On the Origins of Multiple Sclerosis

"Idiopathic autoimmune disease" is the last bastion of cowards.

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Taking any antibiotic increases your risk of getting multiple sclerosis.

This fact raises a lot of questions, like "Why?"—but we'll get to that. The first one is "Are you sure?" And we're pretty sure.

See, it's Danish data. And one nice thing about having a centrally-managed healthcare system like Denmark's is that everybody's full medical records are in one place, rather than being scattered throughout the datacenters of a thousand different hospital networks and private practices the way they are in the US. This makes it easy to do retrospective studies that look at health outcomes for millions of people over entire lifetimes. It's a valuable dataset.

Analyzing this data, some researchers found in 2011 that leaving the doctor's office with a prescription for ANY kind of antibiotic—penicillin, flagyl, azithromycin, you name it—makes it significantly more likely that you'll walk back into a doctor's office to be diagnosed with MS at some point in your life. For some antibiotics, the risk was nearly double that of age-matched people who didn't get the drug. Again we're going to leave aside the "why" for a moment, because this is a great chance to dig in to one of medical science's most core aspects, and the source of its greatest failings: transitive inference.

From a solid study like Nørgaard *et al*, we can start to ask questions. We know that there's nearly a 1:1 correlation between getting diagnosed with an STD and getting a prescription for antibiotics. Wouldn't that mean there's a correlation between STDs and MS?

As it turns out, a literature search turns up a number of frantic epidemiologists trying to inform readers that MS behaves strikingly like an STD in some ways, and scrambling for mechanisms to explain this. I followed up with one of these researchers, Dr. C.H. Hawkes, who told me he had staked a large part of his professional reputation on this hypothesis—and lost.

But reading his work, I can hardly blame him, because it *is* a damn good fit in some ways. Like an infectious disease, MS sometimes emerges in geographic clusters, triggered by an influx of new people. Much of this research comes from places like Iceland, which suddenly became a high-risk area shortly after the arrival of allied troops during WWII. Interestingly, it was found that people born in Iceland who later moved to a low-risk place could "adopt" the lower risk ratio of their destination. The kicker? The strength of that phenomenon abruptly starts declining at age 15 or so—around when people start to become sexually active. The data on MS spans decades, so you can even spot the uptick in MS among women when oral contraceptives were

invented and more people started having unprotected sex. Communities with strict religious morals around premarital sex tend to have lower rates of both STDs and MS. There was such a mass of circumstantial evidence that Hawkes planted his flag on this hypothesis.

Nobody at his institution took it seriously, partly for the simple reason that being married to someone with MS does little to increase your risk. At a societal scale, MS can behave like an STD, but at an individual scale, that behavior vanishes.

These clues are tantalizing, but the fit is not quite right—especially given the lack of an identifiable pathogen that could specifically cause demyelination, optic neuritis, and the other characteristic symptoms of MS. The recent literature on MS as an STD is dominated by a flurry of single-author papers with titles that end in question marks—a common grave marker for dead hypotheses. We have farther to go before we plant the flag.

But Hawkes was onto something. He was close: seeing a real effect, but a *transitive* one—what if STDs DO cause some cases of MS, but only indirectly?

What if antibiotics cause MS, and STDs just cause antibiotics?

The tighter the correlation is between two variables, the more difficult it is to tell them apart with statistics. And unfortunately for Hawkes, the modern medical system does few things more efficiently than it prescribes antibiotics for STDs: there's a solid biological yes/no test, and if it comes back positive, it's practically malpractice *not* to give someone a Z-pack.

The next obvious question—and here we start to get into *why*—is "so what's downstream of antibiotics?"

Because there's no reason to assume that the buck stops here; I said "Antibiotics cause MS", but it's clearly not as simple as that: it's not a one-to-one thing, there's an element of chance involved. But how do antibiotics give you an extra spin on that wheel of fortune?

The researchers in that antibiotics paper offer a hypothesis in line with the current understanding of MS as an autoimmune disease. They suggest that certain pathogens trigger an autoimmune reaction, where the body attacks its own myelin-producing cells, and that these pathogens also lead to antibiotic prescriptions: a common-cause model.

But this hypothesis suffers many of the same problems as Hawke's: Which pathogens, and how? There's been some fuss around Epstein-Barr and MS in the past year or two, but EBV isn't treated with antibiotics, and there's no solid explanation for why it would produce the specific pathology of MS. [1]

While it's possible to postulate complex interactions with people's genomes, there's a much more natural place to look.

A Weed in the Garden

Most of the protein-coding genes in your body right now are not human genes; they are those of symbiotic bacteria that live in your intestines. You inherited many of these bacteria from your parents when you were very young, and many of them will be passed on to your children in turn. This ecosystem inside each of us, cultivated by our ancestors over generations, hosts hundreds of species: a whole extra genome, a hundred times as large as your 23 chromosomes, and controlled only loosely by your body. The immune system can suppress, creating structure by subtraction like a sculptor. Your intestinal cells secrete mucus which feeds certain bacteria. But all in all, we are like a gardener tending herbs: Fertilizing, weeding, propagating, and harvesting.

Clostridium perfringens is a weed in the garden. A sort of bamboo. Not literally of course, but in nearly every other way. For one, it's one of the fastest growing organisms on Earth. A bamboo stalk can grow up to three feet a day, when conditions are right, and likewise *C. perfringens* can double in number every six minutes. Leave a single cell alone for an hour and you've got 1024 cells; leave it for five hours and you've got more than 40 trillion, which is the average bacterial carrying capacity of the human gut.

It's hard to get rid of, too. Everyone who's planted a clutch of bamboo in the garden and then tried to pull it out a few years later knows that its rhizome is hardy and insidious: pull and dig and spray all you want, but some corner of a root will survive, and eventually you'll find the dreaded shoots poking up through your lawn.

While bamboo isn't a problem in a healthy forest—and in fact plays a key role in many ecosystems (if you want pandas, you need bamboo)—its fast growth habit can turn it into a blight. If a forest burns down, and the conifers and hardwoods and pandas perish in the fire, you can end up with a thicket of nothing but bamboo. The thick leaf cover and competitive root system prevents other seedlings from getting the sunlight they'd need to regrow. The birds that would nest in the hollows of trees can't return. And with no pandas to eat the bamboo, the forest falls silent except for the sound of tall canes clattering in the breeze.

C. perfringens is a spore-former, enabling it to survive insults that would wipe out most other species. This combo of durability and rapid growth means that *C. perfringens* thrives in the face of adversity. This ties in to an important finding from the Nørgaard paper, which I mentioned earlier: it's not just one kind of antibiotic that increases your risk of MS, it's **any** kind of antibiotic. Some of these drugs have virtually no resemblance to each other at a molecular or functional level; the only thing they have in common is that they kill bugs dead. This suggests that it's not "off-target" toxicity of the drugs to human cells, but something about the antibiotic-ness itself that's causing problems.

Now, most of us have *C. perfringens* in our guts. It's what we call an *opportunistic* pathogen, meaning it can live in harmony or cause trouble, depending on a few different factors. It's also important to remember that, when you're dealing with microbes, **strains matter**: there's a zoo of different kinds of *C. perfringens* out there—the pathogenic ones are designated strains A through G, and they can produce a variety of toxins, alpha through iota.

Most of the time, if you've got a *Clostridium perfringens* infection, it presents with all the hallmarks of classic food poisoning: diarrhea, gas, etc. This is affectionately known in the medical community as "fried rice syndrome", because acute cases can often be traced back to the blessing and bane that is cheap Chinese food—*C. perfringens* spores can survive most kinds of cooking, and when a pile of rice sits out under a warming lamp for 6 hours, it's a recipe for a pretty hefty dose of bacteria.

But some strains are more subtle. Types B and D produce a really unique toxin called *epsilon toxin*, or ETX.

And now we get into the real *why*.

ETX is a soluble, pore-forming toxin. The bacterium synthesizes it in an animal's gut, and it gets released into circulation. It crosses the blood-brain barrier—we're still not sure exactly how. Once it's in the brain, ETX selectively binds to the oligodendrocytes—the cells responsible for myelination. It then does a little Voltron number with a few of its friends, and unfolds into its final form: a straw shape. It pokes a hole in the oligodendrocytes, and they start leaking like a pouch of capri sun. And then they die.

Interestingly enough, ETX is well-recognized as a cause of disease in veterinary medicine, where it causes something that looks an awful lot like MS in cows, goats, and sheep. The general consensus is that this doesn't happen to humans, although I've yet to hear a good argument for why it wouldn't. When I've brought it up to researchers in the past, people have said "well, where's the people dying of it?". When I bring up MS, they typically go "Well, that's not really my field, and besides, isn't that autoimmune, and besides, didn't they sort that out with the EBV stuff?"

But the greatest enemy of truth isn't ignorance, it's the illusion of knowledge—and "idiopathic, autoimmune" is a cop-out. It's a medical shrug. Yes, we see a lot of inflammatory markers like white blood cells surrounding oligodendrocytes in MS, and the party line is that these are the problem: they've somehow mistaken a healthy cell for a foreign invader, and they're erroneously tearing it apart. But what if that's just the immune system responding the way it's supposed to, to a cell that's issuing distress signals because it's dying? The pores formed by ETX aren't big enough to see in microscopy, or on an MRI.

A glorified case of food poisoning

So here's the hypothesis, long story short:
It's known that we're all exposed to *C. perfringens* all the time. Two-thirds of grocery store chicken samples have detectable amounts. A small fraction of these are ETX-producing strains. In a healthy gut, a few spores of ETX-producing *C. perfringens* isn't enough to cause problems. Even if a small colony manages to establish in your gut, competition keeps it in check.

Then you get an STD, or you're in a bike accident and the scrape gets infected. You take the standard course of antibiotics, and this is where things start to go downhill very quickly. Suddenly, the competition in your intestines is gone. *C. perfringens* blooms, and now you've got a few billion cells pumping out a toxin that makes its way into your bloodstream and starts blowing holes in the cells that are supposed to

maintain the insulation on your neurons. Signals slow down, start petering out before they get where they're going. Your body starts to go haywire.

You go back to the doctor, you get the MRIs, and you've got the characteristic brain lesions. It's MS. Since we currently understand MS as an autoimmune disease, they throw a cocktail of antibiotics, antivirals, and other weird drugs like dimethyl fumarate [2] at the problem, under the logic that something is riling up your immune system and causing it to attack your brain—and that quelling the infection might stop the autoimmunity. If you're lucky, it works! It gets better, or at least stops getting worse.

Why? We're not sure, but you're just glad that the nightmare is over. For the moment. Now you get to spend the rest of your life living in fear of the apparently inevitable relapse, which can be triggered by stress, illness, poor diet, or any number of other things.

Astute readers will notice that this bears some resemblance to the way it often goes with another illness caused by a *Clostridium—C. difficile*—when it's treated with the standard antibiotics. A heavy duty course of antibiotics alone, effectively burning down the forest all over again, is sometimes enough to give the other organisms a chance to grow back, establishing a new—but delicate—equilibrium: Remission.

Because *C. perfringens* is so ubiquitous, this is something we'd miss with standard microbiome analysis techniques: a 16s gene sequence can barely tell you the species of an organism with any degree of reliability. It won't tell you anything about whether or not you've got an ETX-producing strain on your hands.

To be clear: I'm not the only one who thinks this. In 2013, some scientists at Cornell isolated an ETX-producing strain of *C. perfringens* from the gut of a patient presenting with MS. In a followup paper, the same group fleshed out the theory further, pointing out that the earliest MS lesions typically don't have immune cells around them—which suggests that the oligodendrocytes are dying before the immune cells get there.

In 2019, another group published their finding that patients with MS and related diseases are 2.4x as likely as healthy controls to have antibodies to ETX in their serum [3]. And as it turns out, a number of drugs which help with MS—although we don't understand why they help—happen to inhibit the growth of *C. perfringens*. This is not conclusive by any means, but it's a remarkable set of findings given the strength of the mechanistic explanation.

Here, I'm going to add my own finding to the pile. It starts with a look at the odds ratios from that Nørgaard paper, because the most interesting thing about it is that—while nearly all antibiotics increase MS risk, they don't all increase it to the same extent: some are worse than others.

Table 3. Odds Ratio for Multiple Sclerosis According to Use of Any Type of Antibiotic and Different Types of Nonpenicillin Antibiotics in 3,259 Multiple Sclerosis Cases and 32,590 Population Controls, Denmark, 1996–2008[a]

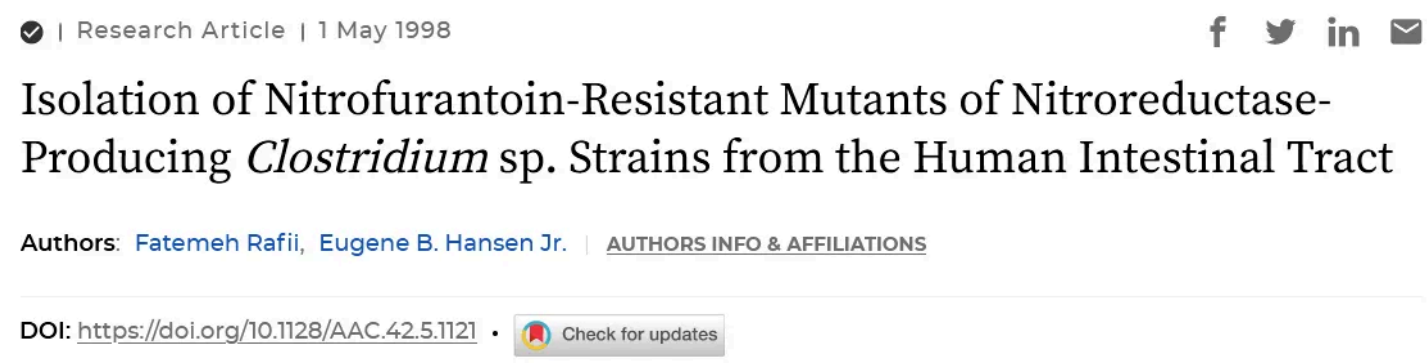
Type of Antibiotic	No. of Cases	No. of Controls	Odds Ratio[b]	95% Confidence Interval
Any antibiotic	2,292	20,802	1.41	1.29, 1.53
Pivmecillinam	168	1,265	1.35	1.14, 1.59
Macrolides	918	7,514	1.31	1.21, 1.42
Tetracyclines	302	2,318	1.33	1.18, 1.51
Sulfonamides/ trimethroprim	507	4,150	1.26	1.14, 1.40
Nitrofurantoin	76	425	1.83	1.42, 2.34
Quinolones	115	1,066	1.08	0.89, 1.32
Metronidazole	298	2,389	1.27	1.12, 1.44

[a] Use of penicillin was recorded from 1995 through the calendar year before the date of clinical onset of multiple sclerosis/index date.
[b] Conditional on date of birth and sex.

Far and away the **worst** is a drug called nitrofurantoin. Where quinolones increase your chance of getting MS by 8%, and flagyl increases it by 27%, nitrofurantoin comes in at a whopping **83%**. So what makes nitrofurantoin so much worse than the others?

A lot of antibiotics have a mechanism of action that makes them selective for one type of microbe over another. I figured maybe nitrofurantoin doesn't kill gram-positive organisms like *Clostridium*, leaving them to thrive in the absence of competition. But as it turns out, nitrofurantoin is basically a molecular grenade: once it gets inside the cell, a common enzyme essentially "pulls the pin" on it—at which point the molecule starts spitting out reactive oxygen species. An equal-opportunity destroyer.

But, on a whim, I plugged some basic keywords (*Clostridium perfringens* nitrofurantoin) into Google Scholar, and…would you look at that.



Clostridium perfringens is specifically resistant to the antibiotic that causes the greatest increase in MS risk. It has an enzyme that dismantles the "grenade" without ever pulling the pin.

Takeaways

Where do we go from here?

I mentioned earlier that ETX is a well-studied problem in veterinary medicine, and vaccines are available to prevent it; maybe one of these can be repurposed. Bacteriophages, viruses which infect certain strains of bacteria, also seem like an obvious approach when you're dealing with a disease that might be caused by a single bacterial pathogen. Phage therapy sometimes requires the offending organism to be isolated from each patient, because strain-level variation in susceptibility means that what works for one patient won't work for another—but it's possible that ETX-

producing *C. perfringens* are homogeneous enough for a general phage solution to be developed. A monoclonal antibody against ETX could neutralize the toxin in the bloodstream, and would make a lot of money if it worked—although this has the downside that it would cost a lot of money, since you'd have to take it regularly for the rest of your life rather than just dealing with the problem at its source.

And as always, the title of this publication applies: there are case reports of people being cured of MS [4] by fecal transplant. Some regained the ability to walk, which is frankly miraculous given the prognosis with standard-of-care treatments.

All in all, it's horrible, the notion that so many people are living and dying debilitated with what amounts to a glorified case of food poisoning—but it's also reason to hope for a cure, if we're willing to reject the conventional wisdom that the best we can do is manage symptoms.

In any case, I'll be steering clear of the fried rice at #1 China Buffet, unless I've just seen them bring out a fresh tray.

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1 EDIT: A commenter helpfully pointed out that there's no reason to disqualify a joint EBV/ETX model, since the available data suggests that EBV might be *necessary* but not *sufficient* for MS to emerge, and pretty much everyone is exposed to EBV at one point or another.

2 An industrial chemical used to prevent furniture from getting moldy, now sold as Tecfidera at a cost somewhere in excess of $50,000/yr in the US. Nice.

3 The actual numbers are 10% among controls vs. 24% among patients. One natural question is "If ETX causes MS, why is it not 100% among patients?". A potential answer is that the body's antibody-generation process is not perfectly efficient; perhaps only some portion of patients' immune systems manage to figure out the right configuration of antibodies to counter the toxin, or only after a certain length of time for trial-and-error. Another possibility is that what we call MS is multiple different diseases, and ETX is only responsible for some fraction of them.

4 Technically "permanent remission", since MS is by-definition incurable.