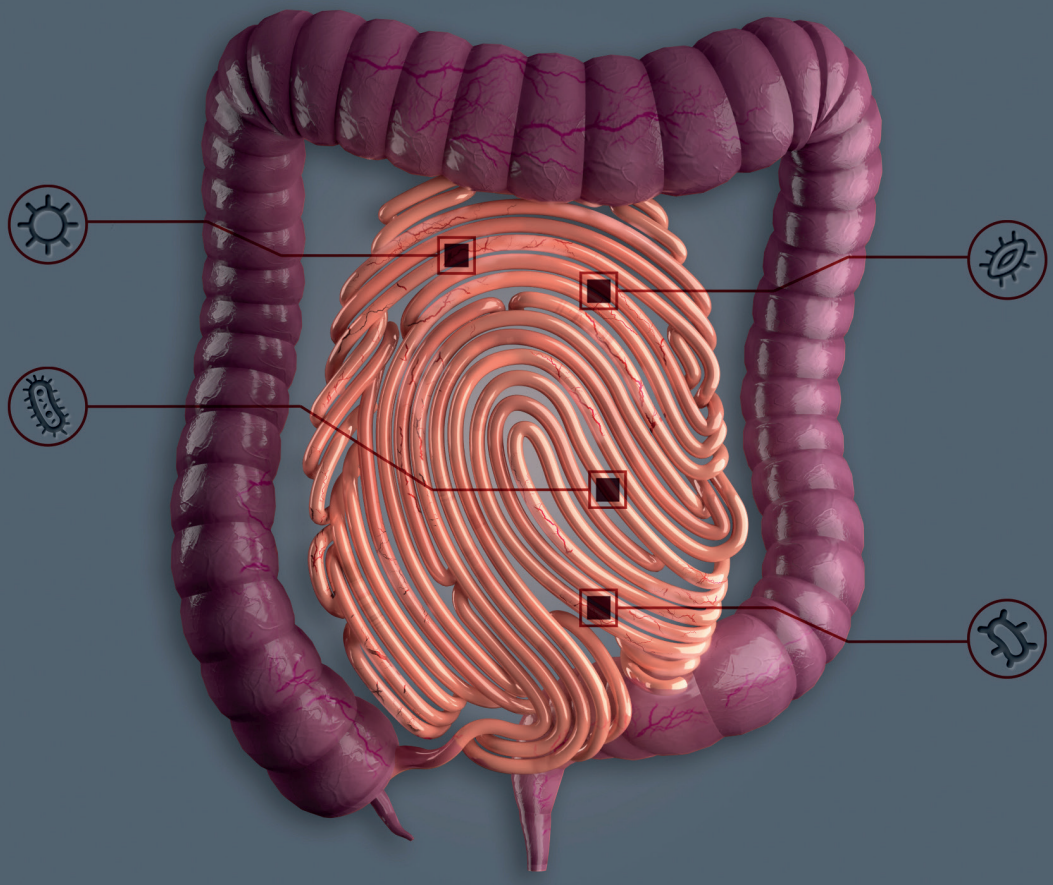
IBSYNCRASY

NOT EVERY IBS IS THE SAME **FIND YOURS**



INDIVIDUALIZED IRRITABLE BOWEL SYNDROME TREATMENT BASED ON **OVER 1400 REAL CASES**

THEODOROS **PREVEDOROS**
Biochemist MSc

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Author: Theodoros Prevedoros

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Disclaimer

The therapies described in this book require supervision by an experienced medical professional. Nutrient overloads or deficiencies can have a powerful effect on body functioning and improper treatment can cause harm. The gastrointestinal system is a very complex organ, and accurate diagnosis of nutrient imbalances requires testing of blood, stools and urine, together with a detailed knowledge of a person's medical history, traits, and symptoms. Readers must not attempt self-treatment based on information in this book. The case histories in this book provide examples of the treatment approach (supervised by their primary physician) for specific biochemical imbalances and describe the experiences of real patients. Names and certain other information have been changed to protect patient confidentiality. The case histories are intended to illustrate the clinical process and should not be regarded as evidence of treatment effectiveness.

Acknowledgements

I would like to thank two people who inspired me in this project.

Galanopoulou Dia Professor of Biochemistry: When I was in Chemistry school, I used to think that just by applying logic to several variables you could explain any system. This was true when it came to solving difficult chemistry equations, or achieving complex experiments and it helped me understand the chaotic world of chemistry and biochemistry and to get me my first job before I had even graduated. However, logic will take you as far as your senses can reach. In order to go beyond that you have to add imagination, and once you have imagination combined with logic, you stop being a scientist and you start thinking more like an artist.

Prof. Galanopoulou was my biochemistry supervisor and a professor at the University of Athens. She was a great storyteller, but, most of all, she would persuade you to doubt everything. You had to discover even the simplest of things by yourself. She would use analogies and examples that everybody would understand and her classes were the only ones in my whole academic course that I never wanted to end.

I now teach biochemistry to high school students myself and it is marvelous to see what Mrs Galanopoulou saw back then; students that are not talking, not moving their eyes and sometimes even forgetting to breathe for a while, waiting for the story to come to an end. Even if the story includes liver enzymes being attacked by paracetamol molecules.

Evan (my son): Well, he didn't really help me write this book. In fact, when I started writing it he could not even speak but he was the very first reason I decided to write it. Anyway, I wanted to thank him... just because.

Instead of preface

Human homeostasis is not something that can be described in a textbook. It cannot even be defined properly because parts of its definition are still not known. It is the sum of all the trial-and-error procedures happening in the human ecosystem, and all the ecosystems before humans, that led to the concept of human life. So, trying to heal a disordered homeostasis by giving a supplement or a drug is not an option, or at least not a viable one. Supplements and drugs are tools. Tools that work only when used properly and timely. The very first prerequisite for healing and curing a diseased state is the adherence to our evolutionary standards and respect to all the components that make us what we are; a multi-system symbiotic multi-cellular machinery with the highest degree of sophistication known so far.

Theodore Prevedoros

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Section A

The whole difference between construction and creation is exactly this: that a thing constructed can only be loved after it is constructed; but a thing created is loved before it exists.

Charles Dickens

Introduction

1.1 Gastrointestinal biochemistry: How it came to be

or From advanced biochemistry to 4,500 medical histories

Working in the medical sector was never my intention; as a biochemist I was always fascinated by science at a different level, **the molecular one.** Back in 2006, I was a scientific advisor in a center for advanced diagnostics in Athens. Luckily for me, this start-up company was very interested in bringing new knowledge to doctors and trying to incorporate these new tests in their daily practice. I was in charge of locating every new non-imaging laboratory biomarker in the market. For this reason, every time a new test was commercially available, I would be educated on its usefulness and then try to enlighten other practitioners. This was not an easy job since most doctors are quite reserved when it comes to innovation in their field, especially if this new knowledge does not stem from a pharmaceutical company representative.

During the first two years I managed to draw the attention of only 9 doctors. Mostly gastroenterologists and pediatricians, these MDs eventually incorporated several new biochemical tests into their daily practice. However, even this small sample of doctors was enough to shift my career from a biochemistry freak to a scientific advisor for several of the greatest medical centers in Greece.

To be exact, it was just one gastroenterologist who changed everything. This one doctor (who I was kindly asked not to name) is the head gastroenterologist in the biggest private hospital in Athens, accepting over 600 new patients per year. Due to our frequent engagement, our common interest in

improving the diagnostic resolution of each patient individually and our personalized disease approach, it did not take long before he asked me to help him take an extensive medical history for some of his patients. Later, I would give him a full report, along with my diagnostic suggestions, depending on the patient's history. The diagnostic center I was working for agreed to let me spend one weekday in the gastroenterologist's office and so the journey began.

In the beginning, it was just three or four patients per week, however, even then, just taking notes of symptoms was not enough. I always delved deeper into their medical, pharmaceutical, nutritional, lifestyle and family history, ending up with over 10 pages of notes. The report I prepared for the MD was extremely analytical. It was not just note taking that made the difference, though; every single one of the patients I took histories from were delighted by our conversation and were talking to the doctor and their friends and relatives about their consultation. Not only did this please the MD, but he started receiving recommendations from other doctors with whom he had no relationship with.

Gradually more doctors asked me to consult with them on difficult cases they had and, within 9 months from when I spoke to the first patient, scientific consulting became my primary job; and it still is. I have consulted with over 35 doctors on over 4,500 patients, mostly belonging to the fields of gastroenterology, pediatrics (autism and functional childhood disorders), autoimmunity, and several rare infectious cases. The basic principles that helped me reach this point, and also helped so many patients and their doctors to make the right diagnostic decisions are twofold: **Biochemical data mining** (embedment of biochemistry in mainstream medi-

cal practice) and **storytelling** (bridging the communication gap between the doctor and the patient).

1.2 Biochemical data mining: Fishing for enzymes in a sea of molecules

or How biochemistry can expand diagnostic accuracy

There are about 23,000 genes imprinted in our DNA, which ultimately get translated into proteins [1]. Their translation will take place at different times and under specific conditions or requirements. From being a bit of information imprinted inside the double helix of DNA, to performing meat protein degradation inside the stomach, these molecules undergo many different steps, requiring different enzymes and co-factors and different conditions. All these processes are tightly supervised by several homeostatic and regulatory mechanisms which ensure that the end product will have the structure that its corresponding gene dictated. While these mechanisms are extremely accurate and there are additional repair systems in case something goes wrong, each one of the 23,000 molecules may go bad and produce pathology, some more frequently than others. Just this number could explain the vastness of the different biochemical alterations that underlie a diseased state.

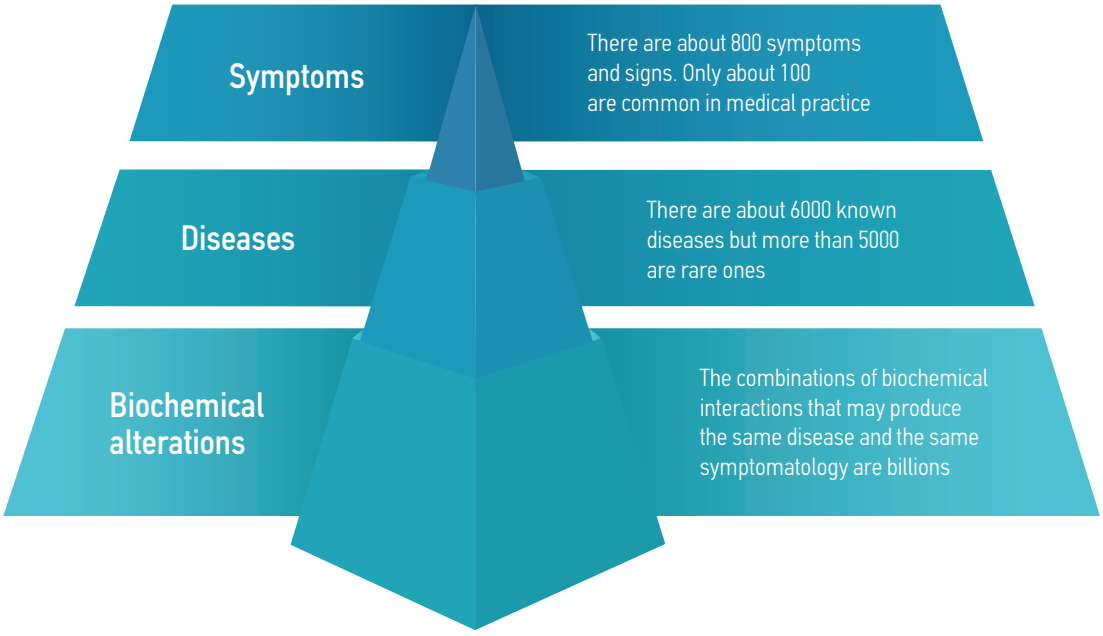
Now add to this all the post-translational modifications these proteins go through and the transcription errors that go unrepaired. What's more, even correctly produced molecules may go bad, influenced by external factors and aging. Moreover, what about coexisting factors? What about toxic substances that enter our body daily? The list of the processes that may produce malfunction at the molecular level is huge. Each one of these malfunctions has the potential to predispose us for

a specific disease. Taking all these into consideration, there are probably billions of different combinations of biochemical predispositions that could lead to disease.

How can so many different molecular alterations only produce the generally accepted 800 symptoms that exist?

It is easily understandable that there are plenty of different combinations that may bring the same disease or the same symptom to the surface.

Finite diseases and symptoms but infinite possible biochemical substrates



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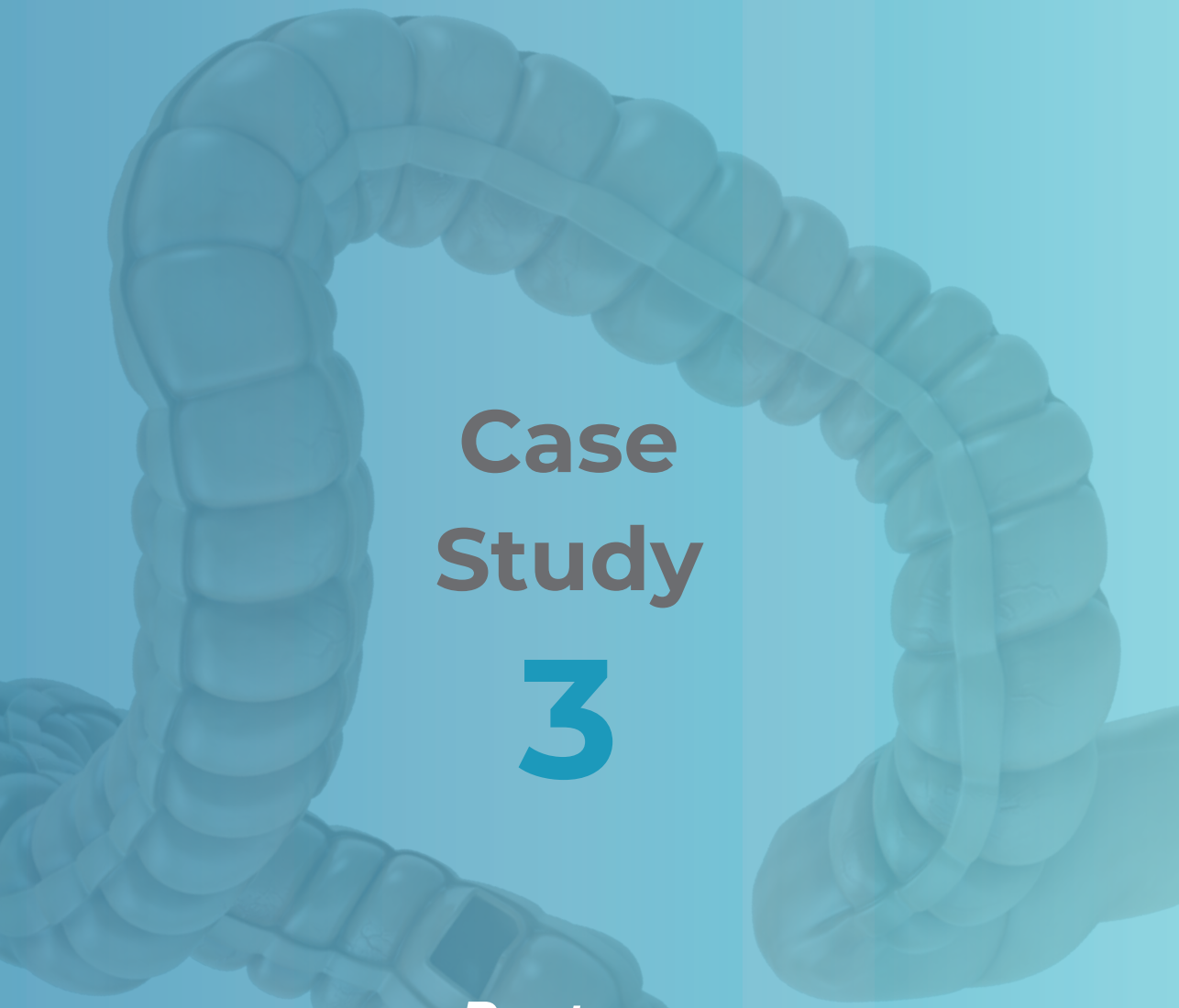
Section B

*The good physician treats the **disease**;*
*the great physician treats the **patient** who has the disease.*

Sir William Osler



Case Study 3

Proteus and Proteus-like dysbiosis

IBS patients whose MS-microbiology/PCR tests reveal massive colonization by Proteus spc

Case Statistics

Number of cases:	75	Mean age:	30-50
Rate of success:	>80%	Most common culprit:	Whey protein and glutamine supplement abuse
Most common symptom:	Urgency for defecation	Treatment length:	3-6 months

Patient reported symptom score (Before-After)

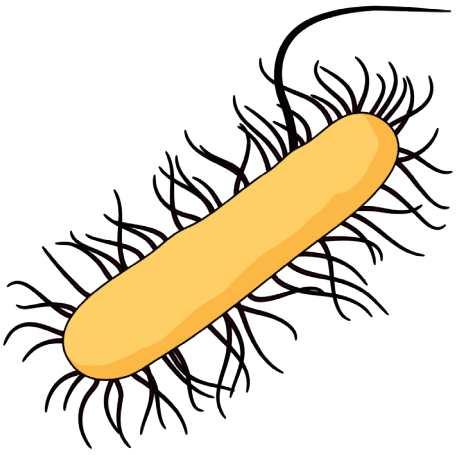
Case abstract

Explanation: *Proteus* and *Proteus*-like bacteria are strong non-commensal bacteria that possess many enzymatic activities and produce several symptoms within the spectrum of IBS. Most common recovered species are *P. mirabilis* and *P. vulgaris*. Other similar bacteria are *Morganella morganii* and *Providencia rettgeri*. Besides their overwhelming histamine–producing capacity, these microbes have the ability to translocate and perform an action that's called "swarming". Swarming takes place in response to several stimuli. One of the most studied stimuli is contact with excess glutamine. This is why glutamine should never be prescribed in IBS-D patients before Proteus colonization is excluded

Similar cases: Usually, this category of IBS patients presents with diarrhea and atopic phenomena (eczema, wheezing, asthma, migraines). During a detailed medical history, the trigger event that caused the initial inoculation of *Proteus*-like microorganisms in the patient's gut may be unveiled. Additionally, It is one of the IBS categories that men are equally affected by women. This is a pattern deviation that cannot be explained, besides the fact that men use glutamine supplements more often.

Treatment implementation: *Proteus* is a rather difficult bug to eradicate and this is why treatment is usually longer. This makes the patients less tolerant and that's why the doctor-patient communication is of big importance. It must be explained to the sufferer that what they are about to do is not a treatment, but a life plan that may last up to 6 months. *Proteus* cases are usually chronic, meaning that the damage that the gut ecosystem has suffered, because of its presence is larger in comparison with other cases.

Case Introduction



Our microbiome is a versatile organ and its composition is subject to very fast and extended modifications. Additionally, in response to several stimuli, like antibiotics, diet, stress etc, it can be extensively modified. Nevertheless, the healthy mucosal environment that our bacteria live and thrive on, possesses certain properties which define the correct genera and species that may inhabit it, while mucosal immunity prevents other, mostly pathogenic bacteria and fungi, to colonize. When these properties are modified (pH, mucus depth, sIgA content etc.) other species are favored which ultimately colonize the mucosal surface. Minor changes confer transient dysbiotic states which are usually resolved by themselves. On the other hand, extended modifications may make the mucosal environment friendly for bacteria like *Proteus mirabilis* to stay and thrive.

Once *Proteus* colonizes, it starts conditioning its environment making it more and more difficult to eradicate. *Pro-*

teus is capable of producing histamine, H_2S, urea and vast amounts of gas. All these can be very toxic to our gut and especially to other beneficial families of bacteria. This is why it is commonly found in stool microbiology tests of patients with Crohn's disease and ulcerative colitis.

Some of Proteus harmful products

Histamine	Biogenic amine that also causes extra-intestinal symptoms
H_2S	In large amounts becomes toxic to mucosal surfaces
Urea/NH_3	Alkalizes the acidic intestinal environment and permits pathogenic bacteria growth
Gas	Flatulence, bloating

Moreover, one of the main aspects of *Proteus* physiology that makes it notorious is the ability to swarm and translocate. Swarming is a property that may be enabled after specific molecular stimuli. Glutamine is well studied and it seems that it gives *Proteus* the ability to form swarms and resist antimicrobial substances. This is the reason why many patients experience worsening of their symptoms after consuming glutamine. This bacterium is also more common in people who use glutamine supplements for sports. The continuous exposure to glutamine favors *Proteus* colonization and expansion.

Another reason why *Proteus* may be difficult to eradicate is that it possesses an inherent resistance against a vast array of antibiotics. It seems that several antibiotics work in favor of *Proteus* as they sterilize parts of our gut making room for *Proteus* to expand. Any antimicrobial therapy against *Prote-*

us-like bacteria should be performed with caution and after analytical sensitivity testing.

Meeting with Jason

Jason's symptoms began about a year before coming to my office. He was on vacation with his family in rural Greece and he first noticed bloating and itching after eating seafood in a taverna. He thought it was just something transient but as the symptoms worsened he visited a gastroenterologist as soon as he got home. The first diagnosis was IBS and the doctor started him on spasmolytics and probiotics. He did not notice any improvement so he went to a second gastroenterologist who made the same diagnosis and prescribed him the same treatment, but with different brands. In the meantime, things were getting worse and he noticed that his stools were looser and the itching had spread throughout his body.

Three terrible months later, he visited yet another gastroenterologist who gave him rifaximin and domperidone in the belief that the problem was the slow passage of food from the stomach to the gut. His symptoms lessened for a while, but within a month of the new treatment he had a regression after eating a salad.

Jason was an open-minded and educated man but he was very anxious about having something serious and I tried to assure him that these symptoms are usual of a functional etiological nature.

The first thing I noticed was that Jason scratched himself throughout our consultation. I also discovered that he had a past history of heavy antibiotic use because as a child he had recurrent episodes of otitis media - we calculated that he had taken up to 30 courses of several antibiotics until the age of 18! He had a car accident a decade ago and had undergone major surgery.

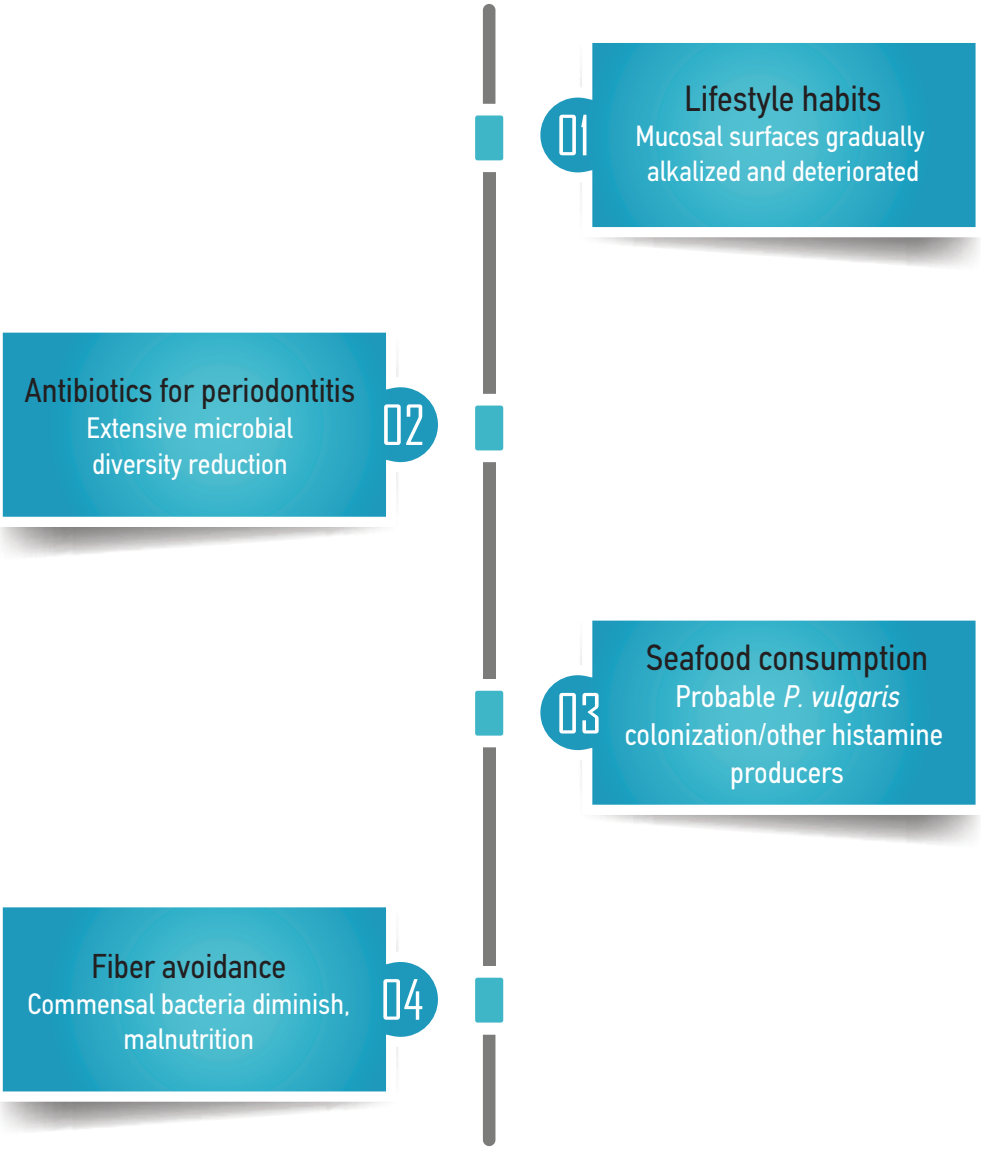
Several months before his seafood incident, he had been diagnosed with periodontitis. He was prescribed 3 different strong antibiotics and he took them for 35 straight days. During this treatment he had felt a bit bloated and he had 2 incidences of diarrhea but he did not consider it to be of great importance. His stools were softer than usual and a strange feeling around his belly button appeared, which disappeared for several hours after defecation. Finally, I discovered that he had included a lot of whey protein and glutamine in his diet as a member of an amateur weight-lifting team as a youth.

Three weeks before Jason came to my office, he went through a full endoscopic check-up which revealed nothing but an unspecific slightly inflamed ileum. His blood test showed low values of vitamin D3, low B12 and very elevated IgE.

IgE is an antibody that reflects the allergic status of a person. Normal values are considered below 100 but Jason's count was 655! This value could explain the allergic reactions he had, mainly the itching and the migraines he was suffering once or twice a week.

Trigger- effect timeline

Proteus dysbiosis



Case Diagnostics

Having already seen a lot of IBS-D patients with similar symptoms, I suspected that a gram-negative, histamine producer with potent fermentative capacity could be the culprit. I told him to stop eating high sulfur-containing vegetables (garlic, onion, broccoli, cabbage, turnips) and everything that comes from the sea. Also, I gave him a potent supplement containing quercetin which is an anti-histamine substance. He did not want to take any more drugs, otherwise levocetirizine would have been an excellent temporary solution.

A complete stool test was ordered to have a thorough look at Jason's microbiota. It also included a measure of eosinophil derived proteins, a check on the status of mucosal immunity, the amount of secretory IgA and the excretion of fats, proteins and starch. In addition, I wanted to measure the activity of the histamine-degrading enzyme DAO, along with the general histamine burden on Jason.

Biochemistry Data Mining

Main	Useful
• Urgency • Residual feeling after defecation • Stomach discomfort • Loose stool >3 times/ daily	• Triggered by seafood consumption • Exaggeration of symptoms after consuming high sulfur foods • Rectal itching and heartbeating (vagotonia) • Chronic use of glutamine supplements • Low grade ileal inflammation • Social life limited due to sudden defecation feeling

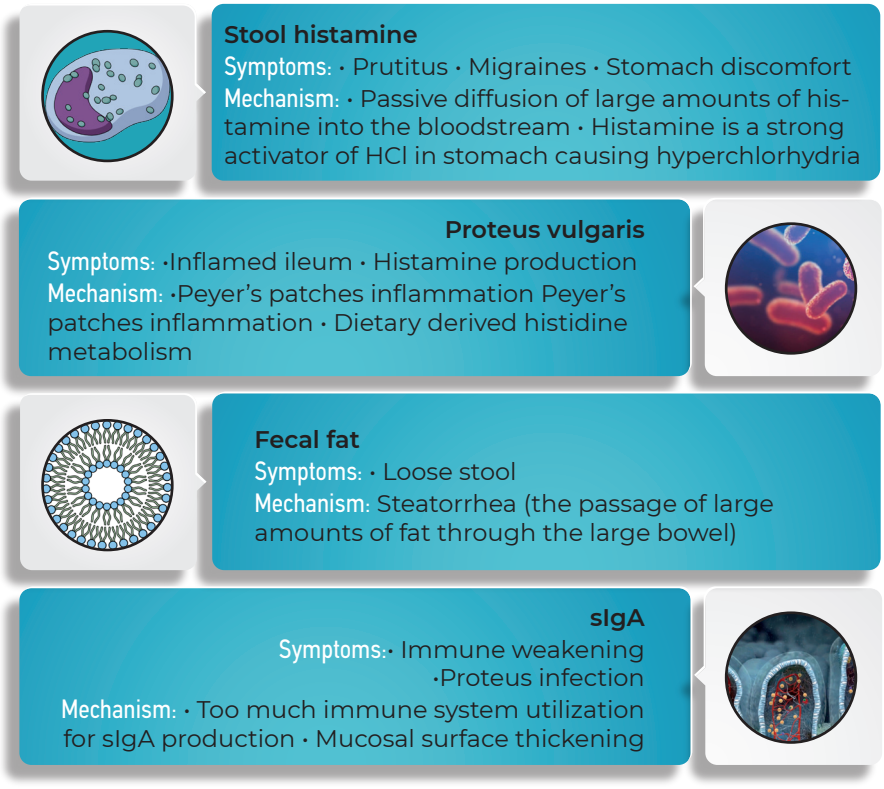
	Possible causes	*Tests Indicated*
Itching/ migraines	· Histamine producing bacteria · DAO insufficiency · Excess histamine	· Stool microbiology/mycology · Blood enzyme activity · Stool histamine/Blood tryptase
Loose stool/ diarrhea	· Bile loss · Rapid transit time · Inflamed ileum	· Fecal bile acids / elastase · Fecal fat/starch · Stool microbiology/sIgA
Bloating	· Disordered microflora · Intestinal immune activation · Undigested particles rotting	· Stool microbiology/mycology · EPX/sIgA · Fecal elastase

Case Results

The results were consistent with what really happened to his gut ecosystem during the past year. The tests revealed a histamine excess in his gut and an elevated sIgA titer, with a bacterium capable of releasing vast amounts of histamine as the culprit. Indeed, his microbiology profile showed markedly elevated levels of *Proteus vulgaris*, and, in fact, the levels were off the upper limit of the test's sensitivity.

In addition, elevated fecal fat was detected on his stool, something that may be explained by the fact that *Proteus* species prefer to inhabit the terminal ileum. This could also be a reason why his ileum looked inflamed during his colonoscopy; as the ileum is inflamed, more fat gets into the large bowel and the looser the stools appear.

What was obvious was that his prior nutritional and lifestyle habits had already weakened his microbiota potential. Once he started the strong antibiotic course for his prostatitis diagnosis, the gut microbial diversity declined substantially and the mucosal properties changed, favoring non-commensal bacteria to colonize and thrive. The first encounter with *P. vulgaris* happened when he ate seafood, and in general, seafood is the major source of histamine-producers. *Proteus* found a very comfortable and alkaline environment and started multiplying by taking advantage of Jason's already glutamine rich diet.



Case treatment

The rationale behind his treatment was based on the vastly disordered mucosal surfaces. These surfaces, along with altered gut environment, favored *Proteus* colonization in the first place, which in turn inflamed the ileum, started producing histamine and caused the bloating, lipid malabsorption and the extra-intestinal symptoms Jason experienced. His treatment would probably produce augmented symptoms for several days, as when *Proteus* cells start dying they release a lot more histamine and LPS which would inevitably get into his bloodstream. Due to the chronic and extensive exposure of Jason's gut to antibiotics, his recovery would certainly be a difficult and time consuming process.

Findings	*Treatment*
Stool histamine	· Quercetin (antihistamine action) · Rutin (antihistamine action) · Curcumin (antihistamine action) · Vitamin C (antihistamine action)
Fecal fat	· Guggul extract
sIgA	· Blend of gut integrity restoring nutrients (except glutamine) · Cranberry extract · Probiotic blend (300x109 CFU) consisting mainly of Lactobacilli and Bifidobacteria. All strains were non-histamine producers.
Proteus vulgaris	· Potent antimicrobial blend · Glutamine scavengers

My first task was to start acidifying his mucosal layer and his microflora and, at the same time, to reduce the burden of *P. vulgaris*. In this case all the therapeutic agents must be administrated concurrently and the treatment must be modulated according to the course of the symptoms.

	Day1 *Baseline*	***Day 8*** *10% improvement*	***Day 29*** *70% improvement*
Vitamin C	✓	✓	✓
Quercetin/ Rutin/Curcumin	✓	✓	✓
Guggul extract	✓	✓	✓
Cranberry extract		✓	✓
Antimicrobial blend	✓	✓	✓
Activated carbon	✓	✓	✓
Probiotic blend	✓	✓	✓
Glutamine scavengers	✓	✓	✓

Case Follow up

Jason started his treatment immediately along with a very strict histamine-free diet. He knew right from the beginning that his symptoms would get worst for at least a week. When such strong bacteria are eradicated a lot of toxins (LPS) and biogenic amines (histamine, putrescine etc) are released and enter the bloodstream. This is why during the first week only half doses of probiotics and antibiotics are given and subsequently they are then doubled or sometimes tripled. Activated carbon should always be administrated in such cases and simethicone may also be added.

Due to family commitments, Jason came to visit me after eleven days rather than the usual seven. He explained that the first five days were very difficult and he had taken two days off work in order to stay at home. He also told me that he tolerated his symptoms because I had told him that this may happen, and neither had he stopped any of his medication. He noticed that on the night of the fifth day he went to the toilet with some urgency passing a stool with a lot of mucus. This eradication was a good sign, meaning that this part of the mucosal tissue was not healthy. On the day that he came he was still presenting many of the original symptoms and his personal evaluation of improvement was only 10%. I did not want to frustrate him so I did not tell him that we were aiming for only 5% with the dosages he was taking.

I doubled the probiotics and the antibiotics and I added some cranberry extract, which has shown promising results in studies about mucosal regeneration and in maintaining healthy sIgA levels. I told him that he may experience an-

other timeframe of worsening since the medications were now stronger. He did not seem very happy about it but he did exactly what I told him. He had already lost 2 kilos due to the antihistamine diet and he was very determined to end his suffering. I saw him again on day 29 of his treatment and the outlook was totally different. He was in a very good mood and full of energy. The first thing he told me was that his migraines and itching were a thing of the past. With regards to his bowel symptoms, he was still feeling bloated but not all day and the severity was milder than before. Up to day 24 of the program his stools remained loose but in the last 4 days he had noticed more formed and complete defecations.

His rating of improvement was 90% but my score was only 70%. Sometimes, when patients get a little better they rate their health very optimistically. I told him to continue his treatment in exactly the same way and to come back and see me in two months.

He returned to my office with his wife, who confirmed his improvement. His mood was great and now he could eat almost everything. I gave him a gradual elimination program for his supplements but told him to continue the probiotics and vitamin C for at least one year. My final advice was to stay away from seafood and dairy and start performing the one day per week fasting diet in order to keep his gut healthy and clean.

Case Conclusion

This case is one version of the spectrum that gram negative histamine-producing bacteria produce in our gut. Generally, these microbes cannot colonize our ileum unless the physiological variants like *p*H, mucosal depth and probiotic sterility allow it. Once these bacteria colonize the gut, they start producing substances that favor their development and produce annoying symptoms to the host.

Treatment is always difficult because these bacteria produce a very intense Herxheimer phenomenon. Patients on antimicrobial treatments should always be warned that an aggressive worsening of their symptoms may take place but it is something that will gradually wear off and also that it is part of the healing process. Moreover, the diet during this treatment should be very strict as any deviation may produce mixed results.

In my experience, any mucosal surface that lets these kinds of bacteria thrive and survive is a much weakened one. Usually, these patients have a past history of strong antibiotic abuse, radiation therapy, chemotherapy, or in younger patients the health history usually unveils birth with C-section, early antibiotic exposure or a lack of breastfeeding.

Finally, I must raise concern about glutamine supplementation. In IBS cases that present with diarrhea or loose stool, glutamine should be avoided unless stool tests are clean form any of the following infections: *Proteus spc*, *Morganella spc*, *Providencia spc*, *E. coli spc* and *Klebsiella spc*. They may utilize glutamine to swarm (mainly *Proteus*) and expand to other places in the mucosal lining making their eradication more difficult and the patient's symptoms worst.

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End of 2nd part of preview

This preview is just the beginning

Inside the full ebook you will find out how your gut works in real life and not in textbooks. The way the sample case is described above is the same way all the different case studies are described, in full detail and in very personalized way.

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IBSyncrasy link

All these people have the same symptoms

But they are all unique, with their own

- unique **medical history**
- unique **genetic constitution**
- unique **biochemical profile**
- unique **lifestyle**
- unique **idiosyncrasy**

Why should they all receive the same treatment?

Irritable bowel syndrome is not a single disease entity with a one-size-fits-all therapy. It is a spectrum of symptoms resulting from a combination of a myriad of factors unique to each individual. By mining every biochemical, medical, lifestyle and pharmaceutical data available a unique treatment is revealed, according to their IBSyncrasy

Theodoros Prevedoros, affectionately dubbed a "biochemistry freak" by his friends, received his MSc in biochemistry from 2003 in 2005) Since that time, working alongside gastroenterologists, he has supervised the treatment and follow-up of more than 1400 patients with Irritable Bowel Syndrome. As a result, Prevedoros has devised an algorithm which combines the framework of biochemical analyses with his years of experience to tease out the various root causes of seemingly identical symptoms of IBS. In this book the 10 most common categories of IBS subtypes are presented with clear explanations and treatment plans for each subtype.

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