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Histamine Issues, and a Follow-up on a Couple of DAO Supplement Test Trials

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As you may recall, about two years ago, the Microscopic Colitis Foundation published a newsletter that included a description of a couple of personal test trials using diamine oxidase (DAO) enzyme supplements in an attempt to prevent reactions from too much histamine in the diet. At the time, the results of the trials were generally good, especially for a product named HistaResist.

But alas, similar to the conclusions reached by many official short-term medical trials, the conclusions stated in the article did not stand the test of time. This appears to be a very good example of the centuries old phenomenon known as:

The Law of Unintended Consequences
Basically, unintended consequences fall into one of three categories:
1. A positive effect — better-than-expected
2. The expected effect, plus an unexpected negative effect
3. A totally unanticipated effect that's radically different from, or opposite the intended effect

Unfortunately, my experience would clearly be classified under the third category of unexpected consequences. An accurate one-word description of my experience would be “catastrophic”. In such situations, and sometimes in medicine, the “law” takes the form of:

"The cure is sometimes worse than the disease".
Getting back to the point made above, regarding the precarious nature of short term trial results, it's worth noting that most trials done by pharmaceutical companies, in order to qualify for FDA approval of a product, are typically way too short to provide any information about the performance of that product when used for

medium or long-term treatments.

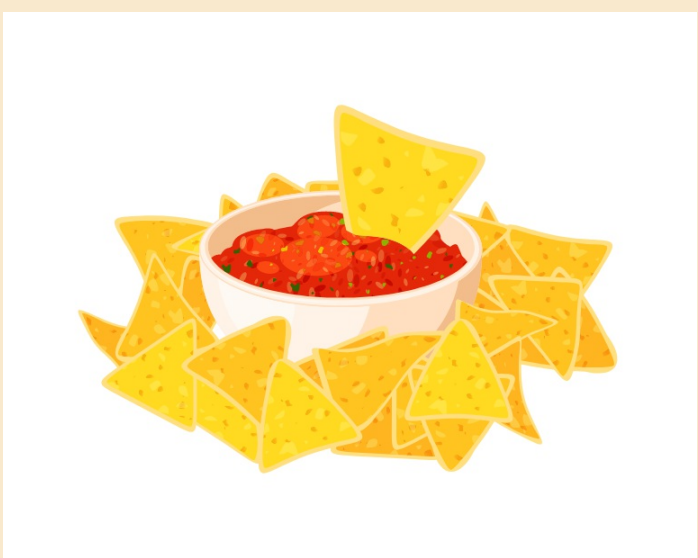
Proton pump inhibitors (PPIs), for example, are a good example of this. Although they appear to provide some benefit when used for a couple of weeks or less, when used longer, they very often have very adverse effects on the digestive system. Published medical research proves that long-term use of PPIs leads to a significantly increased risk of serious adverse side effects. The quote below is taken from an article published on the U.S. Pharmacist website (Ambizas, & Etzel, 2017, July 19):[1]

. . . Since 2010, the FDA has issued various safety warnings regarding the potential effects of long-term use of PPIs: risk of fractures, hypomagnesemia, Clostridium difficile–associated diarrhea, vitamin B12 deficiency, acute interstitial nephritis (AIN), and cutaneous and systemic lupus erythematosus events. . . .

And yet, doctors continue to prescribe PPIs, and when a patient's symptoms continue after an initial treatment period, many of them continue to prescribe PPIs for medium and long-term use. Many, many cases of microscopic colitis have been attributed to the use of PPIs. Yet apparently, the FDA feels no obligation to resend their approval, because according to the article mentioned above, the annual sales value of PPIs in the U.S. alone, was almost $10 billion in 2012, and the market continues to grow. Consequently, the FDA is not likely to withdraw its approval for PPIs, simply because pharmaceutical manufacturers are making huge profits from those sales. This is not likely to be mentioned anywhere else, besides here, but doctors are obviously making a lot of money treating patients because of these iatrogenic effects.

Short term trial success, does not confirm successful long-term results.

So, we have to keep in mind the fact that many medical treatments, and some supplements (other than nutritional supplements, such as vitamins and minerals), should only be used for short-term treatments, because that's the way they were tested. This especially applies to supplements that mimic enzymes that are naturally produced by the body. Regardless of the type of treatment being trialed, the conclusions reached during short-term trials often will not hold up over the long-term. Usually, this happens because the body tends to adapt to the treatment over the long term, thereby altering the pharmacodynamics of the medication or supplement (in this case) to either reduce its efficacy, or in some cases, cause the immune system to begin producing antibodies against it. In a situation where allergic issues are being treated, for example, the supplement or medication may eventually cause the very symptoms that it is designed to treat.



So here's the rest of the story.

Over the years, I had determined that I can safely eat limited amounts of certain high histamine foods, including one snack each morning and each afternoon, consisting of half a large, frozen, barely ripe banana, garnished with a few dabs of cashew butter or almond butter. And I could safely eat a near-normal amount of tomato-based salsa at noon with

tortilla chips and Fritos.

After I discovered that the DAO supplements appeared to work, similar to what most of us would do in a situation such as this, I began to eat somewhat larger amounts of high histamine foods, while taking the supplements to resolve any symptoms. And naturally, typical of human behavior, I consistently pressed the upper limits of the amounts of high histamine foods that I was able to safely consume, as long as the supplement I was taking prevented any histamine reaction symptoms.

But my blissful histamine homeostasis began to deteriorate.
Eventually, I began having histamine reactions that I assumed were due to consuming too much histamine in my food. Instead of half a banana, for example, I was eating a whole banana, and I was eating larger amounts of tomato-based salsa with tortilla chips and Fritos. Unfortunately, cutting my snacks back to half a banana, and eating smaller amounts of salsa, did not resolve the problem, and my histamine reaction symptoms were beginning to become chronic. Completely avoiding bananas and salsa did not seem to resolve the chronic histamine symptoms, even though I was still taking the DAO supplements.

Then I discovered that Benadryl would stop the symptoms.
Life was good again, as long as I took Benadryl throughout the day. I didn't exceed the dose restrictions posted on the label, but I did take it as frequently as the label allowed. Although doing this seemed to work to relieve the symptoms, it didn't take but a few days before I suddenly had a significant allergic reaction.

Had I created a new allergy?
I had taken a Benadryl tablet at 10 PM when I went to bed, at 3 AM, when I woke up itching, and at 8 AM between breakfast and my mid-morning snack. Because of my stroke five years ago, I'm considered a stroke risk, so I take a statin (atorvastatin), a blood thinner (a generic for Plavix), and a blood pressure medication (an ACE inhibitor, lisinopril). Because I'm taking a statin, I take 200 mg of ubiquinol (which is twice as effective as coenzyme Q 10), and because of my limited diet, I take a number of vitamin and mineral supplements. My blood pressure is normally relatively low, so after I eat breakfast, I check my blood pressure and heart rate before I take all my pills. If my systolic blood pressure is 100 mmHg, or less, I don't take the lisinopril that day.

When I checked my blood pressure (BP) at about 7:20 AM, (after breakfast), it was 126/73 mmHg, and my heart rate was 71 bpm. I then took all of my pills, (except that the magnesium glycinate, and magnesium threonate are divided into three doses, and the other doses are taken after lunch, and before bedtime). That was approximately 40 minutes before I took the last Benadryl tablet. A few hours later, I noticed that my heart seemed to be pounding. Obviously, I was having some sort of allergic reaction, so naturally I suspected the Benadryl. Alas, allergic reactions tend to create confusion, so it didn't occur to me to immediately begin checking my BP and heart rate.

Eventually, it dawned on me that I should be checking my BP and heart rate.
I may have missed the peak of the reaction, because I didn't start checking my readings until about 12:15 PM, and by then, the heart pounding had been going on about half-an-hour, or longer. At that

point, my BP was 107/74, and my heart rate was 147 bpm. By about 12:30 PM (only 15 minutes later), my BP had fallen to 89/63, and my heart rate had dropped to 120 bpm. By about 1:00 PM (30 minutes later), my BP was 86/60, and my heart rate was 117 bpm. When I checked at about 2:45 PM (1 3/4 hours later), my BP had increased to 97/55, and my heart rate had dropped to 85 bpm. By 4:30 PM (another 1 3/4 hours later), my BP was 98/63, and my heart rate was 66 bpm. So, I stopped monitoring them at that point, since these were close to my usual readings.

Was this an anaphylactic reaction?
BP and heart rate excursions such as these are common during allergic reactions, although in severe cases, BP fluctuations can be much more extreme. During anaphylactic reactions, BP can get critically low. I didn't notice any breathing problems, a rash, or hives, so this probably wasn't a true anaphylactic reaction, although a repeat reaction might result in much more severe symptoms. Were the tachycardia and blood pressure excursions due to an interaction between Benadryl and ubiquinol?

Was the reaction a response to a Benadryl overdose?
I note that the reaction appeared to occur during the time frame at which Benadryl normally reaches the maximum concentration in the blood, which is typical of an overdose reaction (although I was taking Benadryl according to label directions). Did one of my medications or supplements interact with the Benadryl to increase its efficacy? A search of the Internet didn't turn up any interactions, other than the possibility of an interaction with coenzyme Q 10 (ubiquinol), but even that interaction possibility doesn't appear to have ever been confirmed.

Whatever the cause, at my age (I was 80, then), a heart rate in this range could be life-threatening. The American Heart Association only lists maximum heart rate limits up to 70 years of age, and their limit for that age is 150 bpm.[2] As a side note here, does the American Heart Association believe that we shouldn't live past the age of 70? Or do they just believe that after that age, we shouldn't be interested in any statistics related to heart performance?

If we extrapolate the numbers in their table to match the age of 80, we can see that the resulting average maximum limit would be 140 bpm. This also matches the maximum heart rate result we get if we apply the old formula of 220 minus our age. So my heart rate might have been maxed out at 147 bpm.

It dawned on me that what I was doing was counterproductive.
A little logical thinking unveiled the obvious — I had developed an allergy to the DAO supplement, and it was causing the very symptoms that it was supposed to prevent (itching due to histamine buildup). And it's conceivably even possible that the reaction against the DAO supplement may have contributed to the Benadryl reaction. Obviously, though, that's strictly speculation, because there doesn't appear to be any medical research regarding this issue. So, I immediately stopped taking Benadryl and the DAO supplement (HistaResist). Even then, it took more than a couple of weeks for my histamine reaction symptoms to slowly fade away (after eliminating all high histamine foods from my diet).

I decided to try those high histamine snacks, again.
After my symptoms were gone for a week or so, I decided to slowly

reintroduce frozen banana snacks, with cashew butter or almond butter, and salsa, back into my diet. Not surprisingly, I found that I could eat the same amounts of those foods (without having any histamine symptoms), that I had been eating originally, (before I started using the DAO supplements).

What have I learned here?
Based on my experience, at least, attempting to exceed my histamine tolerance levels by taking a DAO supplement appears to be an exercise in futility, at best. While there might be some short-term benefits, there don't appear to be any long-term benefits. For me, at least, my maximum safe histamine intake level appears to be a consistent threshold, and cannot be extended by the use of DAO supplements.

As long as I stay within these limits, I'm okay, and I don't have any histamine symptoms. That said, during pollen season. I often find it necessary to reduce the amounts of those high histamine foods in my diet, apparently because of the increased histamine in circulation, due to my pollen allergy. But the main point here, is that trying to find ways to get around those limits by taking DAO supplements is obviously risky behavior that I won't be pursuing in the future.

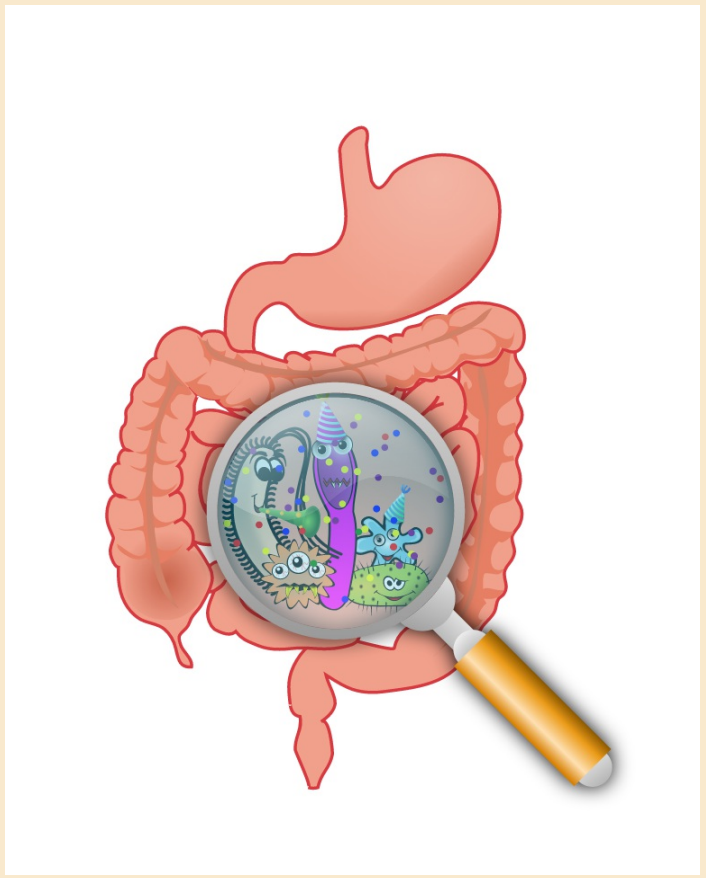
Tracking down the cause of a histamine problem tends to be difficult.
Most foods that are listed as containing high histamine levels are initially low to medium histamine level foods. As they age, unless they are frozen, their histamine levels increase. In some cases, that is, for some foods, histamine levels increase dramatically, especially foods such as bananas, chicken, fish, and fermented foods. Others, such as nuts and grains tend to show histamine level increases much more slowly, depending upon their moisture content.

Note that some foods tend to block DAO production.
Those of us who have histamine problems have to be careful about drinking tea, for example, because both black and green teas can interfere with DAO production. It's known that alcohol and energy drinks also tend to block DAO production, and in theory, caffeine blocks the proper functioning of DAO.

But the metabolism of histamine involves two enzymes, DAO, and HNMT
This is true for all mammals, including humans. HNMT is an abbreviation for Histamine N-methyltransferase. S-adenosylmethionine (SAM) acts as a high-energy methyl donor to allow the methylation of histamine, thereby forming N-methylhistamine (Ouyang, Wu, Li, Sun, & Sun, 2020).[3] Those of us who are familiar with the issues caused by the fact that over half of us have compromised methylation abilities, may recall that for some of us, the production of SAM may be compromised. Methylenetetrahydrofolate reductase (MTHFR) is the primary enzyme controlling folate metabolism. MTHFR gene mutations can cause a deficiency of this enzyme that leads to increased homocysteine levels, and consequently, reduced levels of SAM (Jadavji, Wieske, Dirnagl, Winter, 2015).[4] So those of us who have methylation issues may have compromised SAM production, resulting in limited HNMT metabolism of histamine, that leads to a histamine buildup.

But what happens in the intestines?

According to Johns Hopkins University (2021, December 3),[5] the relative contributions of DAO and HNMT vary in various tissues. For example in the bronchial epithelium, HNMT dominates histamine metabolism. Unfortunately, precious little medical research data exists to provide an indication of which of the two enzymes normally dominates the degradation of histamine in the intestines. Most medical articles seem to basically state that these issues are poorly understood (Smolinska, Jutel, Crameri, & O'Mahony, 2013).[6] HNMT activity has been shown to vary by as much as 5-fold among various individuals, and apparently, according to Johns Hopkins University (2021, December 3), these variations are primarily due to genetics (which brings us back to the MTHFR gene mutation issue).



An article published in the journal Nutrients infers that DAO is the dominant histamine degrading enzyme, by virtue of the fact that it never even mentions HNMT anywhere in the article (Schnedl, and Enko, 2021).[7]

An article published on the Australian website MTHFR Support agrees that DAO is the primary enzyme that breaks down histamine in the digestive tract (MTHFR Support, 2021).[8] The website points out that gut bacteria play an important role in the creation of histamine, and the breakdown of histamine, as they ferment some of the byproducts resulting from the digestion of our food.

Gut bacteria species that cause histamine levels to increase in the gut include:
1.Lactobacillus species, including Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus delbrueckii, Lactobacillus lactis, and Lactobacillus reuteri.
2. Enterococcus species, including Enterococcus faecalis, and some types of E. coli.
3. Klebsiella
4. Enterobacter and citrobacter

Gut bacteria species known to degrade histamine include:
1. Bifidobacteria species, particularly Bifidobacterium infantis.
2. Lactobacillus species, including Lactobacillus gasseri, Lactobacillus Plantarum, Lactobacillus rhamnosus, and Lactobacillus salivarius.

SIBO is a common problem whenever MC is active.
Obviously, if either of these groups gets out of balance, the result will have a significant effect upon histamine levels. And small intestine bacterial overgrowth (SIBO) is very common (in fact, it probably affects virtually all of us) whenever MC is active, because our digestion is severely compromised due to the inflammation.

The predominant histamine degrading enzyme in the gut may be irrelevant.
Which of the two enzymes breaks down histamine in various tissues

(or if some other enzyme is responsible) may be irrelevant, because if we have a histamine issue that causes us to itch, for example, our respiratory system doesn't itch, nor do our intestines. Instead, our skin itches, suggesting that this is a systemic problem, not confined to any particular organs, or tissues. If that's true, logic suggests that both enzymes might be equally important, but there are no research data to justify that assumption. Very little relevant research has been published, because this issue remains largely unexplored by medical researchers.

The take-home message here is:
Our immune system has evolved for at least several hundred thousand generations. It functions autonomously, and not only does it protect our bodies from infection and disease, but it is also responsible for healing, and repairing any damage that's incurred by any organ as a result of infection, disease, or trauma. That's a huge responsibility, so it has become a very complex and sophisticated system. Consequently, we shouldn't be surprised that in order to reliably and consistently perform all its duties, our immune system has become very unforgiving.

Attempting to convince our immune system to overlook a problem that it has detected is typically counterproductive, at least in the long term. Sooner or later, it tends to discover how we're trying to manipulate and deceive it, and it usually punishes us for that transgression by triggering a reaction against the substance that we've been using to attempts to deceive it.

In my scenario described above, for example, I was using a DAO supplement. DAO supplements mimic the natural DAO produced by the body, but they're certainly not identical to the DAO that our body produces. In general, the active ingredient in DAO supplements (as is the case with most commercially produced enzyme supplements) is either animal-based, or plant-based. The particular product that I was using is based on porcine kidney protein concentrate (pig kidney), plus other ingredients. Our immune system is capable of detecting the fact that these supplements are not our own natural DAO.

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