

# A NOTE TO HEALTH-CARE PROVIDERS



This book was written for the general reader. It presents enteral nutrition in a positive light, but attempts to be honest about its limitations. Given its primary audience, it does not include probability figures, confidence intervals, or similar scholarly appurtenances. However, throughout the book any result referred to as significant meets conventional standards of statistical significance ( $P < 0.05$ ). Remission rates were calculated based on intent-to-treat populations, whenever they could be ascertained.

All references cited in short form in the endnotes may be found in the bibliography. The bibliography also includes selected additional references consulted during the preparation of this book that may interest those curious about enteral nutrition. As the scope of the bibliography testifies, enteral nutrition is by no means an untested therapy, in spite of the modest size of many of the studies that explore it. I hope this book will spur further research into a treatment that is sometimes overlooked.

# What is Enteral Nutrition?

Rebellions of the belly are the worst.

*Frances Bacon*

This book describes a treatment for Crohn's disease that involves using **enteral nutrition**—special liquid formulas—to get into remission, stay in remission, gain weight, and reverse nutritional deficiencies.

Enteral nutrition has been prescribed by doctors for patients with Crohn's disease since the late 1960s, and has been evaluated in numerous clinical trials from the 1980s through the present. It has been tested in kids and adults, in patients with both recent and long-standing disease, and in individuals with many different complications of **inflammatory bowel disease (IBD)**. Like all treatments for Crohn's, it doesn't work for everyone. But when it does, here are some of the things it can do:

- Enteral nutrition can induce remission in people with active Crohn's disease in as little as two weeks.
- Enteral nutrition can succeed in people who don't respond to steroids and those who can't discontinue steroids without relapsing.
- Enteral nutrition can restore normal growth patterns in kids who have stopped growing because of Crohn's.

- Enteral nutrition can promote healing in diseased areas of the intestinal tract.
- Enteral nutrition can do these things with almost no side effects.

## **So why haven't I heard about enteral nutrition?**

Well, there is one disadvantage to enteral nutrition. If you want to use it to get into remission from Crohn's (as opposed to taking it simply to maintain remission or gain weight), you can't eat or drink anything except the liquid formula for approximately two to eight weeks. You won't starve—the formula fills you up and provides all of your nutritional needs—but you do have to be willing to give up your regular diet temporarily.

Gastroenterologists in United States rarely mention enteral nutrition as a treatment option because they think it is too difficult to ask patients to give up normal food for a while. You are more likely to have heard about enteral nutrition if you live in Canada, Europe, Japan, or Israel. Doctors in these regions tend to have more experience using enteral nutrition for Crohn's, and are more likely to be aware of its benefits.<sup>1</sup> The Japanese, for instance, use enteral nutrition as a primary therapy for active Crohn's disease and prefer it to steroids.<sup>2</sup> In the United Kingdom, a survey of the members of the British Society of Gastroenterology found that 59% of the specialists who responded had prescribed enteral nutrition for their patients with Crohn's.<sup>3</sup> But in most countries, enteral nutrition is not used as often as it might be. If doctors consider prescribing it at all, they tend to offer it primarily to children because of its beneficial effects on growth, and rarely mention it as a treatment possibility to their older patients.

In part, this useful option may be overlooked because it's just too simple in a modern medical world that focuses on the complex. It's not a hot new treatment; it's been around for a long time,

and many of us—doctors included—tend to look for the newest high-tech solution. To be honest, it's also much easier for a patient to take a medication every day than to comply with a liquid diet. Doctors realize this, and want to prescribe the treatment that is easiest for the patient. There are a fair number of drugs available to treat Crohn's disease, and they can be very effective for many individuals. So why not use them?

The trouble is that the medications don't work for everyone, and even when they do, can have unpleasant side effects. They can also lose their beneficial effects over time. That means that patients with Crohn's disease need to know about *all* their treatment options, just in case the simplest and most convenient methods fail. Enteral nutrition isn't appealing to everyone and doesn't work for everyone. Nevertheless, it is important for patients to know that it exists. That's why I wrote this book.

## What will I learn?

- In this chapter, we will learn what enteral nutrition is, who developed enteral nutrition and why (hint: NASA was interested!), and explore some of the hypotheses on why it works.
- In Chapter 2, we will look at the pluses and minuses of the drugs most commonly used to treat Crohn's disease, and explore why and when you might want to consider using enteral nutrition instead.
- In Chapter 3, we will discover the benefits of enteral nutrition in children with Crohn's.
- In Chapter 4, we will explore the advantages of enteral nutrition for adults, including its use during pregnancy.
- In Chapter 5, we will review the use of enteral nutrition for specific complications of Crohn's disease, such as perianal disease, fistulas, and strictures.

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- In Chapter 6, we will examine whether enteral nutrition is useful in ulcerative colitis, indeterminate colitis, irritable bowel syndrome (IBS), and celiac disease.
- In Chapter 7, we will learn about the different types of enteral nutrition, and find out how each of us can choose a formula that is right for us.
- In Chapter 8, we will get the scoop on how to get started and what to expect during a course of enteral nutrition.
- In Chapter 9, we will examine whether people with Crohn's can benefit from other dietary regimens and supplements such as fish oil, probiotics, and low- or high-fiber diets.

### **Understanding enteral nutrition**

“Enteral nutrition” is not a phrase that's in most people's vocabulary, so before looking at what enteral nutrition does and how it can help you, let's take the time to better understand what it is.

Broadly speaking, enteral nutrition refers to any form of food or beverage delivered directly to the gastrointestinal tract, whether it is chewed and swallowed like normal food, or delivered through a tube directly into the stomach or intestines. Believe it or not, if you ate a sandwich and an apple and a soft drink for lunch, you were consuming enteral nutrition!

But when the term “enteral nutrition” is used in a medical context, it has a more specific meaning. In that case, it refers to special liquid diets used to feed patients who are too sick to eat regular food, or who would benefit medically from replacing normal food with a liquid formula, even if they can eat without difficulty. The formulas are supplied either as powders ready to be mixed with water, or already premixed (in liquid form). They provide all the nutrients that you would otherwise obtain from a varied diet.

There are many different enteral nutrition formulas to choose from, but they are usually divided into three main categories—**elemental**, **semi-elemental**, and **polymeric**—based on the form of protein they provide.

- Elemental formulas contain amino acids, the most basic (“elemental”) building blocks of protein.
- Semi-elemental formulas contain small peptides (amino acids linked together into short chains), or a mixture of small peptides and amino acids.
- Polymeric formulas contain whole protein (made up of long chains of peptides).

We’ll learn more about the differences between the types of formulas in Chapter 7. But for now, all you need to remember is that elemental, semi-elemental, and polymeric formulas are all considered enteral nutrition, and they all work equally well in people with Crohn’s.

## A (very) brief history of enteral nutrition

Special types of liquids have been used for centuries to feed people who are ill and can’t manage normal food. If you were tending a bedridden child or parent a few hundred years ago, you might have given them wine or brandy, or milk or eggs, or broth made from chicken or grain.<sup>4</sup> By the nineteenth century, doctors had even figured out how to use rubber tubing to get liquids straight to the stomach or intestines.<sup>5</sup> But the trouble was that none of these liquids were nutritionally complete. They weren’t suitable for long-term use for patients who couldn’t eat any other food because they didn’t provide all the protein, fat, carbohydrates, vitamins, and minerals that a person needs on a day-to-day basis to stay alive.

The first extended experiments with enteral nutrition formulas that could supply all the nutrients required for human life began in the 1950s. A series of studies performed at the U.S. National Institutes of Health (NIH) and published in 1957 showed that rats could grow, thrive, and reproduce when consuming nothing except amino acid-based elemental diets.<sup>6</sup> The first reports of tests in human patients were published in the 1960s.<sup>7</sup> A key question was whether enteral nutrition formulas could really totally replace all other food for extended periods of time. That question was answered affirmatively in 1964, thanks to prisoners at a California jail who volunteered for a study. Fifteen men received no food except an elemental diet for five months, yet maintained normal weight and nutritional status.<sup>8</sup>

Believe it or not, some of the early research into enteral nutrition was supported by the U.S. National Aeronautics and Space Administration (NASA).<sup>9</sup> With the goal of sending men into outer space for days at a time, NASA had to figure out how to feed its astronauts. After all, you couldn't just send them to the nearest supermarket to refuel. A food suitable for astronauts needed to have certain characteristics. It had to have a long shelf life and be compact to store. Ideally, it would also be low-residue—that is, mostly absorbed by the body so that little remains to be excreted—to minimize the problem of disposing of human feces in space. An elemental diet seemed to be a winner on all counts. A single cubic foot of the powdered formula, when dissolved in water, could feed a 154-pound astronaut for a month, providing a nutritionally complete, low-residue regimen of 2,830 calories per day.<sup>10</sup> Because of NASA's interest in elemental diets, early publications about enteral nutrition formulas sometimes refer to them as “space diets” or “aerospace diets” or even “astronauts' diets.”<sup>11</sup>

From a medical standpoint, enteral nutrition formulas were developed to provide nutritional support to any hospitalized patients who couldn't eat solid food. But doctors soon realized that these

products might be particularly useful for individuals with digestive conditions that interfered with normal food absorption.<sup>12</sup> Enteral nutrition formulas have been used in patients with Crohn's disease since at least 1969.<sup>13</sup>

The big surprise was that patients with Crohn's not only improved nutritionally on enteral nutrition, but sometimes even went into remission or no longer needed scheduled surgery after being on one of these liquid diets.<sup>14</sup> The unexpected findings prompted researchers to conduct randomized, controlled clinical trials to establish whether enteral nutrition was a valid treatment for Crohn's disease. Those trials, along with other clinical studies and case reports discussed in the following chapters of this book, revealed the following:

- **Total enteral nutrition** (that is, not eating any food except an enteral nutrition formula for given period of time) can be as effective as steroids such as prednisone or prednisolone in inducing remission in children with Crohn's.
- It may not be quite as effective as steroids in adults with Crohn's, but still induces remission in some 50% or more of adults who are willing to comply with the treatment.
- Patients who relapse whenever their dose of steroids is lowered or withdrawn may be able to discontinue steroids with the help of total enteral nutrition.
- Total enteral nutrition can induce remission in some people who do not respond to steroids.

Fortunately for those who don't want to give up regular food, even temporarily, the studies also show that:

- **Supplemental enteral nutrition** (using an enteral nutrition formula to supply a portion of one's daily calories while continuing to eat a normal diet) can help people with Crohn's disease stay in remission longer.



- It can help malnourished patients gain weight and reverse nutritional deficiencies.
- It can restart growth in children with delayed growth due to IBD.
- It can help some people discontinue steroids.

Does enteral nutrition cure Crohn's? No. Unfortunately, nothing does. Some people who have mild disease may be lucky enough to only have a few flares, and then remain in remission for many years. But that doesn't mean that the disease is gone; once someone has Crohn's, he or she has it for life. That's why it's considered a chronic disease.

Enteral nutrition is one way to manage this particular chronic condition. It is very useful in helping many people with Crohn's achieve remission. There is no guarantee that it will work for you. Like all the different drugs used to treat Crohn's disease, it is effective in some people and not in others. There are also no guarantees as to how long remission will last; that varies from person to person. Some people are lucky and have a one- or two-year remission after a course of total enteral nutrition. Others are unlucky and relapse in a month. But enteral nutrition can be used more than once. Many people who find it effective return to it when they relapse, and then go back to regular food once they are in remission. Others don't want to try total enteral nutrition, but use enteral nutrition supplements to help stay in remission, prevent weight loss, or for kids, improve growth.

## Is this the same thing as TPN?

If you have had Crohn's disease for a while, you may have heard of, or used, **total parenteral nutrition**, called **TPN** for short. Parenteral and enteral nutrition are both ways of feeding people, but they are not exactly the same thing.

- Parenteral nutrition is liquid food given intravenously—straight into the bloodstream—through a catheter (slender tube) inserted into a vein.
- Enteral nutrition is liquid food that is drunk by mouth or delivered by a tube directly to the stomach or the intestines.

Going on total parenteral nutrition, or TPN, means receiving only intravenous feeding and no regular food, just as using total enteral nutrition means consuming no food except an enteral nutrition formula.

Both TPN and total enteral nutrition can induce remission and reverse malnutrition in patients with Crohn's. However, doctors tend to prescribe TPN rather than total enteral nutrition for seriously ill patients. They assume that enteral nutrition is less effective or impossible to tolerate in patients who are reluctant to eat. Or they may consider it less sophisticated, less high-tech, and therefore less valuable.<sup>15</sup> But total enteral nutrition is just as effective as TPN in most people with Crohn's, including those who are ill enough to need hospitalization. Six different studies, including a total of 293 patients with Crohn's, compared TPN with enteral nutrition. Uniformly those studies found that total parenteral and total enteral nutrition (whether with elemental, semi-elemental, or polymeric formulas) were *equally effective* in producing remission.<sup>16</sup>

They're not equal when it comes to safety, however. In that realm, enteral nutrition is the big winner. With enteral feeding the food goes directly into the intestinal tract rather than into the blood. That allows you, the patient, to avoid the risk of dangerous complications like blood clots and septicemia (overwhelming infection) that are associated with intravenous feeding.<sup>17</sup> Additionally, long-term TPN use can harm the liver, while any liver function abnormalities that occur during enteral nutrition tend to be mild and transient.<sup>18</sup>

❖ **As long as your intestines are functioning even in part, total enteral nutrition works just as well as TPN, without the safety worries of parenteral nutrition.**<sup>19</sup>

That's why this book focuses on enteral feeding. But we'll talk more about the choice between TPN and enteral nutrition in Chapter 8, and look at the special situations in which you might need TPN.

## Why does enteral nutrition work?

The short answer: nobody knows. There have been numerous attempts to find out, but the answer is still not clear. For those who are curious, here are some of the theories.

### Beating the bacteria

One speculation is that enteral nutrition formulas work because they reduce the number of bacteria living in the intestinal tract. Or perhaps they change the balance of bacteria, favoring species that help the intestines stay healthy. In fact, an early study found a dramatic decrease in the number of bacteria in the feces of healthy folks given an elemental diet.<sup>20</sup> Yet later studies found just the opposite: total enteral nutrition had little effect on the number and types of bacteria in stool.<sup>21</sup>

Nevertheless, the intestinal bacteria hypothesis hasn't been abandoned completely. A recent investigation found that the range of bacterial species in feces changed considerably as children treated with total enteral nutrition passed from active disease to remission. In contrast, an untreated control group of healthy children had stable patterns of fecal bacteria.<sup>22</sup> However, this small study is far from the last word in the matter. Is total enteral nutrition effective *because* it alters the bacterial balance, or do fecal bacterial patterns change

as a side effect of going into remission, regardless of the way in which remission is achieved? We don't know.

### **Giving the gut a rest**

Another theory is that giving the intestinal tract a chance to rest and heal might be one of the keys to the success of enteral nutrition. Since most of the formulas typically used in people with Crohn's are fiber-free, the colon doesn't have to ferment as much food residue and the amount of stool produced is greatly reduced.<sup>23</sup> But if it's resting the gut that makes the difference, why isn't TPN more effective than total enteral nutrition? After all, delivering food straight to the bloodstream bypasses the intestinal tract far more completely than a liquid diet.

### **Keeping out foreign proteins**

Another potential explanation rests on the theory that some of the damage caused by Crohn's could be due to proteins from food passing through the ulcerated intestinal wall and setting off an inflammatory immunological reaction, with the body producing antibodies to defend against the "foreign" invaders (i.e., the many different types of protein in our diet). Perhaps elemental diets work because they only contain amino acids, and the body isn't exposed to all of those foreign proteins?<sup>24</sup> Or perhaps not. It turns out that people with Crohn's improve on enteral nutrition formulas that contain peptides or even whole protein. Semi-elemental and polymeric formulas work just as well as the amino-acid-based elementals.<sup>25</sup> Reducing the load of whole protein delivered to the gut might not be so important after all.

But this hypothesis hasn't been discarded entirely. When you consume an enteral nutrition formula as your only food for days at

a time, your digestive tract is exposed to vastly fewer types of protein than when you are eating a normal varied diet, even if you are using a polymeric (whole protein) formula.<sup>26</sup> It's possible that the reduction in exposure to food proteins plays a part in the efficacy of enteral nutrition.

## Reversing malnutrition

It is equally plausible that the beneficial effect of enteral nutrition is due largely to the nutritional support that it provides. There is no question that enteral nutrition formulas are exceedingly effective in reversing the weight loss and nutritional deficiencies that are so common in those with Crohn's. Just getting back to a healthy weight can make a big difference in managing gastrointestinal diseases. Even in people without autoimmune diseases like IBD, malnutrition can affect the way in which the immune system functions, causing impairments that can be reversed by restoring normal nutritional status.<sup>27</sup>

Yet there are problems with attributing all the benefits of enteral formulas to the nutritional supplementation that they offer. Consider these two intriguing findings:

- The average growth rate in children who received intermittent treatment with total enteral nutrition increased from 1" to 3 $\frac{2}{3}$ " per year, even though they didn't consume any more calories during the year of intermittent enteral nutrition than during an observation year that preceded it.<sup>28</sup>
- Total enteral nutrition can reduce disease activity and inflammation in patients who begin treatment with *normal* nutritional status, implying that better nutrition is not the decisive factor in their improvement.<sup>29</sup>

Furthermore, if enteral nutrition works primarily because it reverses malnutrition, then why isn't a normal nutrient-rich diet as effective as enteral nutrition in jumpstarting growth and inducing remission?

## Reducing inflammation

The answer seems to be that enteral nutrition has an anti-inflammatory effect, although *how* it exerts that effect is unknown. The effect on inflammation was demonstrated clearly in a study of children with active Crohn's disease who were treated with total enteral nutrition. Within three days of starting treatment, the children showed a significant decrease (improvement) in **erythrocyte sedimentation rate (ESR)**, a blood test commonly used to measure inflammation in patients with Crohn's disease. Within seven days of starting the formula, **C-reactive protein**, another marker of inflammation, had decreased significantly, too.

In contrast, measures of nutritional status did not begin to improve significantly until the children had received enteral nutrition for two weeks or more.<sup>30</sup> In short, inflammation decreased *first*, and nutritional improvement *followed*, perhaps made possible by the reduction in inflammation.

A study in adults also found that most patients experienced decreased inflammation before any nutritional changes were apparent.<sup>31</sup>

There are other signals that total enteral nutrition is effective in reducing inflammation.

- Total enteral nutrition can reduce the production of cytokines (small proteins produced by cells of the immune system) that cause inflammation, such as tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ .<sup>32</sup>

- It can normalize levels of another protein, orosomucoid, that may be elevated when inflammation or tissue damage is present.<sup>33</sup>
- Endoscopies and x-rays performed before and after enteral nutrition treatment have shown improvement, and in some cases even complete healing, of diseased areas of the intestines. Biopsies have shown improvement on a microscopic level.<sup>34</sup>
- Scintigraphic scans, which track the movement of white blood cells to inflamed areas, have shown marked improvement in small and large intestinal inflammation in patients who responded to treatment with total enteral nutrition.<sup>35</sup>

The reduction in inflammation is probably responsible for a number of other changes that take place when total enteral nutrition is used. For instance:

- Total enteral nutrition can reverse, often completely, abnormal intestinal permeability that frequently accompanies active Crohn's disease.<sup>36</sup>
- Total enteral nutrition can reverse severe protein loss that often occurs during a flare of Crohn's.<sup>37</sup> It reduces the breakdown of protein on the one hand and increases the synthesis of new protein on the other.<sup>38</sup>
- Total enteral nutrition can speed up, and in some cases even completely normalize, intestinal transit time (which can be far slower in patients with active Crohn's disease than in healthy people).<sup>39</sup>
- Total enteral nutrition can improve the reabsorption of bile acid (important to the digestion of fats), reducing bile acid-induced diarrhea.<sup>40</sup>
- Total enteral nutrition can increase the production of insulin-like growth factor, a protein that stimulates growth, in children with Crohn's.<sup>41</sup>

Although it's likely that all of these benefits are secondary to the anti-inflammatory effect of enteral nutrition, we are still left with the basic question, why are these formulas anti-inflammatory at all? Possibly changes in the foods passing through the gut or the effects of those foods on the bacterial content of the intestines can affect the way in which genes are expressed in the outermost layer of tissue (**epithelium**) that lines the intestines. In turn, these changes could affect the way in which the immune system functions in the epithelium.<sup>42</sup> But this is only speculation. We've been using enteral nutrition in Crohn's disease for 40 years, and we still don't know exactly why it works! Still, what matters most is that it does work. In the following chapters we'll look at the studies that prove it.

## WHAT HAVE WE LEARNED?

- ❖ The term “enteral nutrition” is used to describe special liquid diets used for medical reasons instead of, or in addition to, regular food. Enteral nutrition formulas are categorized into three main types—elemental, semi-elemental, and polymeric—based on the form of protein they contain. All three types work equally well for people with Crohn's.
- ❖ Using total enteral nutrition involves eating and drinking nothing except an enteral nutrition formula for a certain period of time. Total enteral nutrition can induce remission in people with Crohn's, heal intestinal inflammation and ulcerations, and offer an alternative to steroids.
- ❖ Using supplemental enteral nutrition involves getting a portion of one's daily calories from an enteral nutrition formula while continuing to eat a normal diet. Supplemental enteral nutrition is an effective maintenance therapy for Crohn's, improves growth in kids with Crohn's, and is a good way to gain weight and reverse nutritional deficiencies.



- ❖ Enteral nutrition has an anti-inflammatory effect in the gastrointestinal tract and can reverse abnormal intestinal permeability. It reduces protein breakdown and increases the synthesis of new protein, and can normalize intestinal transit time in people with Crohn's.

Most of the remaining chapters of this book explore enteral nutrition in more detail. But first, in Chapter 2, we'll take a look at the other treatments available for Crohn's and assess why and when you might choose enteral nutrition instead.