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

Crohn's and the MAP Controversy

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Who could it be?

Although there has been a century-long debate, the role of MAP in Crohn's has evolved from controversial to compelling. **~Dow, 2012**

The evidence to support M. paratuberculosis infection as a cause of Crohn's disease is mounting rapidly. Technical advances have allowed the identification and/or isolation of M. paratuberculosis from a significantly higher proportion of Crohn's disease than from controls.
~Chamberlin et al., 2001

In due course, informed public opinion will judge Gastroenterology harshly if a culture of neglect on this issue, and an inadequate understanding and misinterpretation of available scientific information, in the field, occasionally exemplified in contemporary writing, continues to prevail. **~Hermon-Taylor, 2002**

In this chapter I will share with you the evidence that Crohn's is a disease caused by a pathogen. I, along with many others, have a particular pathogen in mind.

> *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is once again coming under the microscope due to the increased ability to detect its genetic signature. This is the best contender for a causative microorganism of CD [Crohn's disease] which infects macrophages and disrupts the microbicidal and immune signaling function of these cells. (Agrawal et al., 2014)

In this chapter, I present the *compelling* evidence that Crohn's is a disease caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP)—at least in many cases, perhaps in the majority of cases, perhaps in *"all"* cases (Singh et al., 2013). In addition, we will talk about antibiotic therapy that specifically targets this pathogen, and does so where it resides, right inside the macrophage, the only place in nature where this pathogen replicates (Collins, 2003). And as a bonus, we will also meet real people, real people who have achieved remission by antibiotic therapy that specifically targets this pathogen. Perhaps not surprising to those in the know, the success of MAP-targeted antibiotic therapy exceeds the success rate of conventional therapy, even the popular biological agent Remicade (Katz et al., 2007; Chamberlin et al., 2011). If you walk away from this chapter in doubt regarding a role for MAP in the pathogenesis of Crohn's, I don't know what else I can do to help you. Your case may be hopeless. I may throw up my hands! There is so much evidence.

But before we begin

> *As in pneumonia, several pathogens can produce a syndrome clinically, colonoscopically and histologically indistinguishable from CD [Crohn's disease] which, when treated correctly, can result in complete recovery.*
> **~Campbell et al., 2012**

Everything points to an infectious etiology in Crohn's. *Everything!* You the immunocompromised earthling, continuously exposed to a wide

variety of pathogens, some very sinister, and you, the great disruptor of the various layers of defense, all come together to make infection, not autoimmunity, not aberrant reactivity to normal bacteria, the cause of the disease that you have. By *everything* I don't exactly mean everything. Sure, there could be a non-infectious cause of Crohn's in at least some cases, perhaps in many cases, but I just can't remember what they are because the things that point to infection greatly overshadow those that point to something else.

Before we get too far along in the conversation, I must point out that there are other organisms, other than MAP, that can cause what appears to be Crohn's, like *M. tuberculosis* (TB), like *Yersinia spp*, like *E. Histolytica* (a parasite), like Adherent-Invasive *Escherichia coli* (*AIEC*), and like *Campylobacter*. And less commonly: *Salmonella*, *Histoplasma capsulatum*, *Shigalla*, *Cytomegalovarius*, Schistosomiasis, and *Strongyloides stercoralis* can cause pathology that looks identical to Crohn's. (Campbell et al., 2012)

So why focus only on only one pathogen when there are others that can easily give an individual the diagnosis of Crohn's? **If a pathogen can arrive on the scene, advance, exploit defects in host defenses, disturb signaling networks, and successfully replicate within the macrophage of its dreams, certainly it is a worthy candidate in the pathogenesis of Crohn's disease, because, for all practical purposes, Crohn's is Crohn's only because it looks and feels like Crohn's.** Indeed, a strong argument has been made for including a number of pathogens as the cause of Crohn's disease and calling it a "syndrome" arising from multiple causes rather than a disease caused by a single pathogen (Campbell et al., 2012). But because there is an inexplicable resistance to even considering MAP a threat—or at least one of the major causes of Crohn's—I must present a compelling case for MAP. But not my compelling case. I present a compelling case arising from the efforts of others.

> Recent technical advances . . . [have] allowed for more accurate identification of *MAP* via DNA amplification, identifying *MAP* DNA in up to 92% of CD [Crohn's disease] tissues versus only 26% in healthy controls. Another study of resected bowel tissues from 300 CD patients identified *MAP* DNA in 52% of CD patients, 2% of UC [ulcerative colitis] patients and 5% of controls, further supporting a similar study that identified *MAP* DNA in 6/7 (86 %) resected tissue, and 4/20 (20%) biopsy specimens from CD patients, versus 2/36 (5.6%) control biopsy specimens. (Campbell et al., 2012)

The authors of the above paper go on to make this statement:

> These studies underline the high degree of *MAP*-positive results in CD, with higher detection rates obtained from processing of larger tissue specimens. However, an unexplained fierce resistance to the causal role of *MAP* in CD remains, completely at odds with the uncritical readiness to accept the current "aberrant reaction to normal colonic flora" theory.

There are many reasons to place MAP on the top of the list of pathogens involved in the pathogenesis of Crohn's. I will list just a few:

- Crohn's in humans and Johne's disease in cattle look identical. Johne's disease is <u>unequivocally</u> caused by MAP, a pathogen that can not only target the bovine intestine, it can also target the human intestine as well (Campbell et al., 2012; Agrawal et al., 2014).

- *MAP damages the agricultural industry on several continents. As many as 58% of dairy herds in a given geographical area may be affected."* (Greenstein, 2003). *"Enormous numbers of MAP are shed in faeces and contaminate the environment, milk, dairy products and meat."* (Hruska and Pavlik, 2014)

- *"MAP is able to infect, reside, and multiply in . . . human macrophages."* (Bach et al., 2011)

- The same genetic anomalies that impair autophagy and strongly predispose an individual to contracting Crohn's disease also predispose to other mycobacterial infections such as TB and leprosy (Agrawal et al., 2014).

- Both live MAP and the detection of its RNA can be obtained from biopsies and resected tissues of Crohn's patients (Bosca-Watts et al., 2015). Regarding RNA: RNA has a very short half-life, *"measured in minutes,"* indicating the pathogen was very much alive and metabolically active at the time of isolation (Greenstein, 2003).

- MAP is one insidious pathogen—just ask that skinny cow over there, the one who is having great difficulty staying upright. The properties of its cell wall enable it to *"escape immune surveillance by suppression of pro-inflammatory cytokines."* (Janagama et al., 2010) Once inside the macrophage environment, iron acquisition genes, previously dormant, become activated and pathology has its beginnings (Janagama et al., 2010). The pathogen is now enabled to survive, persist and replicate, and destroy.

- *"An increased presence of MAP-reactive T cells has also been found in CD [Crohn's disease] patients but not in controls."* (Bosca-Watts et al., 2015)

- The greater the MAP/Johne's disease burden within a geographical region, the greater the increase in the incidence of Crohn's disease. In countries such as Greenland and more

recently the Czech Republic—where MAP was introduced to livestock herds by sheep and cattle imports, and the incidence of Johne's disease has steadily increased—have experienced a dramatic increase in the incidence of Crohn's. With respect to the Czech Republic: *"The increase in Crohn's disease between 1995 and 2012 is more than 13-fold in all age categories and more than 12-fold in people of 65 and above."* (Hruska and Pavlik, 2014).

- Even when dead or half dead (e.g., from pasteurization), MAP can harm. An MAP wall component, called MDP, is a potent trigger proinflammatory pathways (Hruska and Pavlik, 2014).

That's probably enough (even though I have some of those big black dots left over). You get the point. MAP is clearly a force to be reckoned with. It could be the reason nobody wants to be you . . . including you.

Because the evidence is so compelling, many investigators and clinicians are taking a second look at the role of MAP in Crohn's. Some are reaching the following conclusion:

"No longer in doubt!"

Contemporary research using appropriate laboratory culture and polymerase chain reaction (PCR) and other procedures is confirming ***unequivocally*** *that the chronic enteric pathogen Mycobacterium avium subspecies paratuberculosis (MAP) is present in the chronically inflamed intestinal tissues of the overwhelming majority of people suffering from Crohn's disease (CD), and that MAP is rarely found in people with normal uninflamed intestine.* **~Hermon-Taylor, 2002, emphasis added**

This controversy increased in intensity following the detection of the specific DNA insertion sequence, IS900, of MAP in relatively high numbers of patients with Crohn's disease relative to ulcerative colitis and normal controls, and is now raging as several different groups have detected this

organism in the food chain and water supply, proposed maternal-fetal transmission in human milk, reported long term responses to antimycobacterial antibiotic combinations, and even cultured viable M paratuberculosis in blood samples of Crohn's disease patients. **~Sartor, 2005**

It all changed with our ability to detect and identify living things by the genes they possess. MAP as well as hundreds if not thousands of bacterial species are difficult or next to impossible to culture (Borody and Khortus, 2012), so growing them in a lab to see who is there is a big problem. And then along came the technical advances that have allowed us to detect the DNA and genetic signature of some very tiny creatures. This technology changed everything. And I mean *everything* changed! ***Everything!*** Not only did we determine that there are somewhere between 40 and 75+ genetic anomalies that predispose an individual to develop Crohn's (Fritz, 2011; Sartor, 2010), we had in our possession a new analytical tool that could determine if certain "foreign" genetic material exists in a specific location. We can actually "amplify" even the smallest segments of DNA and determine "Who's been there?" or "Who's lurking in the shadows?" In Crohn's lesions, MAP has been identified in an *"overwhelming majority"* of chronically inflamed tissues (Hermon-Taylor, 2002; Greenstein, 2003). Furthermore, *"until recently, it was impossible to verify the identity of the cell wall-deficient organisms as mycobacteria, or to discern whether they were identical to the acid-fast bacillus (cell wall-intact) form of the bacteria."* (Chamberlin et al., 2001) But now we can. DNA technology, again, has changed everything.

And MAP is not your ordinary pathogen. No. It needs someone like you or that cow over there, in order to thrive. *"M. paratuberculosis cannot exist outside of mammalian hosts due to its inability to obtain iron from the environment."* (Chamberlin et al., 2001) Outside the host, this organism becomes dormant, unable to replicate, bored beyond belief, and so difficult to destroy (Hermon-Taylor, 2002; Karp et al., 2007). But once inside the generous host, given enough time, it's "party time!"

unless the immune system can withhold iron and somehow make the kill. However, if the immune system is compromised—functionally or genetically—or if it is simply overwhelmed, there could be trouble. It, the immune system (and you), may not be able to eliminate the invader, and if not, the disease process may take hold. So I am not at all surprised to read that *"people with CD have a 7:1 odds of having a documented presence of MAP in blood or gut tissues than those without CD."* (Nacy, 2009) It is very clear that *you* are exactly what this pathogen needs, someone with a compromised immune system *plus* a rich source of iron. You are nice and warm, too. And then it's just a matter of time before the unthinkable happens . . .

> The homeostatic balance of the entire immune system is disrupted and chronic inflammation occurs. Ineffective attempts by the immune system to destroy MAP results in tissue damage and the broad spectrum of clinical disease that occurs in patients with CD [Crohn's disease]. (Agrawal et al., 2014)

How am I doing so far? Just as I thought: you're kinda impressed, but you want more. Okay! I'll give you more: *"A recent review from the American Academy of Microbiology also concludes that: 'the association of MAP and CD is <u>no longer in question</u>.'"* (Kirkwood et al., 2009, emphasis added) That's one fairly confident and compelling statement—no one's beating around the bush here! That being said, it was also correctly acknowledged by the "Academy" that all the details and all the caveats have not all been worked out. Yes, there are still many, many questions yet to be answered, as there are with any disease. However, many questions—tough questions—have already been answered. And we are learning more and more about this pathogen that makes us stop and take notice. For example:

> A recent study showed that **MAP isolated from CD patients can evade phagocytosis** in both human polymorphonuclear cells [e.g.,

neutrophils] and macrophage cells, thus permitting survival of a viable and possibly virulent organism. (Kirkwood et al., 2009, emphasis added)

But could another pathogen, besides MAP, be the one stirring up all the trouble? Sure! It *could* be someone else who is up to no good. I have given you a list of the likely contenders. And much is made of **adherent invasive *E. Coli* (AIEC)** and its potential role in the pathogenesis of Crohn's disease. Yes, this guy is a trouble maker, no question, and very opportunistic. Like MAP, AIEC can invade, persist, and replicate within the macrophage. It can even evoke a host reaction that will form a granuloma, a formation created by the body in order to isolate a pathogen within the infected tissue (Glasser et al., 2001; Lalande and Behr, 2010). Indeed, *E. coli* DNA is found in **80%** of the granulomas of Crohn's patients (Caprilli et al., 2010). For a pathogen, that's pretty impressive! Yet, there is another level of evidence that strongly points us in another direction. That's up next, after we carefully consider the following:

MAP is present in **86%** of surgically resected tissue compared to 20% of biopsy specimens of CD patients **compared to 0% of controls**. These data suggest that MAP may be residing in the submucosal layer of ulcerated tissue in CD patients rather than in biopsies obtained from the surface of the mucosal layer. The fact that MAP was cultured in several weeks from resected tissue of CD patients, rather than several months as seen in some positive biopsies, may indicate that MAP in deep tissue is virulent and metabolically active. (Schwartz et al., 2000, emphasis added)

Anti-MAP antibiotic success: another piece of the puzzle

*Anti-MAP therapy (**rifabutin**, **clofazimine** and **clarithromycin**) resulted in profound effects on mucosal healing as demonstrated by longitudinal scarring and histological repair.* ***Such healing of CD-affected intestine has***

not been seen with standard anti-inflammatory and immunosuppressant drugs. **~Sohal et al., 2009, emphasis added**

Antibiotic therapies directed against mycobacterial infection have provided prolonged response rates that are comparable to or better than the present use of biological agents in [the] patient with Crohn's disease. **~Karp et al., 2007**

If you are going to use an antibiotic, better choose the right one, better choose one that specifically targets the pathogen you are trying to kill. Antibiotics specific for mycobacteria have produced some very impressive results. And, most importantly, antibiotics specific for mycobacteria can successfully permeate the macrophage (Hermon-Taylor, 2002), giving them a greater chance to find and eradicate the offending pathogen, hiding and replicating within. Targeted antibiotic use—associated with outstanding results—is a most important piece of the puzzle.

Real people, real results, real nice

A portion of people with severe end-state Crohn's colitis resistant to conventional treatment, who have responded to drug combinations including rifabutin and clarithromycin, have been rescued from otherwise panproctocolectomy [think ileostomy . . . for life] and are living a normal, apparently disease-free state. **~Hermon-Taylor, 2002, emphasis added**

Although I warned you previously of the dangers of antibiotics, I really am a big fan—but only if you actually need them and only if the antibiotic chosen is the right one for the job. I believe these two guys are big fans, too: *"Ward and McManus reported benefit from **dapsone** treatment in four out of 6 (**66.7%**) patients with resolution of symptoms, healing of fistulae and macroscopic and microscopic improvements."* (Chamberlin et al., 2011, emphasis added) That's nice—and you know my ears perk up whenever I hear the words "fistula healing!" Someone must be doing something right!

Rifaximin is another antimycobacterial agent that, reportedly, has an "excellent safety profile." Of course this is nice, too. Under treatment with this particular antibiotic, *"overall, **65%** achieved remission. The remission rate was greater—**70%**—in patients not receiving steroids versus 58% of those who received steroids."* (Chamberlin et al., 2011, emphasis added) Say it with me, **"That's nice!"**

And talk about *nice*: Following a several-month course of antimycobacterial antibiotic therapy involving 20 patients, "Three patients with severe CD facing total colectomy were spared surgery." (Chamberlin et al., 2011) Again, someone must be doing something right! (Could they be playing with power?)

Antibiotics that target MAP, so it appears, are more successful than the anti-inflammatory agents and the biologicals that are currently in vogue. (Katz et al., 2007; Chamberlin et al., 2011) ***"The demonstrated superior results of anti-MAP therapy over treatments currently on the market for CD support their use as a preferred primary treatment."*** (Chamberlin et al., 2011, emphasis added) These are not my words. They are the words of those that have not dismissed a role of MAP in Crohn's. They are the words of individuals who continue the investigation, report their findings (to anyone who will listen), and find it very difficult not to believe.

So perhaps I should ask you, once again, to consider this:

> In due course, informed public opinion will judge Gastroenterology harshly if a culture of neglect on this issue, and an inadequate understanding and misinterpretation of available scientific information, in the field, occasionally exemplified in contemporary writing, continues to prevail. (Hermon-Taylor, 2002)

Harsh words, I know.

If you want to examine the impressive results of anti-MAP antibiotic therapy—and read the stories of real people achieving real results—I *strongly* suggest that you obtain and read the following two papers:

—**Borody TJ, Leis S, Warren EF, Surface R** 2002 Treatment of Severe Crohn's Disease Using Antimycobacterial Triple Therapy—Approaching a Cure? Digest Liver Dis 34:29–38

—**Chamberlin W, Borody TJ, Campbell J** 2011 Primary Treatment of Crohn's Disease: Combined Antibiotics Taking Center Stage. Expert Rev. Clin. Immunol. 7(6):751–760

"And tell me again: why was I not told any of this? And, why has MAP-targeted antibiotic therapy not been offered to me?" (You ask the tough questions, too.) The answer: Medicine, in general, is simply not up to speed on the research on MAP, perhaps thinking that since we, the medical community, have already dismissed this theory, why look any further? Or perhaps Medicine, in general, is no longer attracted to this vein of research. "We have steroids, we have anti-inflammatory agents, we have biologics, and we doing pretty good with what we've got—Not interested!" **Big mistake!** The evidence to date is just too strong to be ignored. It is time—**past time!**—that we focus our attention on MAP and actually target this pathogen in the battle against Crohn's. I am far from alone in this belief. Should your physician express doubts about MAP and its role in the pathogenesis of Crohn's, it may simply be that your physician—who seems very bright to me—has simply niether had the time nor taken the opportunity to personally delve into these issues and is simply relying on conclusions formulated in the past. Perhaps we can help! (More later.)

Spare the children!

The similar rate of MAP identified in children with early-onset CD and UC suggests a role of MAP in the initiation of both forms of disease. The clinical differences apparent between CD and UC could then be a consequence of differences in genetic makeup that alter mucosal and immunological responses. **~Krikwood et al., 2009**

MAP in powdered infant milk is not surprising as milk from paratuberculosis-contaminated herds is used for the production of milk products. **~Hruska et al., 2011**

MAP infection has a significant impact on the agricultural industry around the world. As many as 58% of dairy herds in a given geographical location may be infected with MAP. **~Karp et al., 2007**

It is estimated that nearly 40% of United States dairy herds are infected with MAP and that losses to the dairy industry may exceed $1.5 billion per year. **~Uzoigwe et al., 2007**

I cannot stress this enough: We'd better be on the right side of the MAP controversy, if not for us then for the children. And not just with respect to Crohn's disease and ulcerative colitis, but with respect to other diseases, as well. MS, as well as type 1 diabetes and juvenile idiopathic arthritis, appears to be strongly related to MAP (Hruska et al., 2011). Indeed, the incidence of both Crohn's disease and multiple sclerosis—even type 1 diabetes—is particularly high in one geographical region (Sardinia, Italy) where there is also a very high prevalence of Johne's disease in cattle and sheep (Cossu et al., 2011). Are we paying attention to this association as closely as we should? The answer is no. But some people are.

Due to concerns regarding disease transmission from cattle to humans, one team of investigators set about the task of identifying the extent of MAP contamination in our food supply—particularly in infant formula, particularly formula prepared from cow's milk. In a study of 51

dried baby food products from 10 European Union producers the investigators found that **35%** of dried milk samples were indeed contaminated with MAP. Of course, dried milk is reconstituted with water, another source of this pathogen, making the final product of even greater concern. In four samples, *"more than 10,000 cells per gram of dried milk"* were found. Just to get an idea of how many organisms this may involve, listen to this:

> The concentration of 10,000 cells per gram in one package of 500 g of dried milk represents **5 million MAP cells in one package** of 500 g. Usually two packages of the same batch are purchased together; therefore, the exposure of one baby to immuno-modulators from **10 million** cells is accomplished within several days according to the age of the baby and daily amount of ingested milk. (Hruska et al., 2011, emphasis added)

Boy, I hope the immune system of the hungry little infant is on its toes! Boy, I hope the hungry little infant does not have a genetic weakness that would allow MAP to survive and carve out a replicative niche somewhere within the gut of that hungry little guy! Boy, I hope the hungry little gut does not have a leaky gut! Boy I hope the hungry little guy is getting some vitamin D from somewhere! Boy, I hope the hungry little infant is leading a dirty little life, receiving full and lasting benefit from the *Hygiene Hypothesis*—a good case of worms would certainly come in handy! Boy, I hope . . .

But infant formula is not the only source of MAP to be concerned about. The hungry little infant is born into a world that will constantly expose him or her to MAP, and in very large numbers. It seems there is no place to hide!

> Rain water can wash MAP-contaminated manure spread on fields or crops into nearby bodies of water. MAP has extremely hydrophobic cell wall which causes the organism to adhere to and be concentrated on the surface of bodies of water. Bursting air

> bubbles can then aerosolize and further concentrate the organism. MAP can be concentrated 10,000 fold in the water droplets that "are small enough to enter human alveoli." (Pierce 2011)

And while you are at it, go ahead and add the following to the list of things to worry about: *"seven million mycobacterial cells can be found in one gram of house dust or 10 million per one gram of pork lymph node."* (Hruska and Pavlik, 2014) A high proportion of the mycobacterial cells could be MAP, depending on the circumstances.

So it would appear that the battle against Crohn's includes a battle against rain water, house dust, and port lymph nodes. And it's not just living MAP cells that pose a threat. Even in death, a specific fragment of their cell wall, called MDP, *"has enormous immunomodulatory effects"* and can *"trigger the inflammatory pathways"* we possess (Hruska and Pavlik, 2014). MDP exposure is clearly a threat to the little ones in our midst (Hruska and Pavlik, 2014). And, thanks to our modern society, the threat has become ever present, and it is bigger than you might think. MAP is everywhere!

It is in our food supply. It is in the air we breathe. It is in the water we drink. We even step in it, should circumstances allow. It seems like there is no escape. Actually, there is no escape. MAP is in Greenland! It is in Japan! It is everywhere, found in the poop of cows, camels, sheep, buffalo, birds, and bunnies used in magic shows. Apart from the environmental exposure that places all of us at risk, young and old, we reportedly concentrate MAP and transfer massive amounts of this pathogen to the hungry infant by something as innocent as infant formula. Add the increased iron available in our society (and by the use of children's multivitamins formulated with iron) and we've got problems, big problems! Then it's just a matter of time before the genetically vulnerable in our midst are identified by the disease they contract. Are we, as health care professionals, paying attention to any of this? Or are we hoping that the MAP controversy will just fade away and

quit challenging the status quo as we remain comfortable in the belief that this problem simply does not exist?

Yes, MAP is out there, and it is a threat to our children (and to all of us). And it is not just out there; sometimes our children (and all of us) are exposed to MAP in massive amounts, and nobody thinks a thing about it. Perhaps, after reading this section, you now recognize this threat and are disturbed and concerned (perhaps angry and alarmed) that so little attention is paid to a pathogen clearly associated with Crohn's and clearly bent on destruction. It does not care if an innocent little child becomes its next victim. It is that evil.

And this should make your blood boil!

Many potential pathogens for livestock as well as humans can be found in manure of both livestock and poultry.

M. paratuberculosis [MAP] is the causative organism for Johne's Disease in cattle. Infected cows may shed the pathogen in her feces for months to years before she develops clinical signs. At the peak of shedding, an infected cow may shed ***a million bacteria/gram of manure****. Cows with clinical signs of diarrhea and weight loss tend to shed more bacteria in their feces than non-clinically infected cows. Two thimbles full of manure from an infected cow is enough to infect a calf. Consider forage crops that had fresh manure applied as fertilizer as a feed risk to young stock. The bacteria can live in the environment for up to one year.* **~Kirk, date not specified, emphasis added**

Nutrient recycling offers a possible approach to feedlot waste management. This concept involves utilization of feedlot waste as a feedstuff, with reutilization of nutrients as in natural ecosystems.
~Albin and Sherrod, 1975

It's in our food supply! It's in the milk that we give to our infants and to our children! It's even in the manure that we sprinkle on our garden!

Do we need yet another reservoir that increases our exposure to MAP? Yes, there *is* another source of this pathogen . . . **Stupidity!**

Does this sound intelligent to you? Take poop from a cow, perhaps a cow shedding zillions of MAP cells per day, and feed their poop to a chicken for dinner. Then, take chicken poop and feed it back to the cow for lunch! Sounds crazy to me! But this practice is being done today . . . **to you!** You, the hungry adult, are eating animal products produced by animals that are fed shit! (Harsh words, I know.) This is not only crazy, it is dangerous! In this manner, we may be generating a completely new and totally avoidable reservoir for MAP—cow chow! ***This must stop!*** But there is money to be made here, and there is no public outcry sufficient to stop the practice of adding excrement to the feed of livestock, so it will probably continue. And we wonder why Crohn's disease is on the rise.

This information comes to us courtesy of Dr. Michael Greger, MD, Director of Public Health and Animal Agriculture at the Humane Society USA, probably not some nut-job. He wants you to become a vegan—wonder why? You can read this story on the Huffington Post. Search for:

—Mad Cow California: Stop Feeding Cows Chicken Manure,
posted 04/26/2012

But it gets worse than that: "Let's not feed our new little calves precious milk (rich in health-promoting lactoferrin and colostrum), making sure it is from disease-free cows. **No!** Let's give them processed slaughter-house blood. We can save a lot of money by feeding the little newborn calves the blood of the dead and selling the milk they would otherwise consume to hungry humans for profit." The human could be an infant; the human could be a child. **"Earth to stupid people! This is just plain dumb!"** (The Author, 2016, emphasis added) This story, too, is told by Dr. Michael Greger on the Huffington Post. Search for:

—Mad Cow California: Stop Weaning Calves on Cattle Blood,

posted 04/25/2012

When you study the transmission of diseases from one species of to another, you cannot help but be alarmed (or freaked out) by the agricultural practices just described. We are so screwed! I'm ready to move to another planet.

By the way: Regarding Mad Cow disease, this disease was once transmitted from cow to cow by, once again, **Stupidity!** (**And greed.**) It was only after scientists discovered that the pathogen that caused this disease lived and replicated in the brain and spinal cord of the infected cow that we realized what was going on. And, wouldn't you know, *we* were grinding up the brains and spinal cords of slaughtered cattle and adding it to cow chow! Thankfully, this practice finally came to an end, but not before billions of dollars were lost and about 200 people had perished. (I miss them.) What part of this idea seemed okay? The answer is a no-brainer. Nothing good, except profit, could come out of a practice such as this. Now brace yourself!

Thank goodness that the following *insane* practice has been stopped (I certainly hope):

> In 2008, an undercover investigation of a dairy cow slaughter-plant in California showed that downers [cows that died en route to, or at the door of, the slaughterhouse] were being dragged to slaughter for hamburger meat distributed to the Federal School Lunch Program. (Greger, 2012)

Don't we have enough to worry about in life besides the safety of our food supply? Is anyone paying attention to the transfer of MAP, unnecessarily and unintentionally, to the hungry human due to the stupidity and greed of others? Perhaps only when we realize that diseases like Crohn's, type 1 diabetes, and MS are so related to MAP overexposure that it is *crazy* will we put an end, once and for all, to the disturbing practices outlined above. Until then, have a nice day.

The following “free” references clearly define the role of MAP in the pathogenesis of Crohn’s disease. Please, at least read the first one on the list.

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—**Chamberlin W, Borody TJ, Campbell J** 2011 Primary Treatment of Crohn’s Disease: Combined Antibiotics Taking Center Stage. Expert Rev. Clin. Immunol. 7(6):751–760

—**Karp SM, Koch TR, Pang G** 2007 Is there a Map (*Mycobacterium Avium Subspecies Paratuberculosis*) for Treating Crohn’s Disease? Practical Gastroenterology; April; 31(4):40–50

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—**Chamberlin W, Graham DY, Hulten K, El-Zimaity HM, Schwartz MR, Nasar S, Shafran I, El-Zaatari FAK** 2001 Mycobacterium avium *subsp.* paratuberculosis as One Cause of Crohn’s Disease. Aliment Pharmacol Ther 15:337–346

—**Hermon-Taylor J** 2000 Mycobacterium avium subspecies paratuberculosis in the Causation of Crohn’s Disease. World J Gastroenterol 6(5):630–632

—**Schwartz D, Shafran I, Romero C, Piromalli C, Biggerstaff J, Naser N, Chamberlin W, Naser A** 2000 Use of Short-Term Culture for Identification of *Mycobacterium avium* subsp. *paratuberculosis* in Tissue from Crohn's Disease Patients. Clin Microbiol Infect 6(6):303–307

Your assignment: You *will* print out the above papers and you *will* thrust them into the hand of your physician, right? (At least the first one listed, to see if an interest develops.) If you are serious about perusing this avenue of therapy, anti-MAP antibiotic therapy, or just want to share the latest research on MAP, you should do this. We can help the physician out by giving him or her more homework. It's tough being a physician; we can make it tougher.

Meet my friend, Dr. Ellen Pierce

Yes, surprisingly, I do have friends. One of my friends is a physician who just happens to devote all her energies into researching the relationship between MAP and Crohn's. She, herself a victim of this disease, strongly believes that MAP is the culprit. Crohn's has not been kind to her, to say the least, and her arguments supporting the role of MAP in Crohn's disease are *very* compelling. You need to read her papers. I give you no other choice. Search for . . .

—**Pierce ES** 2010 Ulcerative Colitis and Crohn's Disease: Is *Mycobacterium avium* subspecies *paratuberculosis* the Common Villain? Gut Pathogens 2:21

—**Pierce ES** 2009 Where Are All the *Mycobacterium avium* subspecies *paratuberculosis* in Patients with Crohn's Disease? PLoS Pathogens; March; 5(3):1–11

—**Pierce ES** 2009 Possible Transmission of *Mycobacterium avium* subspecies *paratuberculosis* through Potable Water: Lessons from an Urban Cluster of Crohn's Disease. Gut Pathogens; September 23; 1(7):1–5

—**Pierce ES, Borowitz SM, Naser SA** 2011 The Broad Street Pump Revisited: Dairy Farms and an Ongoing Outbreak of Inflammatory Bowel Disease in Forrest, Virginia. Gut Pathogens 3(20):1–5

—**Pierce ES** 2012 Free-Ranging Rocky Mountain Bighorn Sheep and an Outbreak of Inflammatory Bowel Disease along the Clark Fork River in Plains, Montana. Virulence, October 2; 3(6):546–550

Just so you know, Dr. Pierce is certainly not the only one who thinks along these lines. The following two video clips will help reinforce her findings regarding MAP. **Do not miss these two compelling videos! The first one is mandatory!** Go to Google video and watch:

—**Crohn's Disease May be Linked to Beef Consumption**
www.youtube.com/watch?v=LRbqe5GpgOc

—**Crohn's Disease and Cow's Milk**
www.youtube.com/watch?v=UHKRPEhZRU4

Unintended consequences

There is another agricultural practice for us to be concerned about, one that may be increasing our risk of Crohn's and other diseases as well. It is the practice of dosing of farm animals with antibiotics. Recall, multitudes of harmless organisms in our gut aggressively compete for space and nutrients with pathogens, even MAP. That's their job! Boy, I hope someone doesn't come along and slaughter them in order to make a quick buck. That would be bad. Get used to the word bad.

> In the past six decades, our gut microbes have been under assault in the form of medical therapies and routine use of antibiotics in farming practices. The concerns over potential unanticipated health consequences are only now beginning to be realized, with multiple diseases associated with Western lifestyles

> hypothesized as causally linked to alterations in the gut microbiota, including constipation, IBS, IBD, neurological diseases, cardiovascular disease, obesity, the metabolic syndrome, autoimmunity, asthma and allergic diseases, many of which have reached epidemic proportions in the past few years. (Borody and Khoruts, 2012, emphasis added)

Furthermore,

> Some studies have implicated that an altered microbiota is associated with several diseases that are particularly prevalent in the 21th century. For example, reduced microbial diversity—a sign of a dysfunctional ecosystem that leads to a decreased stability of the microbiotica—has been associated with both inflammatory bowel disease and obesity. (Delzenne et al., 2011)

Speaking of obesity, a problem that is frequently observed in the Crohn's population (Hou and Sellin, 2010), the following has been written:

> The potential role of the gut microbiota and its influence on body size has long been acknowledged in the usage of low-dose antibiotics in farming practices.
>
> Germ-free mice, which have a naturally low body weight, gain more body fat after colonization [think fecal transplantation] with gut microbiota from obese mouse donors compared with lean mouse donors, without increases in food consumption or obvious energy expenditure. (Borody and Khortus, 2012)

Over 50 years ago it was discovered that we could fatten cattle simply by giving them antibiotics. It worked, supposedly, because antibiotics were able to encourage the dominance of certain strains of gut bacteria that could extract more energy from the food the animal had eaten. Unintended consequences followed. *"Antibiotic growth promoters have been criticized because, although they do not reduce the*

total bacterial biomass, they shift the composition of the microbiota and promote dangerous levels of antibiotic resistance." (Willing et al., 2011) All because we wanted fatter cows and increased profits.

Now back to IBD. This practice, the feeding antibiotics to our food animals, seems to be inadvertently fueling our obesity epidemic, as well as increasing our risk of IBD, by negatively "selecting" the bacteria in the gut of the hungry human. When you mess with the normal bacterial flora of the gut of the hungry human, you mess with normal defenses and encourage the growth of pathogens. And when you encourage the growth of pathogens, look out! Clearly, the cow you ate yesterday is not the cow you ate 100 years ago. Now, beef is much lower in both CLA and the omega-3 fatty acids. It is now much higher in the omega-6s, a family of fatty acids associated with many diseases (including the one you now have). Livestock are fed growth hormones and antibiotics (and excrement) in an effort to increase profits. It used to take 4 years for a steer to be ready for market, now it's 14 months! The cereal grains fatten them up right before they are "harvested"—a practice that further reduces the CLA and omega-3 content in beef and, at the same time, boosts its omega-6 content. And who knows what cattle are being fed besides chicken manure? In this day and age, it would not surprise me in the least if they are being fed ground up rats, toenails and all.

Spare the children, again

> That early-life antibiotic exposure can lead to increased body mass is consistent with . . . evidence on the farm of antibiotic-induced weight gain, and with more recent studies in laboratory animals eludicating a link between early antibiotic exposure and changed development in controlled environments. Many of these studies also find that the earliest months of life are periods of unique vulnerability to antibiotic disruption. (Trasande et al., 2012)

I can make this simple, or I can make it complex. I will make it simple.

I know of no little child who wishes to become obese, but today the deck is stacked against him or her. Not only is our Western diet not fit for us, child or adult, it is problematic in another ways. By way of example, antibiotics in our food supply affect the balance between good and bad bacteria in all of us, child or adult. For the very young this can be a disaster.

> While the composition of the microbiota of adults appears relatively stable, the microbiota of children may be considered more variable and more vulnerable to antibiotic perturbation. Increased risks from childhood antibiotic exposure for atopic dermatitis, asthma, and inflammatory bowel disease have been reported. (Trasande et al., 2012, emphasis added)

And there are consequences:

> A recent analysis of the Danish Cohort is suggestive: children of normal-weight mothers who were exposed to antibiotics during the first 6 months of life had increased risk of being overweight when they were 7 years old. (Trasande et al., 2012)

The lesson in all of this: Gut flora does matter. Unfavorable alterations in its composition changes who you are. Clearly, there are forces at work in our society that have negatively altered the largest organ in the body, the community of bacteria that live within the gut. And the data suggests that our population is significantly more at risk for contracting Crohn's due to the use of agricultural antibiotics.

You've got questions, we've got answers

Just in case you are still having trouble believing MAP is the pathogen behind the disease, perhaps you will find this little question and answer session to be of help.

Q: Why has MAP evaded detection in the blood, tissues, and stool of the Crohn's patient for such a long period of time?

A: MAP is one of the most difficult organisms to culture, so it has been very difficult to detect. Even in cows that are infected with Johne's disease, a disease unquestionably caused by MAP, this bacterium is only detectable by culture in about half of the cases, perhaps fewer—and almost impossible to detect by culture in its early stages (Vermont Department of Agriculture; Nacy and Buckley, 2008). In addition, an immune response in the MAP-infected cow only occurs during the late stages of the disease (Nacy and Buckley, 2008). Furthermore, for decades it was not known that the culture medium must contain iron, and its siderophore mycobactin, for the organism to be successfully cultured (Greenstein, 2003; Schwartz et al., 2000). Not taking all of this into account, past efforts to identify MAP using culture mediums deficient in iron and or mycobactin have resulted in a false sense of security and have fostered the belief that MAP is nowhere to be found (when it was indeed present in the tissues under examination). So for decades opinions were being formed, many not in favor of MAP involvement in Crohn's disease. Techniques have since improved and MAP is now much easier to culture. In addition, we now have DNA technology at our disposal that makes the identification of MAP very easy. (Yes, it's in there!) MAP can now be more readily identified in the inflamed tissues of Crohn's patients. But DNA testing is not the last word. Jeyanathan et al report on an oil-immersion microscopy technique that makes it easy to identify MAP from the inflamed tissues of patients with Crohn's, using x1000 magnification

and acid-fast staining in order to directly visualize the creepy little monster (Jeyanathan et al., 2007).

Interestingly, in another mycobacterial disease, leprosy, the bacterium has *never* been cultured, and this disease cannot be transferred from an individual to a cow (Greenstein, 2003), no matter how much you hate that damn cow. There are, indeed, many mysteries to solve regarding infection from mycobacteria, many mysteries indeed.

Q: Why the explosion of Crohn's disease cases in the latter half of the 20th century, and today, if MAP has been infecting cows long before this period of time?

A: Society changed. Iron availability changed. Our diet changed, leading to increased disease susceptibility. Animal husbandry changed, leading to crowed quarters (for cows) and the routine use of antibiotics (for cows). Changes in fatty-acid composition occurred in meat and dairy products, as well as drastic changes in the recipe for cow chow. We have violated every principle of the *Hygiene Hypothesis*. Antibiotic use to treat disease in humans became commonplace, and their use was often unnecessary. The list could go on and on. We are not the humans we used to be. Our cows are not the same cows they used to be. Our society is not the same society it used to be. Today, we shield ourselves from the sun, giving rise to a society of vitamin D-deficient people, therefore anti-microbial peptide deficient people. Our exposure to dirt is limited, and fewer dirty things are being eaten. Today we have to get down on our knees and beg for the doctor to give us a worm infection when previously we just had to exist to acquire one that we could be proud of. All of this matters. All of this increases our risk of failing to defend against a pathogen that is commonplace, insidious, and very difficult to destroy, particularly if you have a genetic defect that impairs your ability to clear pathogens that have somehow evaded your

various levels of defense and found their way into the macrophage, one that is impaired.

Q: Why do those who live and work closest to farm animals not have a greater prevalence of contracting Crohn's compared to others?

A: Well, this is a tough one. But I'll handle it! Now if you were to work on a dairy farm, your risk of contracting ulcerative colitis would be eightfold according to Pierce et al., 2011. Yet there doesn't seem to be much of an increase in Crohn's disease in the dairy farm worker. Importantly, the occupational exposure to MAP-infected cattle is known to increase MAP antibody titers—certainly offering a greater degree of resistance to infection in the dairy farm worker (Hermon-Taylor, 2009). And yet, genetic predisposition and its interaction with lifestyle and environmental factors should not be discounted. The dairy farm worker lives, eats, and breathes the *Hygiene Hypothesis*, whereas you sit in a clean house, planted in front of a TV, clean remote in hand, and a demolished bag of potato chips sitting right in front of you. But being near a cow is not without some danger with respect to Crohn's. If you are a child, one living in close proximity to dairy farms, your risk of Crohn's just may be increased. Dr. Pierce reports on a cluster of Crohn's cases in children living in proximity to dairy farms (Pierce et al., 2011). Perhaps we have not been looking as carefully as we should? And perhaps we are bringing the farm to everyone, regardless of where they live. We introduce MAP in great numbers to children in infant formula, and to everyone by meat, dairy, and the water we drink or inhale during the showers we take, water contaminated by MAP from dairy farm lands many miles away (Pierce, 2010). Not surprisingly, in cities where rivers converge, rivers that drain dairy farm lands, the incidence of Crohn's disease is clearly elevated (Hermon-Taylor, 2009). But let's not forget about our genetics. Genetic anomalies involving pathogen processing and elimination is, more likely than not, what tips the scales

against an individual when it comes to MAP and Crohn's susceptibility. If you can't destroy a pathogen, one that somehow finds its way into the macrophage or makes a home somewhere hidden within the tissues of the gut, then you've got big problems, no matter where you live and no matter what you do.

Q: If Crohn's disease is caused by MAP, why do patients improve when inflammation is controlled by anti-inflammatory and anti- TNF-α agents?

A: This is actually an easy one! I offer this answer: In Crohn's, a fierce battle rages between pathogen and host over iron (Nairz et al., 2010; Porto and De Sousa, 2007). The MAP pathogen is counting on the chaos that occurs during inflammation, inflammation that it and others create in order to extract iron from the host and complicate the efforts of the host to withhold iron from pathogens (Weiss and Gasche, 2010). When inflammation subsides, MAP may simply become helpless, no longer in control of its fate. It may be cleared, over time, and someone gets to live a normal life. MAP is a very slow-growing pathogen, one that can lie dormant for years and cause little or no inflammation until conditions change and the gods are once again angry (at you). In its dormant state, it is defenseless and may eventually be destroyed by the proinflammatory efforts of the host (or not, but it remains inactive, so it is not stirring up trouble). There is one more thing to consider along these lines: Stress actually releases iron from binding molecules such as lactoferrin (Radek, 2011), giving the pathogen an advantage. When you control inflammation, you control stress. When you control stress, you get better. When you get better, you get happy. When you get happy, you live a life of reduced stress. Intriguingly, when you control stress your ability to sequester iron is enhanced, improving your ability to withhold iron, at least to some extent, from the indwelling or invading pathogen (referenced previously).

Others offer the following in answer(s) as to why anti-inflammatory drugs can help a disease caused by MAP: It has been argued that reducing intestinal inflammation by anti-TNF-α agents, such as Remicade, would allow MAP to survive and thrive. Remicade can actually reactivate another mycobacterial infection, TB—yet individuals with Crohn's improve by a variety of anti-inflammatory agents. Why? There is some evidence that typical anti-inflammatory agents used in the treatment of Crohn's (e.g., sulfasalazine, methotrexate, 6-MP and Remicade) are themselves effective anti-MAP agents (Greenstein et al., 2007; Bach, 2012). Actually, anything that effectively reduces inflammation will act to "starve" MAP of iron and could be appropriately regarded as an anti-MAP agent. Consider this: When inflammation is controlled, IL-6 expression will be reduced, hepcidin expression will wane, the transport of iron out of the macrophage is encouraged, and the pathogen will lose momentum and possibly die—problem solved (referenced in *Chapter 5*).

I think I've covered this subject well enough to allow us to move on. Now that you are *totally* convinced, my work here on earth is done. You're thinkin' Nobel Peace Prize in Medicine, too, aren't you? I have prepared my acceptance speech.

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

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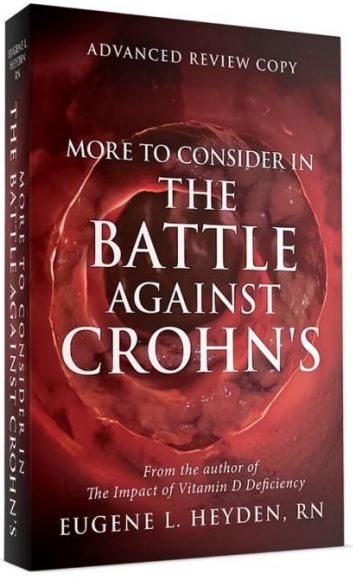

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