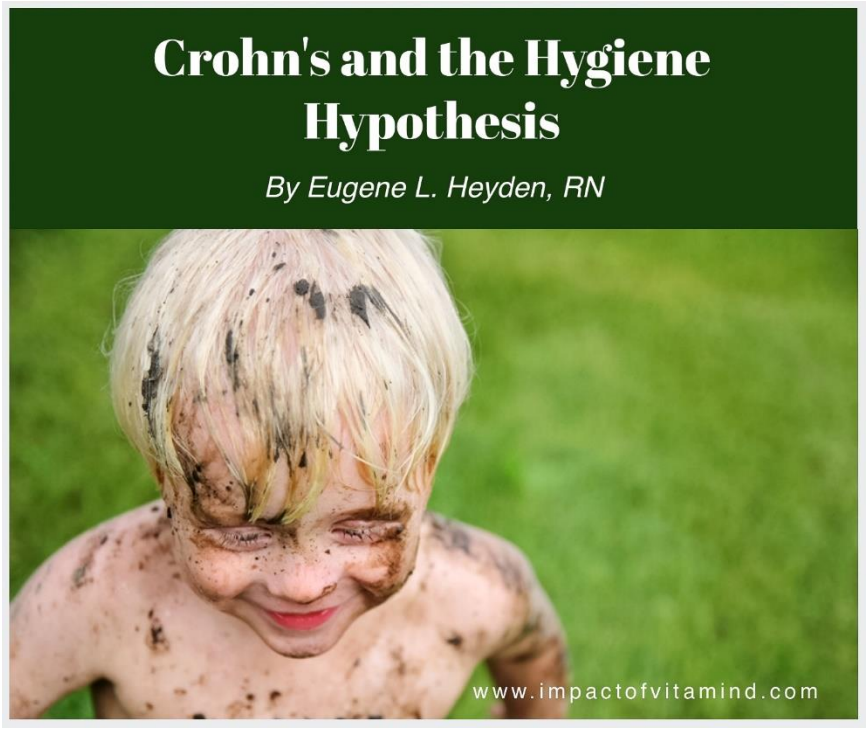

Crohn's and the Hygiene Hypothesis

By Eugene L. Heyden, RN

This kid is doing things right—out in the sun and making lots of vitamin D. And he's dirty, too. How nice! You think he is playing. He is, but he is doing something else. He is preventing Crohn's disease. Yes, vitamin D helps prevent Crohn's disease. And, surprise surprise, so does dirt. There are organisms in dirt—especially bacteria—that help teach his immune system to defend against evil. They may even establish colonies that will play a role in bowel health, perhaps for a lifetime. Think of dirt as a probiotic. It is teaming with organisms; we might as well give them a good home.

Here we will discuss what is called The Hygiene Hypothesis, and it is a big deal in the research literature. It helps explain why one of the most advanced nations on earth has so many chronic, immune system-related

diseases, Crohn's included. We are not the same people we were a generation or so ago. We are cleaner. We should be dirtier. We hide from the sun.

I'll talk more about vitamin D and its role in the prevention of Crohn's in another post. But now, let's take a look at the role dirt and dirty things (like worms) play in protecting us from Crohn's. Crohn's is dreadful. We should prevent it.

Let's get started. Fasten your seat belt; this will be quite a ride.

(Excerpt from ***More to Consider in the Battle against Crohn's***)

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"Yes, we have a worm for that!"

Improved hygiene is believed to result in a limited exposure to micro-organisms. Such exposure is thought to be necessary in programming the immune system of the gut and mitigating its future inflammatory responses, perhaps even resulting in CD [Crohn's disease] when the immune system is challenged. The underlying premise is that early childhood infection helps to establish the immunological balance between pro-inflammatory Th1 and tolerance-inducing regulatory T cells, preventing the subsequent untoward responses to allergens, microbial or other antigenic stimuli. Thus various childhood circumstances such as day care attendance, presence of siblings, and domestic hygiene-related factors can influence the probability of contracting a "viral infection" at a vulnerable time in immunological development. **~Koloski et al., 2008**

Children and adults from developing countries are often infested with helminthic organisms like ascariasis and hookworms. Helminths promote T_H2 responses and blunt T_H1 responses. Exposure to Schistosoma mansoni protects rats from development of IBD. With improved sanitation, helminths have disappeared in developed countries. This disappearance of helminths coincided in time with the emergence of IBD. **~Desai and Gupte, 2005**

Perhaps the most sticking glimpse of the important alliance between mankind and "infectious agents" is the demonstration that the feeding of pig pinworm (Trichuris suis) ova to patients with Crohn's disease results in striking improvement in disease activity. **~Epstein, 2005**

This chapter is based on what is called the *Hygiene Hypothesis*, a theory that helps explain some very intriguing observations related to the pathogenesis of both Crohn's disease and ulcerative colitis. The *Hygiene Hypothesis* is not a silly notion, trivial, or an insignificant train of thought; it is a *big deal* in the research literature. I'm not sure you're ready for this chapter (you're not), but it is time we had this little talk. This will be a most unusual chapter. *Most* unusual.

The *Hygiene Hypothesis* basically states: "If a cookie falls on the floor, of course you pick it up and eat it. Or better yet, you give it to an infant or to a child—and there is no 10-second rule!" Yes, my friend, we can now fight the battle against Crohn's with dirty cookies. Apparently, with dirty cookies, dirty houses, dirty children of dirty working parents, dirty siblings—**dirty everything!**—we can fight the good fight and gain an edge in our battle against this disease. And we all know what dirt means; dirt means automatic exposure to bacteria and other little creatures that roam the earth. *Our immune system learns from this stuff!* (If we survive.) On the other hand, according to the hypothesis, living a clean life is like totally problematic. With limited exposure to pathogenic threats or limited exposure to a wide variety of bacteria, both good and bad, particularly during childhood, our immune system—particularly in the gut—simply lacks the training it will need to defend effectively and do so in an orderly fashion. Even the resolution of inflammation may be impaired for this very same reason (just a guess). Next time you see a clean little infant or child, try not to stare, and try not to shed a tear.

The *Hygiene Hypothesis* helps explain why early childhood infections are protective against Crohn's. It explains why being from a large family living in crowded quarters is protective against Crohn's. It explains why having a pet dog, even a fake pet dog (stuffed animal), is protective

against Crohn's. It also explains why routinely visiting an outhouse is protective against Crohn's. (You didn't do this, did you?) It even explains why antibiotic use can be a set-up for contracting Crohn's at a later period in life—antibiotics effectively reduce the bacterial diversity in the gut, a diversity one relies upon to crowd out bacteria that are evil. It explains so much! It even explains why, once we began to succeed in our quest to rid the world of parasitic worm infestations in various populations, Crohn's disease began to emerge from out of nowhere and begin the ambitious task of conquering the world. So it should come as no surprise, in the crazy world that you live in, that worms are making a comeback. And we're in luck! There are somewhere between 18,000 and 24,000 different species of parasitic worms from which to choose (Nava-Castro et al., 2011).

Behold the helminth!

The "IBD hygiene hypothesis" states that raising children in extremely hygienic environments negatively affects immune development, which predisposes them to immunological diseases like IBD later in life. Modern day absence of exposure to helminths appears to be an important environmental factor contributing to the development of these diseases. **~Weinstock and Elliott, 2009**

Helminths are thought to play an important immunoregulatory role in the intestinal flora and as such have been linked to the development of IBD. Firstly helminthic infection is associated with a strong Th2 response, which opposes the Th1 response associated with autoimmune disease and CD [Crohn's disease]. Secondly, chronic infection with these organisms may generate a network of regulatory T (Treg) cells that secrete transforming growth factor (TGF)-B and interleukin (IL)-10. **~Koloski et al., 2008**

Loss of natural helminth exposure removes a previously universal Th2 and regulatory immune biasing imparted by these organisms. Helminths protect animals from developing immune-mediated diseases (colitis, reactive airway disease, encephalitis and diabetes). Clinical trials show

that exposure to helminths can reduce disease activity in patients with ulcerative colitis and Crohn's disease. **~Elliott et al., 2007**

Let's face it, you were way better off when you had a good case of worms—pin worms, hook worms, even tape worms! But no, you had to go and rid yourself of these pests and become one of them there modern, sophisticated-type human beings—**big mistake!** This category of creatures, known collectively as helminths, played an important role in shaping and regulating our immune responses over the millennia. In fact, not only were they protective against Crohn's (and ulcerative colitis), they were protective against several immune system diseases including asthma, type 1 diabetes, and multiple sclerosis (Elliott et al., 2007). It is clear that having worms (or being wormless) determines who you are, at least from immunological standpoint. And there is hope.

In this modern day and age, you can, if so motivated, infect yourself with worms (you are scaring me!). People actually do this, and their Crohn's disease goes into remission. So how does all this work? Better yet, what can we learn from this . . . so we don't have to do this?

A good worm infection, one that you can be proud of, can be easily acquired in the following manner: Go to a third world country, walk barefoot in contaminated soil, let the worm burrow under the skin between your toes, and enjoy what's up next (besides the intense itching). What's up next? The worm **1)** wiggles and chews its way through the tissues and enters the bloodstream; **2)** migrates to the trachea (your trachea), all the while laying eggs at every stop along the way, lots of eggs; **3)** climbs out of the bloodstream and into the lumen of the trachea; and **4)** crawls around a little, then tunnels through the tracheal wall, slipping smack dab right into the esophagus (your esophagus) where it is subsequently swallowed, as anticipated (by the worm), in order find a home in the gut, your gut. There is no place like home, and the helminth has finally arrived. It sucks up to its new host, you, and drinks your blood. (see Prichard, 2009, for review) Any part of this sound like fun to you? Of interest, and associated with a good worm infection, one that you can be proud of, a million or more worm eggs will

be produced **per day!** (Bundy et al., 2000) Your immune system will be very busy dealing with all the new little hatchlings. You should consider selling at least some of them—have you seen the price of worms these days?

The question is, of course, "How does this worm business protect me from IBD?" The answer is simple, yet so *extremely* complex. Simply put, *"The worm changes you!"* You are modified, and manipulated, by the likes of a little ol' worm! The helminth is a *"master"* at modifying your immune responses so that it gets to live, and it gets to make babies—and it does so in a manner that surprisingly benefits you, the gracious host (Moreau and Chauvin, 2010). How nice! It really is a sweet little story of the length that a loving worm will go to in order to provide the ideal home for itself and for its dear family. But it is still all about you. The worm will modify your immune system in a manner that protects you from a variety of immune system disorders. That being said, it is still all about them. They will render you ineffectual at expelling them—actually hundreds if not thousands of "thems"—that now call you "home sweet home." Providing a suitable home to a family of worms simply underscores what a nice person you have become. But none of this has really happened. Your wormlessness has led you down the path of disease and destruction.

Let's take a look at what the helminth actually does to help an individual in a manner that is pleasing. Preventing Crohn's is pleasing. Placing the Crohn's patient in remission is pleasing, too. I will lay out the most interesting and the most relevant data that I have been able to find on the subject, as follows:

- Helminths broadly alter the balance between the Th1-type cytokines and the Th2-type cytokines, shifting the dynamic toward the Th2 arm of the inflammatory response (Koloski et al., 2008). Recall that the Th1 response is dominant and way out of hand in Crohn's, and the Th2 response presents features such as increased IL-10 and TGF-β production, which help resolve persistent inflammation and promote tissue repair.

- Helminths reduce iron stores. As they live in the gut, they acquire at least some iron from the host to meet their own needs, and subsequently create GI bleeding that leads to anemia in the host (Pritchard, 2009). Anemia or the threat thereof achieved in this manner, although sometimes problematic, not only significantly reduces iron stores but also reduces the availability of iron for acquisition by pathogenic bacteria (Hunter and McKay, 2004).

- Helminths increase goblet cell numbers and accelerate the production of mucus, the carpet of goo that entraps bacteria and sweeps them downstream (Hunter and McKay, 2004). Mucus is one of our vital layers of defense, and this layer of defense is strengthened in response to the helminth. Increased mucus production is actually a defensive strategy directed against the parasite. Accordingly, *"High levels of mucus production trap parasites in the lumen and minimize their ability to anchor in the gut."* (Maizels and Holland, 1998)

- Helminths increase the production of broad-spectrum antibacterial peptides like IgA. IgA spells death to pathogenic bacteria (Hunter and McKay, 2004; Macpherson et al., 2005); hence, the helminth will help you kill others—oh yes, you can be the killer you were always meant to be. The increase in IgA production in the gut is for good reason: it can help keep helminth numbers in check. It attacks the worm in such a way as to interfere with its ability to feed (Moreau and Chauvin, 2010). You are indeed gracious, but you *do* have your limits.

- Helminths accelerate epithelial cell turnover (Allen and Maizels, 2011). Cell turnover frequency, as discussed in *Chapter 3*, is yet another layer of defense. When an infected intestinal cell dies and detaches, it's goodbye mister pathogen! The bacteria that may be adherent to its surface or living inside find it most

difficult to colonize and invade under these circumstances and are swept away in all the madness (Vossenkämer et al., 2011).

- Helminth exposure first elicits a strong Th1 response by the host that lasts approximately 5 weeks (a response thought to be of help in establishing the worm colony) followed by a strong Th2 response by the host that acts to control helminth numbers and to continuously repair the ongoing damage that occurs (Dunne and Cooke, 2005). You have not exactly given up the fight; you are limiting worm numbers as best you can. All the while you are fighting against the continual damage being inflicted by the wascally worm—could come in handy if your gut is continually in need of repair, even apart from the damage caused by the helminth itself. Intriguingly, the intestinal macrophage is also modified during a helminth infection, and modified in a manner so that it, too, becomes actively involved in tissue remodeling and repair (Reyes and Terrazas, 2007).

- Helminths apparently alter the mix of bacteria that populate the bowel, perhaps selecting a more favorable composition for the host and thereby restraining the colonization of pathogenic bacteria (Hunter and McKay, 2004).

(I have to end this summary now—I seem to have run out of those big black dots.)

From the above, one can easily see why a helminth infestation could be pressed into service in the battle against Crohn's—who needs a handful of dirty cookies anyway? Besides, helminths were protecting us against IBD way before the cookie was invented. Perhaps it is the reduction of iron stores that keeps pathogenic bacteria from establishing a toehold that makes the helminth particularly effective in preventing and treating Crohn's. Perhaps it is the ongoing repair of the tissue injury caused by the helminth that

makes the parasite *so very effective* in promoting remission in Crohn's disease. Perhaps it is the river of mucus—jam-packed full of IgA—that traps and kills pathogenic bacteria and prevents their colonization that makes me want to rush out and acquire a good case of worms, one that I can be proud of. Or, perhaps it is the accelerated epithelial cell turnover that protects and helps resolve the inflammation we see in Crohn's that makes the helminth such a tantalizing option to employ in the treatment of this disease. Perhaps it is all of the above, and no single factor that makes the helminth the ideal weapon in the battle against Crohn's. But can we accomplish all of this without actually having to look a worm square in the eyes moments before we swallow it . . . whole? Can we fake a worm infection? The answer is yes!

Previously, we discussed iron withholding as a strategy of war. Perhaps serious attention to the strategy of iron withholding could keep us from doing the unthinkable (actually swallowing the damn worm). I have mentioned vitamin A previously. Perhaps vitamin A could be put to use to increase goblet cell numbers and accelerate mucus production (Skogh et al., 1980)—even increase the production of killer IgA (Coombes and Powrie, 2008)—rendering a worm infestation completely unnecessary? Are you getting the picture? Instead of swallowing a worm, you could put into practice, under physician guidance, at least some of the complementary treatments and strategies that we have discussed thus far. In your quest for healing, you could again read the chapter entitled *Diet for success* and learn an easy method to increase IL-10 and TGF-β levels in the bowel. You don't need a worm for that! For this you need casein, and for this you need colostrum. As far as shifting the Th1 response toward a Th2 response, that's easy, too—no worms required! **Progesterone** may be what you are looking for.

Yes, there are hormones that shift the balance between Th1 and Th2, and in this regard there is nothing quite like progesterone. Intriguingly, and most surprisingly, this hormone is uniquely involved in the *Hygiene Hypothesis*. Progesterone will be the central topic of

an upcoming chapter, but we can talk about it now. **IT CAN CHANGE WHO YOU ARE!** Like the helminth, it can forcibly shift the Th balance away from the Th1 response and toward the Th2 response, certainly in females but also in males!—progesterone is, after all, an active hormone in men as well as in women. Indeed, progesterone has been prescribed for men for a variety of reasons, with minimal, if any, side effects (Goletiani et al., 2007). I take progesterone myself! Progesterone is a *master* at restraining NF-κB activation and inhibiting TNF-α production—could come in handy in the battle against Crohn's.

Progesterone, inflammation, and Th1/Th2 balance

> *Although fluctuation in hormone levels may be regarded primarily as physiological, these hormones also have profound effects on cells associated with the immune system.*
>
> *The general consensus is that progesterone is generally anti-inflammatory, inhibiting the development of a type 1 response while promoting a Th2 response.* **~Roberts et al., 2001, emphasis added**
>
> ***Typically, increased concentrations of progesterone down-regulate immune cell functions, whereas reduced progesterone concentrations up-regulate them.*** **~Vargas-Villavicencio et al., 2005, emphasis added**
>
> *Progesterone is able to increase the synthesis of Th2-related cytokines such as IL-4 and IL-13, diminishing concomitantely the Th1 immune response mainly characterized by IL-12 and INF-γ expression.* **~Escobedo et al., 2011**
>
> *Estrogen acts as an immune enhancer, particularly in regard to humoral immunity and the proliferation of macrophages, whereas progesterone acts as an immune suppressor.* **~Molodecky and Kaplan, 2010, emphasis added**
>
> *In summary, the results of our study demonstrate that P4 [**progesterone] is a potent inhibitor of macrophage TNF-α gene***

> ***activity and TNF-α protein production.*** *This P4-mediated suppressive effect on TNF-α production lends support to the concept that female sex steroid hormones such as P4 are capable of* **profoundly altering** *the outcome of an immune response by regulating macrophage activation and production of inflammatory cytokines in tissues proximal to the production of P4.* **~Miller and Hunt, 1998*, emphasis added***

If you have read somewhere that the Th1/Th2 paradigm is no longer considered valid (Rook, 2008), apparently not everyone is in agreement. This long-held view of the immune system, while it is "training wheels" in a sense—as everything here is so complex and puzzling, sometimes contradictory—it is still a very useful way of looking at the overall nature of our immune response. It will probably be used forever. So I, too, boldly and without hesitation, will espouse this view of our immune response as I talk of progesterone and other hormonal influences on the immune system.

Progesterone, like the helminth, can clearly have an impact on the Th1/Th2 balance. That's its job! Let's see what this progesterone business is all about . . . starting with me and starting with you.

Boy, do I love *this* hormone! I would not be here without progesterone. You would not be here without progesterone. It is progesterone that *Mom* used to prevent an aggressive, lethal inflammatory response directed at me and directed to you, as we were this "foreign thing" that somehow took possession of her body. She apparently loved us even before she knew we existed, and so she put progesterone to use so her immune system would not reject us. She was all into loving us, in addition to the other things she was all into (rather recently). After we began to exist, her use of progesterone profoundly downregulated the Th1 arm of her immune system so she could keep us with the hope that we would eventually grow out of diapers and not turn out to be a serial killer or a politician. And we know <u>for certain</u> that progesterone has systemic effects, as many Th1-type diseases—like MS, like rheumatoid arthritis—improve or resolve during pregnancy (Tate et al., 2008).

Progesterone, like the helminth, changes who you are! You are less immunoreactive when this hormone is in abundant supply (Vargas-Villavicencio et al., 2005). Progesterone during pregnancy even acts to kill the worm (presuming that you are infested), so that the worm will not take nutrients away from the one who is developing inside. Progesterone, in effect, takes the Th2 arm of the immune system to the next level, and does so in order to limit and rid *Mom* of her load of parasitic worms (Escobedo et al., 2011). Progesterone is actually toxic to the helminth (Escobedo et al., 2011). Toxic, of course, means it wants to kill. And there is something else that is out to kill the pesky little worm. You should get quite a kick out of this!

Apparently, during infection the helminth uses estrogen created by the host in order to help meet its growth needs as well as to help meet its reproductive needs (Escobedo et al., 2005; Nava-Castro et al., 2011). Estrogen is *so* easy to come by if you, the lucky worm, have infected a lady but more difficult to come by if you have infected a gentleman. So what does the helminth do? It does what the helminth is programmed to do. It alters the gentleman and turns his nuts into an estrogen factory! (Vargas-Villavicencio et al., 2005. Note: The investigators here were hesitant and, accordingly, did not actually use the word "nuts.") *This is so crazy!* The man becomes more like a woman! He is "feminized!" The sacred part of the man, at least one of the sacred parts, is altered in a manner that it—actually, they—produce excess estrogen and reduced amounts of testosterone in order to provide enough estrogen to satisfy the needs of the worm, perhaps not with all species of worms, but at least in some species of worms. In fact, testosterone levels are reduced by 95% in males with a particular type of worm infestation, with estrogen levels going through the roof! (Vargas-Villavicencio et al., 2005) Interestingly, testosterone administration will act to kill the helminth, just like progesterone administration will act to kill the helminth (Vargas-Villavicencio et al., 2005; Escobedo et al., 2011). But as much as I love testosterone, I would rather talk about progesterone. You will see why as we continue.

So what can we learn from all of this? What is this hormone business all about? And why should progesterone take center stage at this point in our present discussion? Pay close attention now! I don't want to waste my time here! *You need to get this!*

In general terms, progesterone is anti-inflammatory, if in adequate supply, promoting and intensifying the Th2 response (Roberts et al., 2001). In general terms, testosterone is proinflammatory, driving the Th1 response (Giltay et al., 2000). And, in general terms, estrogens are proinflammatory (Klein, 2004), also directing the inflammatory response toward the Th1 pattern of expression (Namazi, 2009). But all of this is context specific and hormone-level specific, with a particular hormone sometimes acting in an uncharacteristic fashion. What I am leading up to is this: The sex hormones, particularly progesterone, have a profound impact on the immune response, and not just during a helminth infection. Accordingly, the hormonal status of the Crohn's patient must be evaluated (my opinion), particularly with respect to progesterone. Later, we will go more in depth in the chapter devoted primarily to this hormone. But in order to get you used to thinking about the use of progesterone as a therapy for Crohn's, and thinking about the concept of individual hormonal balance, I will throw in few hundred quotations for your consideration:

> Progesterone is crucial for reproductive organ development and maintenance of pregnancy, and more recent studies have clearly shown its role as an important immune regulator. (Tait et al., 2008)

> The female sex steroid hormones estrogen and P4 [progesterone], exert both immunosuppressive and immuno-stimulatory effects on the complex process of macrophage activation, resulting in dramatic alterations in cell-mediated and cytokine effector functions. (Miller and Hunt, 1998)

Progesterone can have both stimulatory and suppressive effects on the immune system, but is typically regarded as immunosuppressive.

Progesterone suppresses innate immune responses including macrophage and NK [natural killer] cell activity as well as TNF-α signal transduction. (Klein, 2004)

In the case of innate immune response, P4 inhibits the activation of the nuclear factor kappa B (NFκB) and increases the expression of cytokine signaling (SOSC1) protein expression. (Cabrera-Muñzo et al., 2010)

Additionally, progesterone is able to increase the synthesis of Th2-related cytokines such as IL-4 and IL-13, diminishing concomitantly the Th-1-immune response mainly characterized by IL-12 and INF-γ expression.

It is clear that this hormone has the ability to influence the immune system by effecting cellular differentiation, cytokines and antibodies production, and effector cells activity. (Escobedo et al., 2011)

Several reports suggest that patterns of resistance and susceptibility to infections are closely linked to changes in progesterone concentrations during the estrous cycle.

Typically, <u>increased</u> concentrations of progesterone down-regulate immune cell functions, whereas <u>reduced</u> progesterone concentrations up-regulate them. (Vargas-Villavicencio et al., 2005, emphasis added)

Why do sex steroids affect immune responses? This is not well understood, but is likely that these hormones, which circulate throughout the body, alter immune responses by altering patterns of gene expression, mediated by binding of the receptor/hormone complexes to a specific DNA sequence. (Namazi, 2009)

Well, that's probably enough quotations for now (I could go on and on—really, I could). But perhaps by now you are beginning to get the idea that the hormonal status of the patient with Crohn's should not be ignored. Again, this is my opinion. I honestly do not know of any single agent that so favorably shifts the immune response away from the Th1 arm toward the Th2 arm as safely and as effectively as progesterone, possibly with the exception of a very good worm infection, one that you could be proud of. Well, I think we have learned enough about helminths (and hormones) for the time being. It's time to move things along.

Now suppose a helminth infection is just *not* for you, and the insect parts you are eating day in and day out, although surprisingly satisfying and loaded with nutrients, do not seem to be offering you any help in your battle against Crohn's. Oh yes, you do eat insects; you just don't know it. (Search Google, *Insect Parts in Processed Food.*) There are options, you know!

Why send in a worm when you can send in a germ?

Probiotics are live microorganisms that seem to promote gut health and regulate intestinal homeostasis. Different possible mechanisms of probiotic action have been proposed, including both suppression and stimulation of host immune responses. **~Pegnini et al., 2010**

Generally, probiotics increase the production of intestinal anti-inflammatory cytokines (such as IL-10 and TGF-β), while reducing the production of pro-inflammatory cytokines (e.g., TNF-α, interferon-γ, IL-8). **~Ewaschuk and Diekeman, 2006**

Several mechanisms have been proposed by which probiotics may exert their beneficial activity, including: (a) competitive exclusion of bacterial adherence or translocation, or both; (b) release of bacterocidin and lactic acid, which inhibit growth of pathogens; (c) production of butyric acid, which enhances the turnover of enterocytes; (d) antioxidant effects; (e) probiotic enhancement of barrier function by stimulation of mucus and

sIgA production; (f) an enhancement of macromolecular degradation by gut mucosa, which acts to reduce antigen load; (g) a suppression of immune cell proliferation; and (h) an inhibition of epithelial cell nuclear factor kappa B (NFκB) activation. **~Madsen, 2001**

Taking a probiotic is, in essence, an act of war! You are asking it (them) to invade and colonize the gut in order to crowd out other bacteria—particularly the bad ones—reducing their numbers by poisoning them or simply starving them to death. In the fog of war there is collateral damage, too. By taking a probiotic you could also be wiping out entire families of other "good" bacteria, although in the previous section, it seemed as though you were a very nice person—offering food and shelter to the homeless helminth. Now you want to poison and starve the enemy to death! *And you don't mind killing the innocent, too!* I have serious reservations about you. (You are scaring me.) But you want this Crohn's thing to be a thing of the past and are willing to do just about anything! And so you may turn to a probiotic, food item or supplement, hoping that will do the trick. Good luck! The consensus is that probiotics are not very effective in the treatment of Crohn's disease (Rowland et al., 2010), and there are good reasons for taking this position. Here is one of them:

> Although the beneficial effects of live bacteria, termed probiotics, have gained increasing attention, the main disadvantage of oral probiotics is that they do not readily colonize the gastro-intestinal tract. (Grehan et al., 2010)

A probiotic, is more than just a fresh crowd (billions) of new mouths to feed. It is something else. Rather than suppressing the immune system, a probiotic may actually stimulate the immune system, stimulating both the intestinal epithelial cell and the macrophage to be more immunoreactive (Pagnini et al., 2010). But in Crohn's the immune system seems to have been put into overdrive! Do you want more of this? It may be that probiotics, like vitamin D, are more effective in preventing the disease than in treating the disease once it develops. They

stimulate what is called "physiologic inflammation"—the normal inflammation in the gut that deals with low-level offenders, promptly deals with new threats (before they have an opportunity to amount to something), and continually orchestrates and fine-tunes your normal, everyday inflammatory responses (Pagnini et al., 2010). In theory, however, probiotics should be an ideal weapon in the battle against Crohn's (Schultz et al., 2004).

Did you notice that the content of the last paragraph tells a different story than what you read in the quote by Ewaschuck and Diekeman placed at the beginning of this section? I noticed it. And I don't exactly know what to make of it. (You were probably still a little rattled by the thought of swallowing worms and eating insect parts, and this just slipped past you, unnoticed.) The Ewaschuck and Diekeman reference suggests that probiotics reduce inflammation, while Pagnini et al suggest that probiotics actually stimulate inflammation. Could it be that probiotics are a double-edged sword, with actions occurring in certain contexts differently—possibly detrimentally so—than actions occurring under other circumstances? Let me know when you have it all figured out. Hint: It probably has something to do with that fact that some probiotics shift the Th1/Th2 balance in favor of the Th1 response, while other probiotics act to stimulate the Th2 response (Baken et al., 2006; Rasche at al., 2007).

> Immunoregulatory effects of probiotics have often been ascribed to a shift of the T helper (Th)1/Th2 balance towards Th1 mediated immunity. Release of the Th1 associated cytokines interleukin (IL)-12, interferon (INF)-γ and (TNF)-α by various cell types was repeatedly demonstrated to be increased by LAB [lactic acid bacteria, such as lactobacillus acidophilus]. Moreover, several LAB [strains] reduced production of Th2 related cytokines. (Baken et al., 2006)

My goal here is not to discourage the use of probiotics in the treatment of Crohn's. My goal here is to help you become a little more sophisticated when it comes to understanding and adopting this

approach. As long as you are sending in a germ instead of a worm, you might as well make this effort as successful as possible. There *is* something to the promise of probiotics. I believe that, if the right probiotic is chosen, it can change the nature and course of the inflammatory response, and do so in a beneficial way. It may also be of help in repopulating the bowel with beneficial bacteria, particularly after the use of antibiotics.

You can find a large selection of probiotics on the market. And perhaps any one probiotic can be helpful in certain situations. However, with respect to Crohn's, many if not most will be largely ineffective due to the fact that the bacterial flora you have is so well entrenched (Khoruts and Sadowsky, 2011). Well, we can change this! We can fundamentally change our diet, forsaking the lousy Western diet and adopting a wholesome diet rich in prebiotics—*this* can effectively alter the balance between good and bad bacteria in the gut, and rather quickly. Why not continually select for dominance from the bacteria already present in the bowel, encouraging the growth of good bacteria while at the same time discouraging the growth of bad bacteria? I am of the belief that altering the balance between good and bad bacteria is best accomplished by *pre*biotics as opposed to *pro*biotics. With prebiotics (the good, wholesome foods you should be eating) you are creating conditions favorable for the good bacteria that you already have, encouraging them to thrive and crowd out those that are evil. But we can go one step further. We can use lactoferrin to sequester iron, in addition to iron-restricted dieting, in order to keep this growth and virulence factor away from pathogenic bacteria—measures that may dramatically shift the balance between good and bad bacteria in favor of the good.

The point I want to stress is this: For the Crohn's patient, simply taking a probiotic and hoping for the best is probably a waste of time, if at the same time he or she, via the typical Western diet, is supplying iron in abundance to the pathogenic bacteria that reside within. But there are other problems associated with this diet, too, problems that should be considered at this point in our conversation. For example, the Western diet is a diet that limits the availability of soluble fibers, one of nature's

finest prebiotics. Soluble fibers should be present in our diet in relevant amounts, nourishing the good bacteria and encouraging their growth and dominance. Before I came into your life, were you aware that an individual's diet may be the reason he or she is not realizing the benefits that are promised by the use of probiotics? You know now!

I will conclude this section with this: There are many probiotics from which to choose. Yogurt manufacturers want you to choose their product, but eating yogurt, even in abundance, may not be all that effective. The strains of bacteria used are the LAB-types, the ones found to be inappropriate with respect to Crohn's. Even VSL#3, a probiotic of some prominence in the world of probiotics, is a LAB-based formulation and may not be all that helpful in Crohn's due to its push in the direction of Th1. Discuss these issues with your physician. When considering a particular probiotic, be sure to consider whether it will stimulate the Th1 response (avoid these) or whether it will promote Th2 cytokine release (what we're looking for).

I hope you are ready for this next topic of discussion (and there is no real way to prepare you for this). We are now going to take the *Hygiene Hypothesis* to the extreme. *Quick!* Hide the children!

(This extra space has been provided here to give you time to hide the children.)

Why send in a worm or a germ, when you can send in a friend?

Fecal transplantation, also known as bacteriotherapy, fecal transfusion, or human probiotic infusion, refers to the process of instilling a liquid suspension of stool from a healthy donor into the patient's upper gastrointestinal tract through a nasoduodinal catheter or into the colon through a colonoscope or a enema catheter. **~Guo at al., 2010**

As an extension of probiotic therapy, fecal bacteriotherapy comprises the entire normal human flora. **~Borody et al., 2004**

Let me get this straight. You take poop from one individual and present it to another individual (they could be friends), actually place it inside the other individual, purposefully, *and this is okay?!!* I keep telling you, you picked a crazy world to live in! *Now* do you believe me? This is the story of the length a person, even a segment of the medical community, will go when drugs and the treatment protocols have completely failed to deliver on their promises. Harsh words, I know.

This treatment modality, fecal microbiota transplantation (FMT), *is* the ultimate in probiotics. To the one in need, it is the gift of a brand-new *complete* set of intestinal bacteria to take the place of a very dysregulated and rowdy bunch of bacteria that the patient with IBD has somehow assembled over time. It, fecal microbiota transplantation, is actually brilliant! Here's the scoop.

FMT was first introduced to the modern world in the late 1950s as a last-ditch effort to cure a debilitating intestinal infection called *C. difficile* (Borody and Khoruts, 2012). *C. difficile, or C-diff* for short, is actually a fairly common infection, typically acquired in the hospital setting, and is related to the use of antibiotics and less-than-satisfactory hand hygiene by hospital personnel. You don't want *this* infection! A lot of diarrhea shows up from out of nowhere when you have *C-diff*. Misery is involved. And if that isn't enough, ***C. diff* actually ends the life of between 15,000 and 20,000 individuals in the United States alone, per year!** (Khoruts and Sadowsky, 2011) The gods, they must be *very* angry!

Recently, I took care of a gentleman immediately post op, shortly after his entire colon had been removed due to a *C. diff* infection, because nothing was solving the problem and the patient wanted to survive. I know, this is an extreme case, but it does happen to many people each year. For extreme and nonresolving cases, perhaps it is time to send in a friend. Fecal transplantation just might have helped this gentleman (if it had been put to use before it was too late) and prevented his need for a total colectomy. But *C. diff* is not your problem, probably. (But at some point in time, it could be.) Your problem is a mix of bacteria that is not normal at all; indeed, it is pathogenic and undoubtedly perpetuates the inflammation that you are currently experiencing.

Aside from the "unsavory" nature of fecal transplantation, is this form of therapy for you? Certainly it is if you have *C-diff*, and it may be if you have ulcerative colitis, a disease found primarily in the colon and often involving the rectum. In Crohn's disease, however, the jury is still out. Some believe it just won't work for Crohn's. On the other hand, there are others who do believe. They have names like Fa-Ming Zhang, Hong-Gang Wang, and Min Wang.

A case report—heralded as the first case of severe Crohn's disease to be successfully treated by fecal transplantation—comes to us from China, the birthplace of FMT some 2,000 years ago. The patient, a 32-year-old male, presented to clinic with *"progressive abdominal pain, bloody diarrhea and high fever."* Two and a half years earlier, he had been formally diagnosed as having Crohn's. He undoubtedly had Crohn's for quite some time, as he had experienced gastrointestinal symptoms including pain for five years prior to diagnosis. To make a long story short, this gentleman received one fecal transplant donated from his healthy 10-year-old daughter, instilled in the duodenum via an endoscope. Only one! After one week (only one!), *"his symptoms, such as fever, bloody purulent stool and abdominal pain, were dramatically alleviated."* At one month (only one!), he met the criteria for clinical remission. He continued in remission for 9 months and counting. (see Zhang et al., 2013) If it can happen in China, I guess it could happen elsewhere. Perhaps in North America.

In August, 2011, a 26-year-old gentleman presented to the emergency room (exact location not disclosed—Canada, I think) with a perianal fistula. Surprisingly, he had no gastrointestinal symptoms at the time that would suggest he had Crohn's and was treated with antibiotics and surgery and attained what appeared to be a full recovery. Seven months later another perianal fistula appeared from out of nowhere, so it was off to the emergency room again! This second fistula was also successfully treated with antibiotics and surgery, and life was good once again, but not for long. Five months after his second surgery he returned to the emergency room with all the classic symptoms of Crohn's—abdominal pain, diarrhea, and weight loss. It was time to get to the bottom of things, so to speak, and soon the diagnosis of Crohn's was made. The patient was subsequently started on the typical first-line anti-inflammatory agents, and remission was achieved but did not last. The evil reappeared. What to do next?

Typically, next is the biologics. Heard of Remicade? Unfortunately (or not), this individuals' insurance would not cover the cost for this form of therapy is very, very expensive. (You won't believe how expensive, so I won't tell you.) Since going in this direction was not an option for this patient at the time, his gastroenterologist had to come up with something. And in this instance, up with something . . . really meant . . . up with something. After discussing the FMT option with the patient who was all ears and most agreeable—and having donor stool readily available in the local stool bank—a fecal transplant was performed, placed with a colonoscope as high up as reasonably possible. Within days the patient felt better (and had quite a story to tell) and . . . well, let's just see what happened next:

> Two days after FMT, the patient reported 2 to 3 formed BMs per day, associated with decreasing abdominal pain. He continued to improve and reported 1 formed BM per day, 1 week after FMT and remained in remission for 4 weeks after FMT. By this time, his insurer had agreed to cover a biological agent, but the patient wanted to pursue further FMT instead. At the time of his second

FMT, there was complete mucosal healing of his colon, and colonic biopsies showed no active inflammation. (Kao et al., 2014)

This is a *great* story! And the patient lived happily ever after—at least up until the paper detailing his experience was written for publication. You can read this story and view the before and after photos of this gentleman's cecum. The paper is available free on the internet, currently offered at no cost by researchgate.net. Search for:

—**Kao D, Hotte N, Gillevet P. Madsen K** 2014 Fecal Microbiota Transplantation Inducing Remission in Crohn's Colitis and the Associated Changes in Fecal Microbial Profile. J. Clin Gastroenterol; August; 28(7)625–628

Of course, the question pops up, "Would you do it?" "Would you have a fecal transplant?" If it is "Yes!" for you, than you have your work cut out for you. You have some convincing to do or have some people to find. As for me, there is no way in hell that I would not give FMT at least some *very* serious consideration. Knowing me, I would find someone experienced in this form of therapy. I would keep track of the latest developments in this vein of research and I would learn what this form of therapy is all about. And I would probably go to **www.openbiome.com** and under the FOR PATIENTS tab, I would click on WHERE TO FIND A PRACTITIONER. There, I would find a map showing medical centers that perform FMT. Maybe I could become involved in a clinical trial using FMT for the treatment of Crohn's. Who knows, I might even get lucky enough to find an enterprising gastroenterologists who would order the required testing for a donor of my choosing and provide me with a do-it-at-home set of instructions.

If you wish to learn more about FMT, may I suggest the following?

—**Borody TJ, Warren EF, Leis S, Surace R, Ashman O** 2003 Treatment of Ulcerative Colitis Using Fecal Bacteriotherapy. J Clin Gastroenterol 37(1):42–47

—**Borody TJ, Khoruts A** 2012 Fecal Microbiota Transplantion and Emerging Applications. Nature Reviews Gastroenterology & Hepatology; February; 9:88–98

Since FMT is one hot topic, you would expect that there are websites dedicated to this form of therapy. You would be right. I will share with you my favorites (I need to get a life).

—**The Power of Poop** www.thepowerofpoop.com

—**OPENBIOME** www.openbiome.com

—**Fecal Microbiota Transplantation** | **Facebook**
https://www.facebook.com/pages/Fecal-Microbiota Transplantation/359253944182000

Based on the evidence and the success stories presented, it would not surprise me to see FMT become an accepted therapy for Crohn's in the not too distant future. Only time will tell.

I could certainly go into more detail here about FMT, how it is performed and why it works, but you are probably in some sort of overload right now, so I won't. Instead, I'll let you do your homework and sort out all the details yourself. While sorting things out, and determining if FMT is right for you (right up you your alley, so to speak—I'm having too much fun!), you might consider the following:

> Current treatment [of IBD] relies heavily on corticosteroids and broad-spectrum immunosuppressives that have significant side effects. The situation is unsatisfactory for both the patient and the attending physician. (Hunter and McKay, 2004, emphasis added)

> Modern-day therapeutics for IBD have limited efficacy and are not without their danger. (Weinstock and Elliott, 2009, emphasis added)

Because they suppress the immune system, all biologics carry an increased risk of infections, which in rare cases can be serious. Cimzia, Humira, and Remicade carry a boxed warning for increased risk of serious infections leading to hospitalization or death. If someone taking a biologic develops a serious infection, the drug should be discontinued. People with tuberculosis, heart failure, or multiple sclerosis should not take biologics because they can bring on these conditions or make them worse.

In rare cases, some people taking TNF inhibitors have developed certain cancers such as lymphoma. Lymphoma is a type of cancer that affects the lymph system, which is part of the body's immune system. (*Web*MD, 2012, emphasis added)

There is no place like home

One nice thing about FMT, is that it can be done in the privacy of your own home. A physician can carefully screen a candidate donor, order the appropriate labs, review the results, try not to crack a few jokes, and provide a detailed set of instructions, if so inclined. This form of therapy is, of course, only for the brave and the very motivated. You can meet one very brave and motivated individual, a lady by the name of Sky Curtis. She tells her story, and that of her son, in a book entitled *A Gut Reaction: A True Story About a Mother's Fight to Save Her Son's Life and His Amazing Recovery from Crohn's Disease*, available on Amazon.com. She has also written the book *The Fecal Transplant Guidebook,* also available on Amazon. Once she heard of FMT, there was no stopping her, for she was out to save her son. It took an astonishing number of transplant sessions in order to achieve remission; a feat that, realistically, could only have been accomplished at home.

There is another individual you should become acquainted with if at-home FMT is right for you. His name is Michael Hurst. He tells the story of his ulcerative colitis, and how he put it behind him with FMT (there is a pun in here somewhere). He has a series of videos on YouTube (like, who doesn't?) about FMT, including DIY instructions. The name of the instructional video is *DIY Fecal Transplants to Cure Yourself*

of Ulcerative Colitis. Michael's story can be read at his website, www.fecaltransplant.org. He also has a book for sale (like, who doesn't?). This website is a great one to visit to learn more about FMT.

There's Something about Jordan

Previously, I promised that I would introduce you to perhaps the most well-known Crohn's patient on the planet. His story is a great one! His name is Jordan Rubin.

You should see him!—actually you can. Type his name in *Google Images* and pictures of him will pop up from out of nowhere. Take notice of the "before" and "after" photos (after you hide the children). How did he transform himself from one so gravely ill and so profoundly malnourished to the picture of health? I've read his story; it is very compelling. I will tell it to you, briefly, as follows: Once upon a time . . .

Jordan Rubin was a healthy, athletic college student, but during this period in life he became quite ill—experiencing diarrhea the likes of which no one should ever experience (or wish on their worst enemy—okay, you can do that), and which resulted in a 20-pound weight loss over a brief period of time. Although not sure what was wrong, his doctor prescribed a course of antibiotics and back to school Jordan went . . . only to become progressively more ill. By "more ill," I mean *"12 to 30 bowel movements, mostly bloody*" per day, along with episodes of intense abdominal pain. Later, it became very clear that this gentleman was suffering from Crohn's disease. And when you suffer from Crohn's disease you go to the doctor. And when you go to the doctor, the doctor gives you drugs. And when the doctor gives you drugs, you get better or you don't. Jordan did not get better—not even close—and tried everything that the medical establishment had to offer, and I mean *everything!* His health deteriorated in spite of all that was done on his behalf. Jordan had lost a total of **81 pounds** during the course of this disease and had become so weak that he was eventually fitted for a wheelchair. He looked like death warmed over, and that would have

been a compliment. He certainly could have died from his illness. (Can you relate to any of this?)

To make a long story short, Jordan embarked on a journey, a personal quest to find alternatives to conventional therapy—something out there should be able to help! This, too, was a bumpy ride, until he bumped into probiotics—but not your average, run-of-the-mill probiotics! Jordan was introduced to a probiotic comprised of soil organisms. And by using soil organisms, a formulation available at the time, he was able to resolve his symptoms and regain his health, and do so over a relatively short period of time—and he has been in remission from Crohn's disease for over 15 years! **I love this story!** And it is a story not at all difficult to believe once you realize that soil organisms, like the helminth, have been our faithful companions throughout the ages—and they do have an impact on the immune system, particularly in the gut.

> Hygiene is also a risk factor for IBD. IBD is more common in urban versus rural areas and less common in people who have jobs exposing them to dirt. (Weinstock et al., 2004)
>
> Specific components of soils, if assimilated into the tissues via ingestion of plant or animal food or drinking water, could possibly strengthen host defenses against infection. (Weinberg, 1987)
>
> Several changes in life-style are associated with this transition [the decrease in infectious diseases and the emergence of inflammatory diseases, like Crohn's], including diminished exposure to soil and animals, nutritional bias, obesity and increased exposure to pollution and antibiotics, which all impact the intestinal microbiota. (Ehlers and Kaufmann, 2010)
>
> People with blue collar jobs exposing them to dirt and physical exercise are less prone to IBD. (Weinstock et al., 2004)

Perhaps it was the *Hygiene Hypothesis*, in action, that saved the life of Jordan Rubin. Who knows? He also changed his diet to a more

"natural" one. But what I do know is this: Medicine, at the time, was simply not ready for Mr. Jordan Rubin, and his experience was completely dismissed, and over time—even now—the Jordan Rubin story has been largely ignored.

In my opinion: What should have been analyzed to death, this experience of Jordan Rubin, never was—and is still being largely ignored by a skeptical, dismissive medical establishment. Millions of individuals, however, have read the story, as his book ***Patient Heal Thyself*** has sold over a million copies. So it is not as if this story is not out there! And yet soil organisms, and their potential as probiotics, are like *never* mentioned in the research literature.

You can read Jordan Rubin's story online. You can purchase his book. You can be inspired. Take the time to read the following:

—***Homeostatic Soil Organisms for One's Primal Defense*** by Morton Walker, DPM. It is currently available from Crohn's.net, free for all to read.

—***Patient Heal Thyself: A Remarkable Health Program Combining Ancient Wisdom with Groundbreaking Clinical Research*** by Jordan Rubin, with Gary Gordon. I purchased my copy on Amazon.com.

If you would like to see Jordan Rubin in action, I have a nice little video for you to watch, recorded at a religious service some 15 years after his recovery. Go to YouTube and find:

—Jordan Rubin—Personal Philosophy and Story
www.youtube.com/watch?v=5b5pzVmhlY0

You can purchase soil-based probiotics online. Jordan Rubin owns a company named **Garden of Life** that sells soil probiotics, offering some 13 different probiotic strains in a product called *Primal Defense*. **Swanson** sells a product called *Soil-Based Organisms* that contains 15 different probiotic strains. There is also a product offered by **LL's Magnetic Clay, Inc.** called *Perscript-Assist*. This product boasts of a grand total of 30 soil probiotic species, and I cannot pronounce the

names of any of them. This product is formulated *"to increase the gastrointestinal microflora that have been disrupted by antibiotics."* I think this is a great idea! We should be doing this! But is this formula, or any other probiotic—even soil-based probiotics—right for you? Ask your physician. The first two formulas mentioned above are heavy into lactic acid bacterial strains, but these have been shown to increase Th1 responses and depress the Th2 response; therefore, they may not be right for you, the Crohn's patient, an individual who needs an increase in Th2 responses and a corresponding decrease in the Th1 pattern of response. We have read this before:

> Immunoregulatory effects of probiotics have often been ascribed to a shift of the T helper (Th)1/Th2 balance towards Th1 mediated immunity. Release of the Th1 associated cytokines interleukin (IL)-12., interferon (INF)-γ and (TNF)-α by various cell types was repeatedly demonstrated to be increased by LAB [lactic acid bacteria such as lactobacillus]. Moreover, several LAB [strains] reduced production of Th2 related cytokines. (Baken et al., 2006)

So what is a patient to do? Before you proceed with the use of a probiotic—any probiotic—show your physician the list of bacterial strains contained in the product in question. Have a serious talk. And please keep this in mind: *The Th1/Th2 balance is at stake!* Then proceed as advised. But is there something else that is not being generally considered in the probiotic conversation? (Pst! There is!)

Overlooked!

In my opinion, a probiotic particularly suited for the Crohn's patient, and the ulcerative colitis patient as well, is one that provides bacterial strains and organisms that will **compete for iron.** And I believe that soil-based probiotics are what we are looking for in this regard. Consider this line of reasoning:

Soil contains approximately 4,600 **species of microorganisms per gram**, most of which are entirely harmless (or we would all be dead).

Both children and adults inadvertently eat a little dirt each day. And, of course, dirty little children eat more dirt than clean little children. And in dirt there are *"large numbers"* of mycobacteria. (see Callahan, 2003) Mycobacteria, so it seems, have a fundamental requirement for iron. Therefore, mycobacteria in the gut, and elsewhere, will compete amongst each other for any iron that comes their way. The fighting is ugly! And if you are a pathogen, like the one I will feature in the next chapter, the presence of zillions of harmless, soil-derived mycobacteria passing through the gut, day in and day out, will make your life difficult. You, the iron-loving pathogen, just may be "out-competed" for an essential growth and virulence factor, namely iron, and may simply not have what it takes to be truly evil, in a diabolical sort of way. Yes, there is so much promise when it comes to the power of soil organisms, but they need to be the "competing-for-iron type" to be most effective (again, my opinion). My hope is that we will pay more attention to soil-based probiotics, with particular attention to probiotics that compete for iron. Now with respect to yogurt, we need to get real. Yogurt, rich in lactic acid bacteria, is clearly a waste of time in the battle against Crohn's. The probiotic needed are bacterial species that will compete for iron.

> Lactic acid bacteria (LAB), frequently employed as probiotics, are unusual in having little or no requirement for iron.
>
> We propose that the inability to compete with potential pathogens under conditions of high iron availability such as stress and trauma may contribute to the lack of efficacy of many LAB-based probiotics in treating disease. (Bailey et al., 2011, emphasis added)
>
> Recent trials have questioned the safety of untargeted oral iron supplementation in developing regions. Excess luminal iron could select for enteric pathogens at the expense of beneficial commensals in the human gut microflora, thereby increasing the incidence of infectious diseases.

These results fit with the finding that enteric pathogens have the potential to outgrow the commensal population when large amounts of unabsorbed dietary iron enter the colon.

Besides enteroinvasive strains like *S. typhimurium*, there are many other enteric pathogens that do not translocate across the bowel wall, but can cause severe intestinal inflammation. The virulence of such pathogens is also likely to be positively influenced by increased iron availability. (Kortman et al., 2012)

Should you doubt the role of iron in all of this, and the need to withhold it from the pathogen—any pathogen!—I will ask you to once again read the following:

The authors [investigating the association between iron in municipal water supplies and the incidence of IBD] found that risk of developing inflammatory bowel disease was associated with high iron content. **The relative risk of developing inflammatory bowel disease, including ulcerative colitis and Crohn's disease increased by 21% . . . when the iron content in drinking water increased by 0.1 mg/l.** (Aamodt et al., 2008, emphasis added)

Are you beginning to see that we are at war with iron, too? So it stands to reason that a probiotic that competes for iron and withholds it from the pathogen would be a very useful weapon to use in the battle against Crohn's, even the battle against ulcerative colitis.

Iron is an important factor for the growth of bacteria and their expression of virulence. When the level of iron increases, the balance between the quantities of different bacteria species in the gut is altered, depending on their ability to compete for iron. The interaction between bacteria and host tissue will also be altered when iron levels are enhanced, <u>including the ability for the bacteria to express virulence</u>. (Aamodt, 2008, emphasis added)

> Being essential and at the same time hazardous, abundant yet elusive, iron plays a decisive role in the success of an infection. For a pathogen that completely adapts itself for extracting macro- and micro-nutrients from the host, extracting free iron remains a major challenge. For the host, keeping iron away from the pathogen becomes an important defense mechanism. (Banerjee et al., 2011)

I think that I've made my point here, and I do apologize for the length of this gray box. **But this is important stuff!** Perhaps you should read again my chapter entitled *Ironing things out.* One more item to discuss, then we will move on.

"Yes, we have a probiotic for that!"

Johne's (pronounced "Yo-nees") disease in cattle looks exactly like Crohn's. No one questions this! And no one questions that Johne's disease is caused by a pathogen know as MAP, **and I mean no one!** Why do I mention this here? It is because I am so excited about **Dietzia!** (And I am about to share with you my belief that MAP is the pathogen behind the disease we call Crohn's.)

Dietzia is a probiotic organism and is the ***only*** effective treatment for Johne's disease—it can save a cow! This rarely-studied, mycobacteria-like bacterium may be effective due to its ability to compete for iron (see Click, 2011). Furthermore, it is safe—it can be injected in the abdomen of a mouse, and the mouse will do just fine (although its feelings will be hurt). And wouldn't you know, this type of bacterium just happens to be a soil organism! (Kim, 2011) **There is so much promise here!** But I guess we will have to wait until more research is being done before Dietzia becomes commercially available for humans. The story is told in the following papers (and you get to meet a few lucky cows along the way):

—**Click RE** 2011 Successful Treatment of Asymptomatic or Clinically Terminal Bovine *Mycobacterium avium* subspecies *paratuberculosis* Infection (Johne Disease) with the Bacterium Dietzia Used as a

Probiotic Alone or in Combination with Dexamethasone. Virulence; March/April; 2(2):131–143

—**Click RE** 2011 A 60-Day Probiotic Protocol with *Dietzia* subsp. *C79793-74* Prevents Development of Johne's Disease Parameters after in utero and/or Neonatal *MAP* Infection. Virulence; July/August; 2(4):337–347

—**Click RE, Van Kampen** 2010 Assessment of Dietzia subsp. *C79793-74* for Treatment of Cattle with Evidence of Paratuberculosis. Virulence; May–June; 1(3): 145–155.

—**Click RE** 2012 A Potential "Curative" Modality for Crohn's Disease—Modeled after Prophylaxis of Bovine Johne's Disease. J Mycobac Dis 2:117 doi:10.4172/2161-1068.1000117

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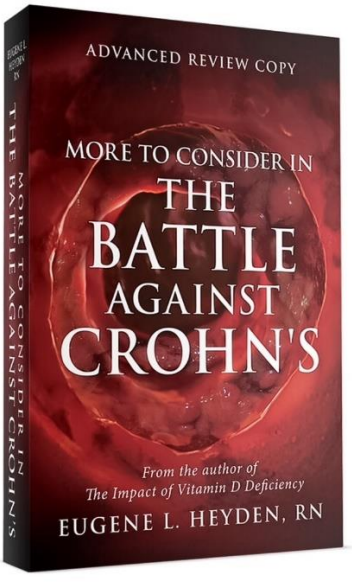

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