?order=1. Page last updated December 2003. (Accessed 2 November 2004).

[133] Thompson Scientific. London, UK. "Current Patents Gazette: Drug Patenting in Context," www.current-patents.com/news/2004/0430/30.asp. 23 July 2004.

might quickly follow. This has been the path for drug therapy among the subtypes of autoimmune disease—rheumatoid and psoriatic arthritis drug therapy, for example.

Epanova™ may soon become a prescribed therapy like Omacor® (n-3 PUFAs prescribed for people who have had heart attacks) in the UK.[134] Omacor® is a product of Solvay Pharmaceuticals. Omacor® is delivered as a one gram capsule of ethyl esters of EPA and DHA. The evidence for the use of Omacor® in heart attack patients came from a very large Italian study, the GISSI Prevencione (GISSI-P) Trial.[135] Omacor® is not, however, prescribed in the U.S. for reasons that are unknown to the author.

Hopefully, Epanova™, if shown to be effective, would be available as a prescription in the U.S. Tillotts is already seeking licensing for Epanova™ for marketing worldwide.[136] In fact, Epanova™ may actually be superior to Omacor® for n-3 PUFA applications such as heart disease and autoimmune disorders because of its more bio-available form (FFA vs. ethyl esters) and its application for vegetarians.

Regardless of optimism over the results of the EPIC studies, patients who are suffering in the present should be aware of what they can do while the studies are being completed and Tillotts Pharma AG is figuring out how to get Epanova™ to patients. The next section includes recommendations based on the information we have to date. These recommendations are made both to gastroenterologists and patients, and to research funding groups.

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[134] Solvay, "Professional Omacor Website," http://www.omacor.co.uk/pages/productinfo_A1.asp.
[135] Morris Brown, "Do Vitamin E and Fish Oil Protect Against Ischaemic Heart Disease?" *Lancet* 354 (1999): 447-455.
[136] Tillotts Pharma AG, "Epanova," http://www.tillotts.com/tillotts.asp?nodeId=241. Contact is Dr. Carina Spaans.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

Up to this point, this project has been primarily a discussion of existing research; but—based on the information presented—recommendations can be made for gastroenterologists and patients and for research funding groups. The project's patient recommendations focus on using the current level of understanding to its fullest potential, while its recommendations to research-funding groups focus on furthering what is currently known.

5.1. Recommendations to Gastroenterologists and Patients

The correlation between intake of n-3 PUFAs and lowered inflammation is clear. However, demonstrating this correlation strongly and directly in an IBD application has yet to be accomplished. It will also be helpful for practitioners when effective doses have been determined—in relation to body weight and disease subtype—and when it has been elucidated whether genetics play an additional role in determining the effective dose of n-3 PUFAs for each patient.

5.1.1. Patients who Prefer Conventional Medicine Should not be Pursued to use Omega-3 Fatty Acids

Until research provides more conclusive evidence that n-3 PUFAs are effective in treating IBD, patients who are satisfied with their medical treatment should not be aggressively pursued to undergo this adjunctive treatment. Doing so may decrease their

compliance with what was previously an effective regimen, and such patients may be resentful of feeling pressured to undertake what they perceive as an "experimental therapy." This conclusion is based on preliminary discussions with patients from a variety of backgrounds.

5.1.2. Reasons to Inform Patients who Show Interest in Alternative Medicine

Patients who have decided that they are not satisfied with their current medical treatment should be encouraged and educated in supplementation of the diet with n-3 PUFAs as a complement to their existing therapy. If patients are not provided with accurate and useful information (preferably at their gastroenterologist's office), they may miss out on a possibly effective adjunctive therapy.

Patients who are unsatisfied with conventional medicine may seek information on alternative medicine by word of mouth, popular health books, and over the internet. Not only may this method undermine the gastroenterologist's credibility as an information source, but it also entails the problem of the patient wading through information that may be incorrect and result in less than optimal treatment.

Furthermore, patients who feel their gastroenterologists disapprove of alternative medicine are not likely to tell their gastroenterologists what they are doing, compromising the patient/doctor relationship (see Section 2.6.1). Therefore, it is important that this group of patients be exposed to accurate information on n-3 PUFAs as a possible complementary therapy for IBD.

An important point for gastroenterologists to keep in mind is that there have been no detrimental health effects associated with increased n-3 PUFAs as part of a nutritionally

complete diet.[137] Rather, they have been shown to decrease heart disease, arthritis, depression, and other afflictions. There is no known harm in supporting responsible n-3 PUFA supplementation—i.e., supplementation that is not in excess nor increases mercury intake to dangerous levels—a concern especially for pregnant women. The risk of mercury is greatest in shark, swordfish, tilefish, and fish from contaminated waters.[138] Fish oil capsules do not contain mercury because of the processing they undergo.

Also the use of n-3 PUFAs may give patients a feeling of control over their illness. N-3 PUFA supplementation is something they can do for themselves without fearing possible harmful side effects from medications. For instance, people feel better about taking a multi-vitamin than an antibiotic. It seems to be a perception that is hardwired into human nature that taking a concentrated form of a food is superior to taking a synthetic chemical.

5.1.3. Therapeutic Dosage of Omega-3 Fatty Acids

At this point in time, the best estimate of a therapeutic dose of n-3 PUFAs comes from the Belluzzi study, which used 2.7 g total of EPA + DHA per day. Patients could aim for 3 g daily because there will probably be days when they consume less than 2.7 g because they forget to take the capsules or are in an environment where they cannot select foods that are rich in n-3 PUFAs. A slightly higher goal for daily intake might help compensate for days with lower consumption.

However, the ideal dose for each patient is likely to vary as a function of total caloric intake, weight, genetics, and environment. Above all it seems important that the total dose be

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[137] This assertion is based on consultation with several experts within the International Society for the Study of Fatty Acids and Lipids and reading of many studies on the subject. The only possible "detrimental effects" are anticoagulation of the blood (helpful for preventing heart disease) and slightly lower birth weight for infants born to mothers taking fish oil, which is not associated with negative effects for the baby.

[138] FDA/Center for Food Safety & Applied Nutrition.. "Mercury levels in fish and shellfish." Updated March 19, 2004. http://www.cfsan.fda.gov/~frf/sea-mehg.html.

consumed as portions taken throughout the day with meals to avoid the side effects of fishy burps and smells (based on conversations with patients).

5.1.4. Strategies for Increasing Intake of Omega-3 Fatty Acids

There are several approaches patients with IBD could use to incorporate more n-3 PUFAs into their diets. One strategy would be to replace meats such as beef, chicken, and pork with oily, cold-water fish such as salmon, herring, mackeral, and sardines. Eating a variety of different fish is one way to reduce exposure to toxins such as polychlorobenzenes, dioxins, and methylmercury that can be stored in the tissues of fish inhabiting polluted waters. For convenience, **Table 5.1** contains a listing of the serving size of fish needed to provide 1 g of EPA + DHA. Patients could select three choices to obtain about 3 g/day.

Table 5.1. Serving Size of Fish that Provides 1 Gram of Eicosapentaenoic Acid + Docosahexanenoic Acid. Serving size determined from USDA Nutrient Databank, United States Department of Agriculture, "Nutrient Data Laboratory" http://www.nal.usda.gov/fnic/foodcomp/ (Accessed 10 February 2005).

Source	Amount Required to Provide One Gram
Salmon (Pink)	2.5 oz
Salmon (Atlantic)	2 oz
Salmon (Sockeye)	4.5 oz
Mackerel	5 oz
Herring	2 oz
Rainbow Trout	3 oz
Halibut	5 oz
Pacific Oyster	2.5 oz
Founder/Sole	7 oz
Farmed Oyster	8 oz

Another dietary source—which is new and particularly interesting—is "designer" n-3 eggs. They have recently risen in popularity due to their association with increased heart health. These eggs come from chickens fed flax seed or algae and can contain anywhere

from 0.1 g to 0.6 g of EPA + DHA per egg. It is necessary to read the label to know the amount specific to each brand.[139]

Table 5.2. Number of Omega-3 Eggs Needed to Provide 1 Gram of Eicosapentaenoic Acid + Docosahexaenoic Acid. (This range of values is what the author was able to find in several grocery stores. Most commonly eggs contained 0.2-0.3 g EPA + DHA per egg.)

Source	EPA + DHA per egg	Amount Required to Provide One Gram
Omega-3 Eggs	0.1 to 0.6 (Read the label)	2 to 10 eggs (depending on brand)

Many people find that using n-3 supplements takes the guesswork out of planning increased intake of n-3 PUFAs. These n-3 supplements are usually "fish oil" capsules. They can be very convenient and are widely available at grocery stores, general needs stores like Wal-Mart and Target, and health stores—where one would shop for vitamins.

These fish oil supplements generally contain 0.3 g of EPA + DHA per capsule, so three at each meal would provide the dose used in the Belluzzi study. Concentrated capsules contain 0.5 g or more of EPA + DHA per capsule, so it is again necessary to read the label.

Table 5.3. Number of Omega-3 Capsules Needed to Provide 1 Gram of Eicosapentaenoic Acid + Docosahexaenoic Acid. (Amounts based on author's personal research at stores where these supplements are sold.)

Capsules	Grams EPA + DHA per capsule	Amount Required to Provide One Gram
Standard fish body oil	0.3	About 3 capsules
Omega-3 Concentrate	0.5 to 0.8	About 2 capsules

Consumer Reports did a cost-quality comparison of 16 leading brands of fish oil products in July 2003 and found that all contained roughly as much n-3 PUFAs as their labels claimed; none were contaminated with mercury or other chemicals, and none were spoiled.[140] Their conclusion was to choose a supplement based solely on price.

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[139] Quanities are usually listed in milligrams which can be divided by 1000 to give the number of grams.
[140] Consumer Reports Group, "Omega-3 Oil: Fish or Pills?" *Consumer Reports* (July 2003): 30-32.

Liquid n-3 PUFA (fish oil) supplements are now available, as well, which may carry the label, "molecularly distilled," and have different flavors such as lemon or mint. The liquid n-3 PUFAs are useful for people who do not wish to—or find it difficult to—swallow capsules; they may—in some cases—also be more cost-effective.

As discussed extensively in this project, enteric-coated capsules may decrease side effects. All n-3 PUFA supplements should be stored in the refrigerator or freezer. Heat and light can cause these oils to become rancid (oxidized).

Flaxseed contains a very high concentration of alpha-linolenic acid (ALA), the shorter precursor to EPA and DHA (see Section 2.7.2.) The conversion of ALA to EPA seems to be an inefficient process in which probably less than 10% of ALA becomes EPA.[141] Therefore, much larger increases in ALA would be required to obtain the immune-modulating effects of n-3 PUFAs. In the case of IBD, nobody knows how much. However, ALA (especially from whole flaxseed) still provides health benefits[142] and could be a useful supplement, especially for vegetarians, people who do not consume fish, and pregnant women whose fetuses are particularly vulnerable to the effects of the toxins found in fish.

One particularly cost-effective way to increase intake of ALA is to purchase whole flaxseed in bulk at a whole foods store (usually around one dollar per pound). The flaxseed can then be freshly ground using a coffee grinder and sprinkled onto yogurt or hot cereals, or added into baked goods (personal observations).

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[141] Brenda C. Davis and Penny M. Kris-Etherton, "Achieving Optimal Essential Fatty Acid Status in Vegetarians: Current Knowledge and Practical Implications," *American Journal of Clinical Nutrition* 78 suppl (2003): 640S.
[142] Ibid., 642S.

Flax oil can also be used in homemade salad dressings. As discussed earlier, heat and light promote oxidation of unsaturated fatty acids. N-3 PUFAs are highly unstable to heat,[143] so flaxseed oil should never be used for frying. Deep-frying fish might also oxidize their n-3 PUFAs—undoing the benefits of consuming fish.

Another caution to consumers is that many products which claim to contain n-3 PUFAs—such as chips or snacks—either contain rancid oils or whole seeds from which the body is unable to extract the oils. Margarine-like spreads that contain n-3 PUFAs and are trans-fat free are an exception because they have been protected from light and refrigerated. These spreads may serve as an additional means for patients to add ALA to their diets.

There are also some less common sources of EPA and DHA. Grass-fed meat also contains n-3 PUFAs, but is more difficult to obtain in industrialized areas. At ISSFAL, a vendor displayed n-3 supplemented milk. It's important to always read labels and be skeptical.

Decreasing the amount of n-6 PUFAs in the diet may decrease the competition between n-3 and n-6 PUFAs for enzymes. This can be accomplished by decreasing intake of high-fat meats and limiting anything partially hydrogenated (n-3 PUFAs are chemically altered by hydrogenation). Additionally, corn oil, safflower oil, and cottonseed oil are high in n-6 PUFAs and can be decreased in the diet.

5.1.5. Strategies for Gastroenterologists to Inform Patients about Omega-3 Fatty Acids

To introduce the idea of n-3 PUFA therapy to interested patients, specialists could provide brochures in the waiting room or give brochures directly to the patient during a visit—as is the practice for some prescription medications. That is the purpose of the

[143] The double bonds between carbons that exist in PUFAs are susceptible to oxidation under conditions of high heat.

brochures in *Appendix C*. The patient's brochure (entitled *Omega-3 Fatty Acids and IBD: A Patient's Guide*) has been designed with the intent to provide brief—yet complete—information. The brochure for gastroenterologists (entitled *Omega-3 Fatty Acids and IBD: Answering Your Patient's Questions*) provides greater detail and expands upon the points in the patient's brochure.

For the satisfaction of both specialist and patients, certain questions are encouraged. How do you feel about using this nutritional therapy? How much are you taking per day, and what are the sources? How have you perceived this to affect your symptoms? Keeping dialogue open is important for optimizing this adjunctive therapy.

It is hoped that a prescription high-quality supplement will soon be available in the United States. However, n-3 PUFAs will probably not replace stronger medications for acute flares. The benefit of n-3 PUFAs is that they are safe for long-term use, may enhance the effectiveness of other medications, and may decrease the need for medications with side effects. Though they may not entirely replace current medications, n-3 PUFAs may be able to play an important complementary role in treating IBD as they are already being implemented in treating heart disease and other conditions.

5.1.6. Other Dietary Factors Important in Inflammatory Bowel Disease

A patient with IBD who is willing to take a holistic approach to treatment may have questions about other dietary factors. Although this project did not discuss them, most "whole foods" (e.g. fruits, vegetables, legumes, and teas) contain anti-inflammatory compounds. Dr. Kris-Etherton and associates wrote a review on this topic.[144] Many more beneficial phytonutrients ("plant" nutrients) likely remain to be discovered.

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[144] Penny M. Kris-Etherton, M. Lefevre, G. R. Beecher GR, M. D. Gross, C. L. Keen CL, T. D. Etherton, "Bioactive Compounds in Nutrition and Health-Research Methodologies for Establishing Biological Function:

N-3 PUFA therapy will probably do very little to complete an otherwise deficient diet. Patients should be encouraged to eliminate highly processed "junk" foods, including refined carbohydrates (white bread and flour), sugar, any hydrogenated or partially-hydrogenated oils (including margarine), and deep-fried foods. This advice greatly conflicts with the low residue diet espoused by many literature sources for patients. People battling a chronic disease should not be advised to increase caloric intake through nutritionally empty, refined foods that may further promote the imbalances present in their bodies. Instead, care should be taken to distinguish "good fats" from "bad fats" and "good carbohydrates" from "bad carbohydrates" for better long-term nutrition.

Gastroenterologists do not have to feel compelled to play the role of dietitians, but they should be able to provide commonsense advice on eating practices when treating a disease of the digestive system. When not experiencing an acute flare, patients should be encouraged to eat fruits, vegetables, and whole grains, in forms that their bodies can tolerate. To be clearer on this point, many IBD patients do not digest coarse or fibrous material (e.g., carrots, nuts, skinned and seeded fruits and vegetables) well, but finely ground bran, greens, applesauce, and blueberries may be more tolerable sources of phytonutrients and fiber. These nutrients found in foods containing fiber are an important part of the diet, and therefore, patients cannot thrive long-term eating a low-residue diet.

Diet is not the cause of IBD. However, in individuals who have inherited susceptibility genes and are exposed to the environmental triggers (diet included) needed to develop IBD, an optimal diet is an important part of treatment.

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the Antioxidant and Anti-inflammatory Effects of Flavonoids on Atherosclerosis," *Annual Reviews of Nutrition* 24 (2004):511-538.

5.2. Recommendations to Research-Funding Groups

Certainly, publication of the results of the EPIC studies will be helpful in providing future directions for studies of n-3 PUFAs and IBD. Until this study has been published, there are questions in the realm of dietary strategies and IBD that may have useful answers.

Although all of the studies of n-3 PUFAs and IBD used fish oil capsules, it should be asked, "Can a therapeutic dose of n-3 PUFAs be achieved through diet alone?" A small study has investigated means of increasing n-3 PUFAs completely through food items rather than fish oil capsules (on the grounds of preventing heart disease),[145] but this type of study has not been performed specifically using patients with IBD. Also, the diet used in this small study used supplemented foods (spreads, gravies, and flaxseed oil added to muffin mixes) and fish, which is naturally rich in n-3 PUFAs. With the advent of designer eggs from chickens fed algae and/or flax seed, milk fortified with n-3 FAs, and our knowledge that grass-fed meat is higher in n-3's, there may be more flexibility in an experimental design including effective dietary options.

One possible study design would provide patients with some of the more difficult-to-obtain or expensive foods (like high n-3 fish). Another option is to provide reimbursement to patients for the items included in the recommendations. People respond to incentives, so leaving patients with more choices and economic incentives to participate may increase compliance with the study.

Determining how intestinal endothelial cells of IBD patients respond to n-3 PUFAs on a genetic level might provide more insight on the mechanism by which n-3 PUFAs might work to decrease inflammation in the gastrointestinal tract. Microarray technology allows

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[145] Evangeline Mantzioris, Leslie G Cleland, Robert A Gibson, Mark A Neuman, Maryanne Demasi, and Michael J James, "Biochemical Effects of a Diet Containing Foods Enriched with N-3 Fatty Acids," *American Journal of Clinical Nutrition* 72 (2000): 42-48.

the screening of numerous genes at one time. Microarrays could be used to specifically examine the genes of inflammation involved in IBD. In this way, more information might be compiled about the mechanism by which n-3 PUFAs suppress intestinal inflammation on the level of gene expression.

The "ideal" dosage of n-3 PUFAs for each person is probably based on several combined factors: the person's weight, total calorie intake per day, genetic profile, severity of disease, subtype of IBD, gender, age, etc. Getting closer to answering this question of "nutrigenomics" (nutrition in gene expression) would be useful in individualizing therapy with n-3 PUFAs.

The role of dietary probiotics and cultured foods should be further explored. In addition to being high in "bad" fats, most foods in the Western diet are subjected to high heat (pasteurization) and processing (refinement) which remove all forms of bacteria—even those that may be beneficial to health. It seems that all of the long-lived (and low incidence of chronic diseases, such as IBD) cultures have a fermented food that is regularly consumed (personal observation). Consider for example, the miso and tempeh of Asian cuisine and the yogurt and aged cheeses of the Mediterranean. There are plenty of un-researched products in the market place that consumers eagerly purchase. Clearly there is great interest in the potential gains of probiotic therapy.

An interesting experiment could answer the question, "Would treatment of IBD be more effective if, after reducing the inflammation of IBD, the natural bacterial flora were reestablished via dietary or supplemental means?" Long-term fish oil use may prevent recurrence of the inflammation that disrupts the delicate ecosystem of the gut. A two-pronged approach—reduction of inflammation through intervention followed by

reestablishment of intestinal bacterial populations—may be more effective than either approach by itself. Furthermore, it would be useful to determine if and how active inflammation alters the type of bacteria housed in the intestines.

The research questions surrounding natural medicine and IBD are many, but there currently seems to be little allocation of funds in this area. Perhaps a logical methodology toward picking the research questions to answer would be to begin by conducting a survey of IBD patients (possibly through the CCFA which contains a large membership of IBD patients) in order to identify which forms of complementary medicine are most commonly used by IBD patients. Then it would be known what percentage of patients use fish oil, probiotics, and other agents. These findings could be submitted to the NCCAM to help it determine which research funding priorities to establish in complementary and alternative medicine.

It is also important that NCCAM be aware of the importance of standardizing n-3 PUFA supplements so that bearers of chronic disease have access to the best possible formulation (n-3 PUFA contents) and preparation (capsular construct). A high quality concentrated n-3 PUFA supplement should be available for prescription in the United States, and NCCAM may play a role in making this prescription form of n-3 PUFAs available by having it used in the studies they fund.

There is also the question of whether n-6 PUFAs should be reduced in the diet to enhance the effectiveness of n-3 PUFAs. This reasoning is because—as discussed in Section 2.7.3.—n-3 and n-6 PUFAs compete for the same enzymes when carrying out their respective biological roles. There seem to be three general views on the issue of n-6 PUFAs in the diet. These views include: (1) the quantity of n-6 PUFA is not important, (2) only the

presence of AA is detrimental to the effects of n-3 PUFAs, and (3) all n-6 PUFAs—including the short chain LA—should be limited in the diet. Research could be performed to answer this question by using controlled feeding studies with different percentages of fatty acids. After being fed these diets with different levels of the n-6 PUFAs, the participants' blood would be measured for markers of inflammation.

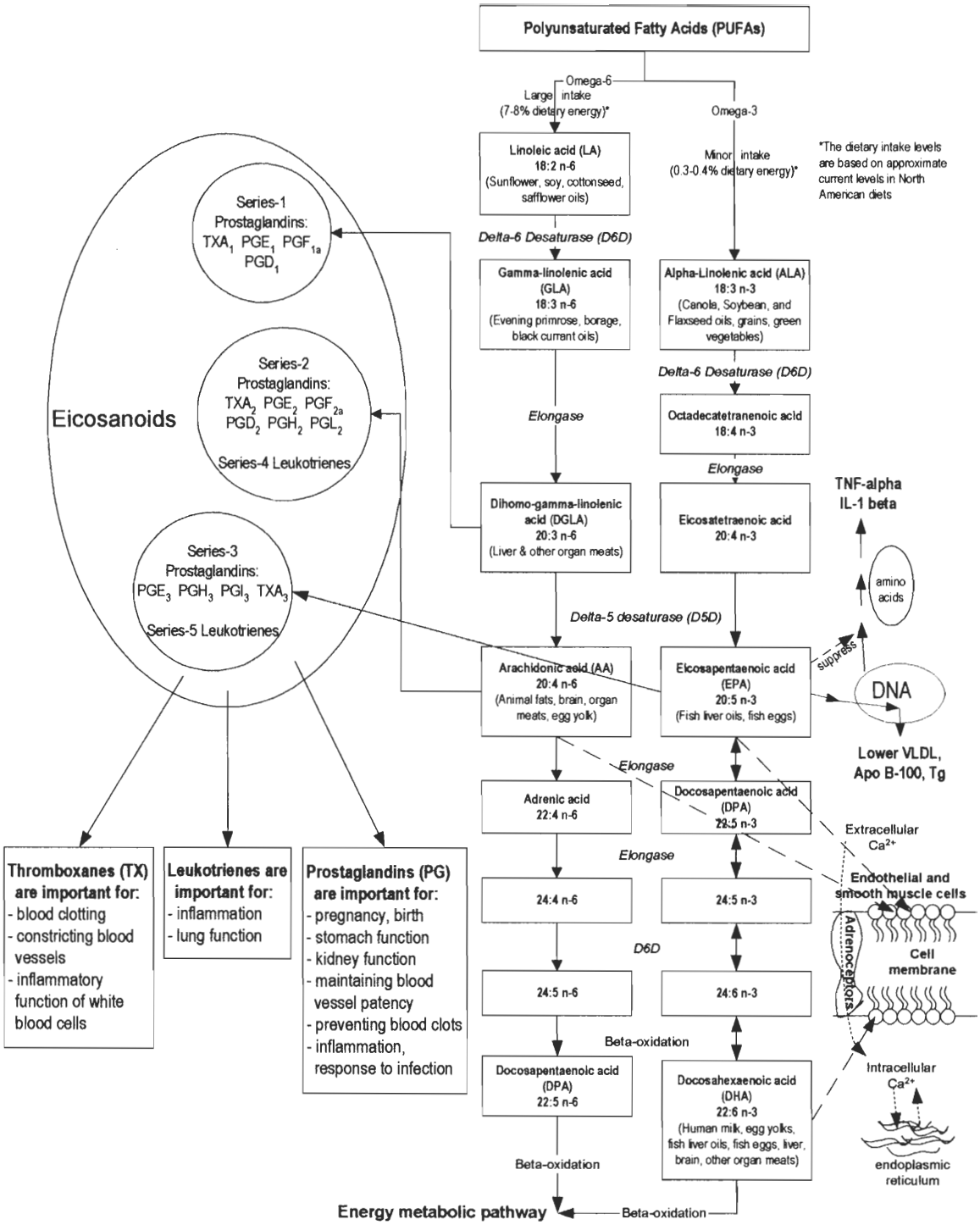
Finally, and importantly, there is still ambiguity over the specific roles of the different n-3 PUFAs ALA, EPA, and DHA in affecting the immune response and health in general. This project has assumed that EPA and DHA are equipotent and that ALA is inferior in immunological roles. Research should continue in the area of defining the specific roles of ALA, EPA, and DHA in the immune response and general health.

APPENDIX A:

Detailed Schematic of Omega-3 and Omega-6 Fatty Acid Synthesis Pathways and the Role of Omega-3 Fatty Acid in Regulating Health/Disease Markers.

Source: The Agency for Healthcare and Research Quality. "Omega-3 Fatty Acids, Effects in Type II Diabetes, Rheumatoid Arthritis, and Other Diseases" http://www.ahrq.gov/clinic/evrptfiles.htm

MacLean CH, Mojica, WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, Newberry SJ, Jungvig LK, Grossman J, Khanna P, Rhodes S, Shekelle P. Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis. Evidence Report/Technology Assessment. No. 89 (Prepared by Southern California/RAND Evidence-based Practice Center, under Contract No. 290-02-0003). AHRQ Publication No. 04-E012-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2004.


Polyunsaturated Fatty Acids (PUFAs)
Omega-6
Large intake (7-8% dietary energy)*
Omega-3
Minor intake (0.3-0.4% dietary energy)*
*The dietary intake levels are based on approximate current levels in North American diets
Linoleic acid (LA) 18:2 n-6 (Sunflower, soy, cottonseed, safflower oils)
Delta-6 Desaturase (D6D)
Gamma-linolenic acid (GLA) 18:3 n-6 (Evening primrose, borage, black currant oils)
Alpha-Linolenic acid (ALA) 18:3 n-3 (Canola, Soybean, and Flaxseed oils, grains, green vegetables)
Delta-6 Desaturase (D6D)
Elongase
Octadecatetranenoic acid 18:4 n-3
Elongase
Dihomo-gamma-linolenic acid (DGLA) 20:3 n-6 (Liver & other organ meats)
Eicosatetraenoic acid 20:4 n-3
TNF-alpha
IL-1 beta
amino acids
Delta-5 desaturase (D5D)
Arachidonic acid (AA) 20:4 n-6 (Animal fats, brain, organ meats, egg yolk)
Eicosapentaenoic acid (EPA) 20:5 n-3 (Fish liver oils, fish eggs)
suppress
DNA
Lower VLDL, Apo B-100, Tg
Elongase
Adrenic acid 22:4 n-6
Docosapentaenoic acid (DPA) 22:5 n-3
Extracellular Ca2+
Elongase
Endothelial and smooth muscle cells
24:4 n-6
24:5 n-3
D6D
Adrenoceptors
Cell membrane
24:5 n-6
24:6 n-3
Beta-oxidation
Docosapentaenoic acid (DPA) 22:5 n-6
Docosahexaenoic acid (DHA) 22:6 n-3 (Human milk, egg yolks, fish liver oils, fish eggs, liver, brain, other organ meats)
Intracellular Ca2+
endoplasmic reticulum
Beta-oxidation
Energy metabolic pathway
Beta-oxidation
Eicosanoids
Series-1 Prostaglandins: TXA1 PGE1 PGF1a PGD1
Series-2 Prostaglandins: TXA2 PGE2 PGF2a PGD2 PGH2 PGL2
Series-4 Leukotrienes
Series-3 Prostaglandins: PGE3 PGH3 PGI3 TXA3
Series-5 Leukotrienes
Thromboxanes (TX) are important for:
- blood clotting
- constricting blood vessels
- inflammatory function of white blood cells
Leukotrienes are important for:
- inflammation
- lung function
Prostaglandins (PG) are important for:
- pregnancy, birth
- stomach function
- kidney function
- maintaining blood vessel patency
- preventing blood clots
- inflammation, response to infection

APPENDIX B:

The Crohn's and Colitis Foundation of America Brochure: "Diet and Nutrition"

http://www.ccfa.org/media/pdf/diet.pdf. Accessed 15 March 2005.

Crohn's Disease and Ulcerative Colitis:

Diet and Nutrition

CCFA

CROHN'S & COLITIS FOUNDATION OF AMERICA

Since Crohn's disease and ulcerative colitis are digestive diseases, patients have many questions about diet and nutrition. You may be surprised to learn that there is no evidence that dietary factors cause or contribute to these inflammatory bowel diseases (IBD). Once you develop IBD, however, attention to diet may reduce symptoms and promote healing. The purpose of this brochure is to provide an overall dietary guide for patients and their families. This information is based on the results of ongoing studies and the accumulation of knowledge gained in recent years. As this research continues, we will learn even more about the relationship between nutrition and IBD.

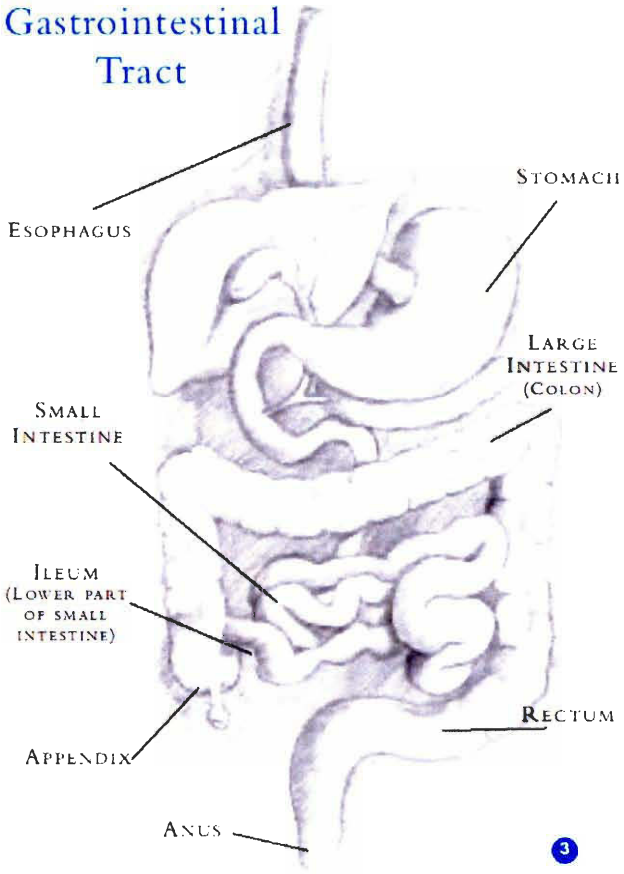
How do Crohn's disease and ulcerative colitis interfere with digestion?

The real work of digestion goes on in the small intestine, which lies just beyond the stomach.

"Should milk be avoided?") Elimination tests are better at diagnosing which foods must be avoided or modified than the standard allergy skin or blood testing. Many good books discuss the proper way to follow such an "elimination diet," which involves keeping a food and symptom diary over several weeks.

About two thirds of people with small bowel Crohn's disease develop a marked narrowing (or stricture) of the lower small intestine, the ileum. For these patients, a low-fiber with low-residue diet (see below) or a special liquid diet may be beneficial in minimizing abdominal pain and other symptoms. Often, these dietary modifications are temporary; the patient follows them until the inflammation that caused the narrowing responds either to treatment or to a corrective surgery. Individual experience, sometimes with the guidance of a registered dietitian,

The Gastrointestinal Tract



remains the single most useful guide to selection of foods for any person with IBD.

What is a low-fiber with low residue diet?

This diet minimizes the consumption of foods that add "scrapy" residue to the stool. These include raw fruits, vegetables, and seeds, as well as nuts and corn hulls. The registered dietitian associated with your IBD treatment program can assist you in devising such a diet when appropriate.

Is nutrition of special importance to IBD patients?

Yes, vitally so. IBD patients, especially people with Crohn's disease, are prone to becoming malnourished for several reasons. First, the appetite is often reduced. Second, chronic diseases tend to increase the energy (calorie) needs of the body. This is especially the case when IBD is "flaring up." Third, IBD, particularly Crohn's disease, is often associated with maldigestion and malabsorption of dietary protein, fat, carbohydrates, water, and a wide variety of vitamins and minerals. Thus, much of what one eats may never truly get into the body. On the other hand, good nutrition is one of the assets the body uses to restore itself to health. Therefore, the tendency to become malnourished must be resisted. Restoration and maintenance of good nutrition is a key principle in the management of IBD.

When IBD is active, which foods should be eaten?

An appropriate diet should contain a variety of foods from all food groups. Meat, fish, poultry, and dairy products, if tolerated, are sources of protein; bread, cereal, starches, fruits, and vegetables are sources of carbohydrate; margarine and oils are sources of fat. Your physician and the registered dietitian with whom he or she is associated can help you with meal planning. Generally, if the colon is inflamed, avoiding scrapy foods such as nuts, corn hulls, and raw vegetables is advised until some healing has occurred.

Should milk be avoided?

Some people cannot properly digest lactose, the sugar present in milk and many milk products, regardless of whether they have IBD. This may occur because the inner surface of the small intestine lacks a digestive enzyme, called lactase. Poor lactose digestion may lead to cramps, abdominal pain, gas, diarrhea, and bloating. Because symptoms of lactose intolerance may be very similar to the symptoms of IBD, recognizing lactose intolerance may be difficult. A simple "lactose tolerance test" can be performed to identify the problem. If there is any question, milk ingestion may be limited. Alternatively, lactase supplements may be added to many dairy products, so that they no longer cause symptoms. Your registered dietitian may assist you and/or your child with this. It is desirable to maintain intake of at least some dairy products, because they are such a good source of nutrition, in particular calcium and protein.

Do any specific foods worsen the inflammation of IBD?

No. While certain foods in any individual may aggravate symptoms of these diseases, there is no evidence that the inflammation of the intestine is directly affected. Any contaminated food that leads to food poisoning or dysentery will aggravate IBD.

Is IBD caused by allergy to food?

No. Although some people do have allergic reactions to certain foods, neither Crohn's disease nor ulcerative colitis is related to food allergy. People with IBD may think they are allergic to foods because they associate the symptoms of IBD with eating.

Do patients with these diseases absorb foods normally?

Most often, yes. Patients with inflammation only in the large intestine absorb food normally. People with Crohn's disease may have problems with digestion if their disease involves the small intestine. The degree to which digestion is

impaired depends on how much of the small intestine is diseased and whether any intestine has been removed during surgery. If only the last foot or two of the ileum is inflamed, the absorption of all nutrients except vitamin B-12 will probably be normal. If more than two or three feet of ileum is diseased, significant malabsorption of fat may occur. If the upper small intestine is also inflamed, the degree of malabsorption in Crohn's disease is apt to be much worse, and deficiencies of many nutrients, minerals, and more vitamins are likely. Some IBD therapies, especially the 5-ASA medications (e.g., Asacol®, Canasa®, Colazal®, Dipentum®, Pentasa® and Rowasa®), cause interference with the absorption of folate, so this vitamin, so essential in preventing cancer and birth defects, should be supplemented.

Should any supplemental vitamins be taken?

Vitamin B-12 is absorbed in the lower ileum. Therefore, persons with ileitis (Crohn's disease that affects the ileum) may require injections of vitamin B-12, because they cannot absorb enough from their diet. If you are on a low-fiber diet, you may be receiving an inadequate supply of certain vitamins common in fruits, such as vitamin C. In the setting of chronic IBD, it is worthwhile for most persons to take a multivitamin preparation regularly. If you suffer from maldigestion or have undergone intestinal surgery, other vitamins, particularly vitamin D, may be required. Vitamin D supplementation should be in the range of 800 U/day, especially in the non-sunny areas of the country, and calcium intake should be emphasized, with calcium citrate for those older or on acid-reducing medications. Steroid use and Crohn's disease itself are linked to bone thinning and osteoporosis, so screening with bone density studies is suggested for those at risk.

Are any special minerals recommended?

In most IBD patients, there is no obvious lack of minerals. However, calcium, phosphorus, and magnesium supplements may prove necessary in people who have extensive small intestinal disease or who have had substantial lengths of intestine

removed through surgery. Iron therapy is helpful to correct anemia. Oral iron turns the stools black, which can sometimes simulate intestinal bleeding.

SHOULD PEOPLE WITH IBD BE CONCERNED ABOUT FLUID INTAKE?

Yes. In a condition with chronic diarrhea, there may be a risk of dehydration. If fluid intake does not keep up with diarrhea, kidney function may be affected. Patients with Crohn's and other diarrheal diseases have an increased incidence of kidney stones, which is related to this problem. Furthermore, dehydration and salt loss create a feeling of weakness. For these reasons, people with IBD should consume ample fluids, especially in warm weather when skin losses of salt and water may be high.

DOES NUTRITION AFFECT GROWTH?

In young people with IBD whose IBD began before puberty, growth may be retarded. Poor food intake may contribute to poor growth. Thus, good nutritional habits and adequate caloric intake are very important. Control of the disease with drugs or, less often, surgical removal of a particularly diseased region of intestine, is most successful when appropriate dietary intake is maintained.

WHAT IS NUTRITIONAL SUPPORT?

Because IBD, especially Crohn's disease, may improve with nutritional support, enteral nutrition (a nutrient-rich liquid formula) or tube feeding may be necessary. Due to its taste, enteral nutrition is given overnight through a tube, most commonly from the nose to the stomach. Patients are taught to pass a tube each night, so that they can receive nutrition while sleeping. In the morning, they remove the tube and go about their normal activity. In this way, patients receive all the nutrition they need and are free to eat normally—or not—throughout the day.

Enteral feedings can also be given through a gastrostomy tube (G-tube). This is a tube located on the abdominal wall that goes directly into the stomach. The feedings are most commonly given overnight, but they can also be given intermittently throughout the day.

Parenteral nutrition (nutrition delivered through a catheter placed into a large blood vessel, usually one in the chest) is rarely needed. Parenteral nutrition has more complications than enteral nutrition and does not nourish the gastrointestinal tract itself.

What's new in nutritional therapy for IBD?

Eating to help the gut heal itself is one of the new concepts, and numerous experimental studies are being conducted in this area. Fish or flaxseed oils, in the diet or as supplements, have helped fight the inflammation in IBD. The complex carbohydrates that are not digested by the small bowel, such as psyllium, stimulate the bacteria in the colon to produce short-chain fatty acids, which help the mucosa (the lining) of the colon to heal itself. L-glutamate may be helpful in healing some of the small bowel abnormalities of early Crohn's, since that compound nourishes the lining of the small intestine.

Probiotics are just beginning to be appreciated as a therapeutic aid in IBD. These are "good" bacteria that restore balance to the enteric microflora—bacteria that live in everybody's intestine. Lactobacillus preparations and live-culture yogurt can be very helpful in aiding recovery of the intestine. There is much work being done in the use of diet and supplements to aid in the healing of IBD and much more to be learned.

Cancer chemoprophylaxis with minerals (selenium, calcium), vitamins (folic acid) and medications (the 5-ASA drugs seem to fulfill this role for many with IBD) is a developing field, and there will be more about this as new research studies are published.

In summary, while diet and nutrition do not play a role in causing IBD, maintaining a well-balanced diet that is rich in nutrients can help you to live a healthier life. Proper nutrition depends, in large part, on whether you have Crohn's disease or ulcerative colitis, and what part of your intestine is affected. It's important to talk to your doctor (and it also can be helpful to ask your physician to recommend a dietitian) in order to develop a diet that works for you.

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APPENDIX C:

Prototype Brochures for Communicating Project's Recommendations to Gastroenterologists and Patients

Appendix not included
in original submission

IQP/MQP SCANNING PROJECT

APPENDIX D:

Dietary Sources of Omega-3 Fatty Acids per 100 g Food

Source: MacLean CH, Newberry SJ, Mojica, WA, Issa A, Khanna P, Lim YW, Morton SC, Suttorp M, Tu W, Hilton LG, Garland RH, Traina SB, Shekelle PG. *Effects of Omega-3 Fatty Acids on Cancer.* Evidence Report/Technology Assessment No. 113. (Prepared by the Southern California Evidence-based Practice Center, under Contract No. 290-02-0003.) AHRQ Publication No. 05-E010-2. Rockville, MD. Agency for Healthcare Research and Quality. February 2005, p 14. http://www.ahrq.gov/downloads/pub/evidence/pdf/o3cancer/o3cancer.pdf

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Cooked in dry heat unless otherwise specified)				**Fish, continued**			
Anchovy, European	0.8	1.3	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.3	0.5	0.1	Tuna, Light, Canned in Oil	trace	0.1	trace
Bass, Striped	0.2	0.8	trace	Tuna, Light, Canned in Water	trace	0.2	trace
Bluefish	0.3	0.7	-	Tuna, White, Canned in Oil	trace	0.2	0.2
Carp	0.3	0.3	0.3	Tuna, White, Canned in Water	0.2	0.6	trace
Catfish, Channel, farmed	trace	0.1	0.1	Whitefish, Mixed Sp.	0.4	1.2	0.2
Cod, Atlantic	trace	0.2	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	0.1	0.2	trace	Wolf fish, Atlantic	0.4	0.4	trace
Eel, Mixed Sp.	0.1	0.1	0.6				
Flounder & Sole Sp.	0.2	0.3	trace				
Grouper, Mixed Sp.	trace	0.2	-	**Shellfish (Raw)**			
Haddock	0.1	0.2	trace	Abalone, Mixed Sp., fried	0.1	0.1	0.1
Halibut, Atlantic and Pacific	0.1	0.4	0.1	Clam, Mixed Sp., moist heat	0.1	0.1	trace
Halibut, Greenland	0.7	0.5	0.1	Crab, Alaska King, moist heat	0.3	0.1	-
Herring, Atlantic	0.9	1.1	0.1	Crab, Blue, moist heat	0.2	0.2	-
Herring, Pacific	1.2	0.9	0.1	Crayfish, Mixed Sp., Farmed	0.1	trace	trace
Mackerel, Atlantic	0.5	0.7	0.1	Lobster, Northern, moist heat	0.1	trace	trace
Mackerel, Pacific and Jack	0.7	1.2	0.1	Mussel, Blue	0.3	0.5	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Farmed	0.2	0.2	0.1
Ocean Perch, Atlantic	0.1	0.3	0.1	Oyster, Eastern, Wild	0.3	0.3	0.1
Pike, Northern	trace	0.1	trace	Oyster, Pacific	0.9	0.5	0.1
Pike, Walleye	0.1	0.3	trace	Scallop, Mixed Sp.	0.2	0.2	-
Pollock, Atlantic	0.1	0.5	-	Shrimp, Mixed Sp.	0.2	0.1	trace
Pompano, Florida	0.2	0.5	-	Squid, Mixed Sp., fried	0.2	0.4	0.1
Roughy, Orange	trace	-	trace				
Salmon, Atlantic, Farmed	0.7	1.5	0.1				
Salmon, Atlantic, Wild	0.4	1.4	0.4	**Fish Oils**			
Salmon, Chinook	1.0	0.7	0.1	Cod Liver Oil	6.9	11.0	0.9
Salmon, Chinook, Smoked (lox)	0.2	0.3	-	Herring Oil	6.3	4.2	0.8
Salmon, Chum	0.3	0.5	trace	Menhaden Oil	13.2	8.6	1.5
Salmon, Coho, Farmed	0.4	0.9	0.1	Salmon Oil	13.0	18.2	1.1
Salmon, Coho, Wild	0.4	0.7	0.1	Sardine Oil	10.1	10.7	1.3
Salmon, Pink	0.4	0.6	trace				
Salmon, Pink, Canned	0.8	0.8	0.1				
Salmon, Sockeye	0.5	0.7	0.1	**Nuts and Seeds**			
Sardine, Atlantic, Canned in Oil	0.5	0.5	0.5	Butternuts, Dried	-	-	8.7
Sea bass, Mixed Sp.	0.2	0.6	-	Flaxseed			18.1
Sea trout, Mixed Sp.	0.2	0.3	trace	Walnuts, English	-	-	9.1
Shark, Mixed Sp., battered and fried	0.3	0.4	0.2				
Snapper, Mixed Sp.	0.1	0.3	0.1	**Plant Oils**			
Swordfish	0.1	0.7	0.2	Canola (Rapeseed)	-	-	9.3
Trout, Mixed Sp.	0.3	0.7	0.2	Flaxseed Oil	-	-	53.3
Trout, Rainbow, Farmed	0.3	0.8	0.1	Soybean Lecithin Oil	-	-	5.1
Trout, Rainbow, Wild	0.5	0.5	0.2	Soybean Oil	-	-	6.8
Tuna, Fresh, Bluefin	0.4	1.1	-	Walnut Oil	-	-	10.4
Tuna, Fresh, Skipjack	trace	0.2	-	Wheat germ Oil	-	-	6.9

Source: Figures adapted from USDA, 2003; * Sp = species.

APPENDIX E:

Amounts of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide Approximately 1 g of EPA + DHA per Day

Source: Kris-Etherton, Penny M., Harris, William, S., Appel, Lawrence J for the Nutrition Committee of the American Heart Association. "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease." *Circulation* (2002) 106 (21): 2747-2757.

Amounts of EPA+DHA in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide ≈1 g of Eicosapentaenoic acid (EPA) + Docosahexaenoic Acid (DHA) per Day :

	EPA+DHA Content, g/3-oz Serving Fish (Edible Portion) or g/g Oil	Amount Required to Provide ≈1 g of EPA+DHA per Day, oz (Fish) or g (Oil)
Fish		
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24–1.28	2.5–12
Sardines	0.98–1.70	2–3
Salmon		
Chum	0.68	4.5
Sockeye	0.68	4.5
Pink	1.09	2.5
Chinook	1.48	2
Atlantic, farmed	1.09–1.83	1.5–2.5
Atlantic, wild	0.9–1.56	2–3.5
Mackerel	0.34–1.57	2–8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Halibut	0.4–1.0	3–7.5
Cod		
Pacific	0.13	23
Atlantic	0.24	12.5
Haddock	0.2	15
Catfish		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.47	6.5
Farmed	0.37	8
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan King	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5
Capsules		
Cod liver oil*	0.19	5
Standard fish body oil	0.30	3
Omega-3 fatty acid concentrate	0.50	2
Omacor (Pronova Biocare)†	0.85	1

Data from the USDA Nutrient Data Laboratory. The intakes of fish given above are very rough estimates because oil content can vary markedly (>300%) with species, season, diet, and packaging and cooking methods.

†Not currently available in the United States.

APPENDIX F:

Contact Information for Organizations with Interest in Inflammatory Bowel Disease and Organizations with Interest in Omega-3 Fatty Acids and Disease

Sources: Information obtained from websites of respective organizations.

Organizations with Interest in Inflammatory Bowel Disease

(All information is from each organization's webpage on March 14, 2005.)

Crohn's and Colitis Foundation of America (CCFA)
CCFA sponsors basic and clinical research. The foundation also offers a wide range of educational programs for patients and health-care professionals, and provides supportive services to help people cope with these chronic intestinal diseases.
Phone: 800-932-2423
Electronic mail: info@ccfa.org
Mailing Address:
Crohn's & Colitis Foundation of America
386 Park Avenue South 17th Floor
New York, NY 10016
Webpage: www.ccfa.org

Crohn's and Colitis Foundation of Canada (CCFC)
The Crohn's and Colitis Foundation of Canada (CCFC) is a national not-for-profit voluntary medical research Foundation. Its mission is to find the cure for inflammatory bowel disease. To achieve its mission, the Foundation is committed to raising increasing funds for medical research.
Phone: 416-920-5035, 1-800-387-1479
Electronic mail: ccfc@ccfc.ca
Fax: 416-929-0364
Mailing Address:
60 St. Clair Avenue East, Suite 600
Toronto, ON M4T 1N5
Web page: www.ccfc.ca

American College of Gastroenterology (ACG)
The American College of Gastroenterology (ACG) was founded in 1932 to advance the scientific study and medical practice of diseases of the gastrointestinal (GI) tract. The College promotes the highest standards in medical education and is guided by its commitment to meeting the individual and collective needs of clinical GI practitioners.
Phone: (301) 263-9000
Mailing Address:
P.O. Box 342260
Bethesda, MD 20827-2260

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is part of the National Institutes of Health. The Institute supports basic and clinical research through investigator-initiated grants, program project and center grants, and career development and training awards. The Institute also supports research and development projects and large-scale clinical trials through contracts.
Mailing Address:
Office of Communications and Public Liaison
NIDDK, NIH, Building 31, room 9A04 Center Drive, MSC 2560
Bethesda, MD 20892-2560
Web page: www.niddk.gov

United Ostomy Association (UOA)
Through the last four decades, the United Ostomy Association (UOA) has had a profound influence on improving the quality of life for individuals with an ostomy or continent diversion. UOA is making a difference in a number of ways, including patient-to-patient support, educational literature, a helping cyber-community, advocacy and promoting earlier detection of colon cancer.
Phone: 800-826-0826, 949-660-8624
FAX: 949-660-9262
Electronic mail: info@uoa.org
Mailing Address:
19772 MacArthur Blvd., #200
Irvine, CA 92612-2405
Web page: http://www.uoa.org

The Foundation for Digestive Health and Nutrition (FDHN)
The FDHN is the foundation of the American Gastroenterological Association (AGA), the leading professional society representing gastroenterologists and hepatologists worldwide. It is separately incorporated and governed by a distinguished board of AGA physicians and members of the lay public. The Foundation raises funds for research and public education in the prevention, diagnosis, treatment and cure of digestive diseases. Along with the AGA, it conducts public-education initiatives related to digestive diseases.
Phone: 301-222-4002
Fax: 301-222-4010
Toll-free number: 866-337-FDHN (866-337-3346)
Electronic mail: info@fdhn.org
Mailing Address:
Foundation for Digestive Health and Nutrition
4930 Del Ray Avenue
Bethesda, MD 20814-3015
Web page: http://www.fdhn.org/

Organizations with Interest in Omega-3 Fatty Acids and Disease

International Society for the Study of Fatty Acids and Lipids (ISSFAL)
The purpose of the Society is to increase understanding through research and education of the role of fatty acids and lipids in health and disease.
Telephone: (44) 1884 257547
FAX: (44) 1884 257547
Mailing Address:
P.O.Box 24,Tiverton
Devon EX16 4QQ, UK
Electronic mail: rayrice@issfal.org.uk
Webpage: www.issfal.org.uk

American Oil Chemists Society (AOCS)
The AOCS mission is to be a global forum to promote the exchange of ideas, information, and experience, to enhance personal excellence, and to provide high standards of quality among those with a professional interest in the science and technology of fats, oils, surfactants, and related materials.
Phone: +1-217-359-2344
Fax: +1-217-351-8091
Mailing Address:
2211 W. Bradley Ave.
Champaign, IL USA 61821
Web Page: http://www.aocs.org

National Center for Complementary and Alternative Medicine (NCCAM)
NCCAM is dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training complementary and alternative medicine (CAM) researchers, and disseminating authoritative information to the public and professionals.
Toll-free in the U.S.: 1-888-644-6226
International: 301-519-3153
TTY (for deaf or hard-of-hearing callers): 1-866-464-3615
Mailing Address:
NCCAM, National Institutes of Health
Bethesda, Maryland 20892 USA
Webpage: nccam.nih.gov
Electronic mail: info@nccam.nih.gov

NCCAM Clearinghouse (Information on CAM)
E-mail: info@nccam.nih.gov
Address: NCCAM Clearinghouse, P.O. Box 7923, Gaithersburg, MD 20898-7923
Fax: 1-866-464-3616
Fax-on-Demand service: 1-888-644-6226

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Example Sources of One Gram EPA + DHA (Pick 3 daily)

Source	Amount Required to Provide One Gram (From USDA nutrient databank)
Salmon (Pink)	2.5 oz
Salmon (Atlantic)	2 oz
Salmon (Sockeye)	4.5 oz
Mackerel	5 oz
Herring	2 oz
Rainbow Trout	3 oz
Halibut	5 oz
Pacific Oyster	2.5 oz
Founder/Sole	7 oz
Farmed Oyster	8 oz

Source	**EPA + DHA per egg**	**Amount Required to Provide One Gram**
Omega -3 Eggs	**0.1 to 0.6 (Read the label)**	**2 to 10 eggs (depending on brand)**

Capsules	Grams EPA + DHA per capsule	Amount Required to Provide One Gram
Standard fish body oil	0.3	About 3 capsules
Omega-3 Concentrate	0.5 to 0.8	About 2 capsules

Possible Side Effects:

Some people may experience "fishy burps" or other fishy smells (in gas or sweat) when consuming this amount of omega-3 as fish oil capsules. Using enteric coated capsules, dividing the dose among 3 meals, and gradually increasing intake is helpful.

Fats that oppose the effects of omega-3s

- Omega-6 fatty acids may block the beneficial effects of omega-3s.
- AVOID: partially hydrogenated and hydrogenated fats (margarine, shortening) and deep fried foods.
- Switch to olive and canola oil instead of corn oil or safflower oil.

What about flax seed?

- Flax seed is rich in a shorter omega-3 fatty acid.
- It is very nutritious freshly ground on hot cereals or in baked goods, but it does not contain EPA or DHA.

The rest of the diet is also important.

- A good diet is a complete diet.
- Omega-3s won't be any help if the rest of your diet is junk food, so also avoid sugary, processed, and "fake" foods.

For more information on omega-3 fatty acids, check out www.fatsoflife.com.
For more information on IBD, go to www.ccfa.org.

References:

[1]Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, and Miglioni M (1996) Effect of an enteric-coated fish oil preparation on relapses in Crohn's disease. New Engl J. Med 334: 1557-1616.
[2]http://www.epanova.com/epic_studies/general_information.php. Epic-Studies. Tillotts Pharma AG.

This brochure was created by Ann C. Skulas based on results of a Worcester Polytechnic Institute Interactive Qualifying Project. Ann was diagnosed with ulcerative colitis at the age of 10. She is a member of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and the American Oil Chemists Society (AOCS).

Omega-3 Fatty Acids and IBD

A Patient's Guide

Inflammatory bowel disease (IBD) is a frustrating illness. Flares often come without warning, leading to pain and embarrassment. Reducing the symptoms of IBD is a top priority for all of us!

It is intuitive that some foods should be better or worse for IBD. The information of dietary strategies can be overwhelming, and not all of it is based on scientific research.

However, there is scientific evidence that omega-3 fatty acids may offer a safe and effective means of complementing your medical care.

You may have heard that eating fish is good for your heart. It's the type of fat in the fish, omega-3, that provides the benefits.

- Different types of fats in the diet serve as the building blocks for inflammatory or anti-inflammatory chemicals that play a role in the inflammation in IBD.

- Almost all Americans eat a diet that is much higher in the fats that lead to greater inflammation.

Omega-3s are anti-inflammatory fats. This brochure will give you an introduction to omega-3s. Your healthcare provider may be able to tell you more.

What are omega-3 fatty acids?

- Omega-3s are a type of fat that are eaten as part of your diet.

- They are also called "essential fatty acids" because they are necessary for life.

- There are two main types of omega-3's that are beneficial for IBD: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA.)

- Oily fish are the richest source of EPA and DHA.

- Other names include: n-3 fatty acids, ω-3 fatty acids, fish oil, or n-3 polyunsaturated fatty acids (PUFAs.)

What is the evidence that omega-3 fatty acids can help treat IBD?

- Many studies have shown on a cellular level that EPA and DHA are able to reduce inflammation.

- A study on 78 people showed that 2.7 grams of omega-3 fatty acids daily reduced flares in Crohn's disease.

- A large follow-up study is scheduled to be completed in 2005.

- Additionally, omega-3s have been shown to be helpful in other disorders—arthritis, heart disease, and psychiatric disorders—without negative health risks.

What are rich sources of omega-3s?

- Fatty, cold-water fish:
  - **salmon, sardines, mackerel**, herring, and **anchovies.**
  - tuna, but do not eat more than one or two cans a week (6 oz) to minimize mercury.
  - AVOID: shark, swordfish, or tile fish for omega-3s (these are the highest in mercury).

- Omega-3 eggs (chickens are fed flax seed or algae.)

- Grass-fed meat and omega-3 fortified milk.

What about supplements?

Although most supplements are basically "fish oil," there are a variety available including vegetarian forms made from algae.

Some supplements have a special enteric coating that keeps the capsule from dissolving until it's past the stomach. This is useful for people who are prone to fishy burps.

Also, liquid supplements are available and may offer a more convenient option if you can tolerate the taste.

How should omega-3 capsules be taken?

- Take the omega-3 capsules with meals.

- Start with 1 or 2 capsules and gradually build up to 9 per day (2.7 grams of omega-3s.)

- Long-term use is required for effectiveness.

- Storing capsules in the refrigerator or freezer may help them stay fresh longer.

Example Sources of One Gram EPA + DHA (Pick 3 daily)

Source	Amount Required to Provide One Gram (From USDA nutrient databank)
Salmon (Pink)	2.5 oz
Salmon (Atlantic)	2 oz
Salmon (Sockeye)	4.5 oz
Mackerel	5 oz
Herring	2 oz
Rainbow Trout	3 oz
Halibut	5 oz
Pacific Oyster	2.5 oz
Founder/Sole	7 oz
Farmed Oyster	8 oz

Source	**EPA + DHA per egg**	**Amount Required to Provide One Gram**
Omega -3 Eggs	**0.1 to 0.6 (Read the label)**	**2 to 10 eggs (depending on brand)**

Capsules	Grams EPA + DHA per capsule	Amount Required to Provide One Gram
Standard fish body oil	0.3	About 3 capsules
Omega-3 Concentrate	0.5 to 0.8	About 2 capsules

Possible Side Effects:

Some people may experience "fishy burps" or other fishy smells (in gas or sweat) when consuming this amount of omega-3 as fish oil capsules. Using enteric coated capsules, dividing the dose among 3 meals, and gradually increasing intake is helpful.

Fats that oppose the effects of omega-3s

There is some evidence that omega-6 fatty acids oppose the beneficial effects of omega-3s. The American diet is very high in these fats. The worst culprits are partially hydrogenated and hydrogenated fats (such as margarine and shortening) and deep-fried foods. Corn oil, safflower oil, and cottonseed oil are also very high in omega-6 fatty acids. It is best to switch to extra virgin olive or canola oil for cooking needs.

What about flax seed?

Flax seed is a very nutritious food, especially when the seeds are bought whole and freshly ground with a coffee grinder. They are high in anti-cancer lignins and fiber. However, the fatty acid in flax seed is the short chain omega 3 fatty acid; ALA. It must be lengthened to be therapeutic. In the high fat American diet, the enzymes that do this may work very slowly. Do eat freshly ground flax sprinkled on your cereal and in baked goods, but also consume a source of the longer-chain fatty acids as well.

The rest of the diet is also important.

A good diet is a complete diet. Omega-3 won't be any help if the rest of your patient's diet is "junk" food. A balanced diet contains adequate levels of vitamins, minerals, protein, and fiber; and contains minimal levels of sugar and processed foods. Patients should make a special effort to find fruits, vegetables, and whole grains (like oats and brown rice) that their bodies can tolerate. Eating probiotic foods like yogurt may also be helpful.

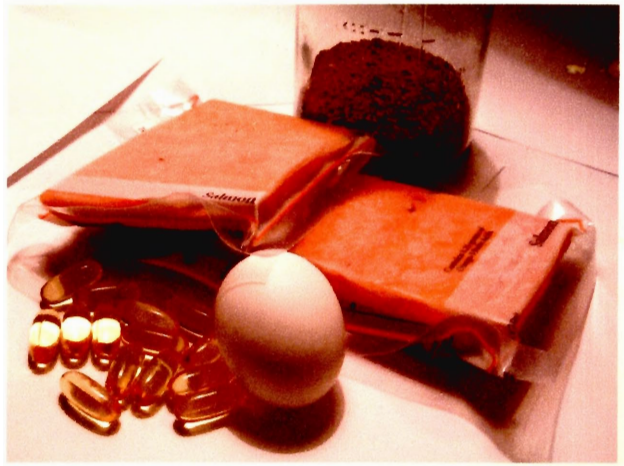
References:

[1]Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, and Miglioni M (1996) Effect of an enteric-coated fish oil preparation on relapses in Crohn's disease. New Engl J. Med 334: 1557-1616.
[2]http://www.epanova.com/epic_studies/general_information.php. Epic-Studies. Tillotts Pharma AG.

For more information on omega-3 fatty acids, visit www.fatsoflife.com.

This brochure was created by Ann C. Skulas based on results of a Worcester Polytechnic Institute Interactive Qualifying Project. Ann was diagnosed with ulcerative colitis at the age of 10. She is a student member of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and the American Oil Chemists Society (AOCS).

Omega-3 Fatty Acids and IBD



Answering Your Patients' Questions

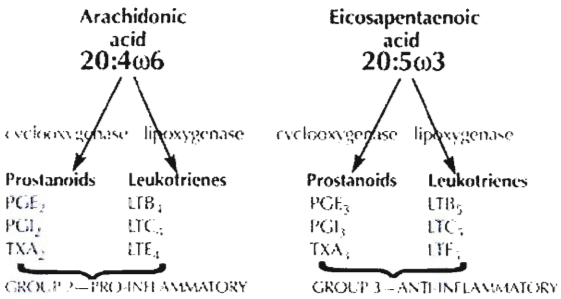
Inflammatory bowel disease (IBD) is a frustrating illness. Your patients often experience flares without warning, leading to pain and embarrassment. Reducing the symptoms of IBD is a top priority for all of us!

The idea of dietary modification is often approached by patients. It is intuitive that some foods should be better or worse for their condition. Some ideas can be the result of clever marketing by supplement groups, or are just plain misinformed. However, there is scientific evidence that omega-3 fatty acids may offer a safe, adjunctive treatment to medical therapy. Maybe you are already familiar with omega-3 fatty acids for their role in heart health, but you may not know that:

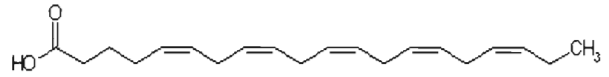
- Different types of fats in the diet serve as the building blocks for inflammatory or anti-inflammatory eicosanoids that regulate the inflammation in IBD.

- Industrialized countries (where incidence of IBD is higher) eat a diet comprised of much more inflammatory fat than anti-inflammatory fat.

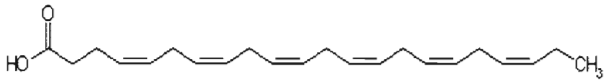
Omega-3s are anti-inflammatory fats. This brochure will give you the ins and outs of omega-3s, evidence for their role in treating IBD, and provide you with the answers to some questions your patients may ask.



Omega-3 Fatty Acids are the Precursors to Anti-Inflammatory Eicosanoids



Eicosapentaenoic Acid (EPA)



Docosahexaenoic Acid (DHA)

What are omega-3 fatty acids?

Omega-3s are a type of fat that are eaten as part of the diet. All people need to eat some omega-3s because the human body does not have the ability to make them. Omega-3s are used to build cell membranes and are modified to create chemicals in the immune system. They are also called n-3 fatty acids, ω-3 fatty acids, fish oil, or n-3 polyunsaturated fatty acids (PUFAs) or essential fatty acids (EFAs). The two so-called long chain fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alpha-linolenic acid (ALA) is also an omega-3 and is very healthy to eat, but it is a short-chain fatty acid and is not as biologically active in the immune system as its long-chain cousins EPA and DHA. Oily fish is the richest source of EPA and DHA.

What is the evidence that omega-3 fatty acids can help treat IBD?

Many studies have shown on a cellular level that EPA and DHA are able to reduce inflammation which is a goal of medication prescribed for IBD.
One Italian study of 78 patients conducted in 1996 concluded that 1.8 g of EPA and 0.9 g of DHA daily (2.7 g total omega-3) reduced relapse of Crohn's disease[1]. Studies of this scale have not been successfully carried out for ulcerative colitis, but there is no reason to doubt that fish oil would also be effective in reducing its symptoms and their frequency. Also, there is evidence that fish oil can be helpful in arthritis, heart disease, and psychiatric disorders.
A much larger study on omega-3 fatty acids called the EPIC trials will be completed in 2005[2]. Pending the results of this study, omega-3 fatty acids may one day become a prescribed therapy for IBD.
Omega-3s are not a cure for IBD, but they may help reduce your patients' dependence on medication and prolong remission.

What are rich sources of omega-3s?

- Fatty, cold-water fish are the best dietary sources of omega-3s. These included **salmon**, **sardines**, **mackerel**, **herring**, and **anchovies**. Tuna also contains omega-3s but these big fish sometimes have worrisome levels of mercury, so it is best not to eat more than a can or two (6 ounces) a week and to avoid albacore tuna. Do NOT eat shark, swordfish, or tile fish for omega-3s (these are the highest in mercury).

- New "designer" eggs coming from chickens fed flax seed and algae can contain anywhere from 100 mg to 600 mg of n-3 fatty acids per egg.

- Grass-fed meat and fortified milk are also sources of n-3 fatty acids (although these are more difficult to obtain in the U.S.)

What about supplements?

A safe and convenient way to increase n-3s is through supplements. There are a variety of supplements available including vegetarian forms made from algae. Some supplements have a special enteric coating that keeps the capsule from dissolving until it's past the stomach. This is useful for people who are prone to fishy burps.
Some formulas are more concentrated than others. This means fewer capsules are needed for a therapeutic dose. The label lists how much EPA and DHA the product contains per dose. Adding those two numbers indicates how much omega-3 each dose contains.
Liquid supplements are convenient if the taste is tolerable.

How should omega-3 capsules be taken?

Since the omega-3 capsules are an extracted dietary component, you should take them with meals throughout the day. You can advise your patients to take just 2 capsules a day and work up to 12 or to take anything in between. Most fish oil capsules contain 300 mg of n-3 fatty acids per capsule, so 9 capsules contain 2.7 g. 1 g (about three capsules) is often recommended for heart health. Taking a very large amount of omega-3 fatty acids may thin the blood.
It takes time for the fatty acids to build up in cell membranes and have their beneficial effects, so best results will be seen long-term. Storing the capsules in the refrigerator or freezer may help them stay fresh longer.