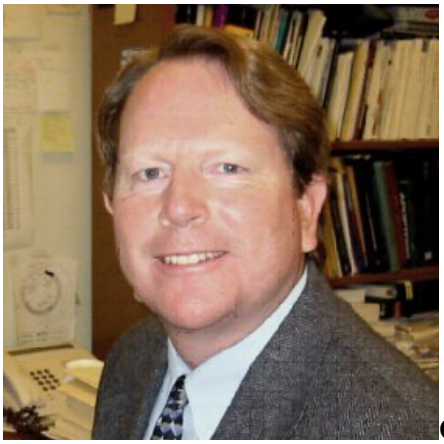
Dr. Naviaux has published a ground-breaking study “Metabolic Features of Chronic Fatigue Syndrome.” Below are answers regarding his results.

Link to published paper



Q1. Some people still argue that CFS is not a real illness but all in the mind. Does your discovery of a chemical signature help shatter this myth?

Yes. The chemical signature that we discovered is evidence that CFS is an objective metabolic disorder that affects mitochondrial energy metabolism, immune function, GI function, the microbiome, the autonomic nervous system, neuroendocrine, and other brain functions. These 7 systems are all connected in a network that is in constant communication. While it is true that you cannot change one of these 7 systems without producing compensatory changes in the others, it is the language of chemistry and metabolism that interconnects them all.

Q1.1. If you found that CFS is caused by chemical changes, why do you ask about childhood trauma in your new questionnaire for the expanded CFS metabolomics study? The questions made me think you were just like all the other doctors who told me that CFS was all in my head?

The answer to this question has several layers. Perhaps the most important is founded on our discovery that the brain controls metabolism. Any factor that causes a chronic change in how the brain works will produce objective chemical changes in the blood. Reciprocally, any chronic change in any of the 7 systems listed in Q1 will produce compensatory chemical changes in the blood that are coordinated by the brain, but can also change brain function. Profound personal loss, grief, depression, fear, chronic pain, anxiety, and PTSD all cause chemical changes in the blood that we can measure with metabolomics. In the case of PTSD, scientists have found that one of the strongest predictors of risk of a veteran coming home from Iraq or Afghanistan with PTSD was a history of childhood psychological trauma. We are trying to study this chemistry of risk objectively. The science behind the expanded CFS metabolomics study demands that we ask both CFS subjects and normal controls about psychological trauma to see if this can increase the susceptibility to CFS later in life, and to see how previous trauma might influence current metabolomics.

Q2. How does chronic fatigue syndrome fit in with other kinds of hypometabolic states or syndromes?

All animals have ways of responding to changes in environmental conditions that threaten survival. We discovered that there is a remarkable uniformity to this cellular response, regardless of the many triggers that can produce it. We have used the term, the cell danger response (CDR) to describe the chemical features that underlie this response. Historical changes in the seasonal availability of calories, microbial pathogens, water stress, and other environmental stresses have ensured that we all have inherited hundreds to thousands of genes that our ancestors used to survive all of these conditions.

The body responds differently to the absence of resources (eg, caloric restriction or famine) than to the presence of pathogens and toxins. We can classify two responses: a single-step response to the absence of resources, and a two-step process in response to the presence of a threat. Both responses are completed by a return to normal metabolism and function. When resources are severely curtailed or absent, the full CDR is bypassed, and the flow of nutrients through metabolism is decreased to conserve limited resources in an effort to "outlive" the famine. This is often called a caloric restriction response. On the other hand, when the cell is faced with an active viral, bacterial, or fungal attack, or certain kinds of parasitic infection, exposure to certain toxins, or severe physical trauma, this activates the two-step response. The first step is to acutely activate the CDR. Innate immunity and inflammation are regulated by the metabolic features of the CDR. Activation of the CDR sets in motion a powerful sequence of reactions that are tightly choreographed to fight the threat. These are tailored to defend the cell against either intracellular or extracellular pathogens, kill and remove the pathogen, circumscribe and repair the damage, remember the encounter by metabolic and immunologic memory, shut down the CDR, and to heal.

In most cases, this strategy is effective and normal metabolism is restored after a few days or weeks of illness, and recovery is complete after a few weeks or months. For example, only a small percent of people who are acutely infected with Epstein-Barr virus (EBV) or human herpes virus 6 (HHV6), or Lyme disease go on to develop chronic symptoms. If the CDR remains chronically active, many kinds of chronic complex disease can occur. In the case of CFS, when the CDR gets stuck, or is unable to overcome a danger, a second step kicks in that involves a kind of siege metabolism that further diverts resources away from mitochondria and sequesters or jettisons key metabolites and cofactors to make them unavailable to an invading pathogen, or acts to sequester toxins in specialized cells and tissues to limit systemic exposure. This has the effect of further consolidating the hypometabolic state. When the hypometabolic response to threat persists for more than 6 months, it can cause CFS and lead to chronic pain and disability. Metabolomics now gives us a way to characterize this response objectively, and a way to follow the chemical response to new treatments in systematic clinical trials.

Q3. You talk about the chemical signature being similar to a state of hibernation. What sort of animals exhibit a similar signature in hibernation?

I wouldn't use the term hibernation to describe chronic fatigue syndrome. Humans do not hibernate. But I can see how it would be a way that people might get a general idea of the chemistry that we found. Hibernation is just one of a handful of hypometabolic states that has been studied in different animals. There are many others that go by names like dauer, diapause, torpor, estivation, caloric restriction, etc. Many environmental stresses will trigger hypometabolism in humans. In our experience, the metabolic signature of dauer is more similar to CFS than some of the other hypometabolic states that have been studied. One of the main points of our metabolomics study of CFS was to give other scientists a new tool to analyze all of these hypometabolic states, developmental stages, and syndromes so that the similarities and differences can be objectively studied, and rational new therapies developed.

Q4. Are men and women really that different in CFS?

Yes. About 40-50% of all the metabolites that we measure in our method have a different normal concentration in males and females. This is not all related to testosterone and estrogen. Literally hundreds of metabolites are tuned to different concentrations in men and women. At the pathway level, we found that men and women shared 9 (45%) of the 20 biochemical pathways that were disturbed in CFS patients. Eleven pathways (55%) were more prominent in males or females. We find that to do metabolomics properly, you need to have an adequate number of age- and sex-matched controls. If healthy males and females are lumped together as controls, the power to see metabolic differences in CFS and many other diseases is much decreased. Likewise, the metabolism of a 25-year old male is different from a 35-year old male, and categorically different from a 25-year old female. In each decade of life there are many metabolic changes that occur as part of normal development and aging. When proper age- and sex-matched controls are used, metabolomics is one of the most powerful new tools available to physicians and scientists to study chronic complex disease.

Q5. How do the metabolic changes you identified in CFS relate to the recent interest in epigenetics and methylation pathways?

All the covalent chemical modifications of DNA and histones that regulate gene expression are the result of metabolic changes controlled by mitochondria. For example, all DNA and histone methylation depends on the availability of S-Adenosylmethionine (SAMe). Phosphorylation reactions depend on the availability of ATP. Acetylation depends on the availability of Acetyl- CoA. Demethylation depends on the availability of oxygen and alpha-ketoglutarate. Other demethylation reactions require the availability of FAD+ and generate peroxide. Deacetylation depends critically on the availability of NAD+. DNA ADP-ribosylation also depends on the availability of NAD+. The master fuel regulator AMP kinase (AMPK) activity depends on the build-up of AMP or the de novo purine biosynthesis intermediate AICAR (aminoimidazole carboxamide ribotide). mTOR is another key barometer of cellular fuel status. mTOR activity requires the availability of leucine. All of these metabolites that regulate epigenetics and gene expression are controlled primarily by mitochondrial metabolism. This makes sense because all cellular activities must be responsive to local resource availability and remain flexible to respond to potential threats that alter cellular health, and mitochondria are the prime monitors and regulators of cellular metabolism.

With regard to cytoplasmic methylation reactions that involve folate and B12 metabolism, mitochondria also play a key role by regulating the release of formate, the balance of NADPH to NADP+, NADH to NAD+, FADH2 to FAD+, propionyl-CoA to succinyl-CoA, and glycine to serine. Ultimately, all of these mitochondrial reactions influence the tide of substrates available for methionine, cysteine, glutathione, and taurine metabolism. The ebb and flow of these metabolites determines the balance between cell survival and death, controlling epigenetic modifications and gene expression. These reactions are illustrated in supplemental online Figure S6 of our paper.

Q6. How might your results help with treatment of CFS?

This first paper was not focused on treatment. However, metabolomics reveals a new window into the underlying biology of CFS that makes us very hopeful that effective treatments will be developed soon and tested in well-controlled clinical trials. Metabolomics will be an important component of any clinical trial of new treatments for CFS. It will also play an important role in analyzing the similarities and differences of classical laboratory models of hypometabolic states like dauer.

Q7. How would you respond to Dr. Ronald Davis's recent statement: "What is important to note is that in the absence of evidence of an active infection, it is plausible that the long-

term antimicrobial treatments often used for ME/CFS patients are doing more harm than good."

I am in complete agreement. Many antibiotics like tetracyclines, erythromycin, and the fluoroquinolones (eg, Cipro), and antivirals like acyclovir, fialuridine, AZT, and ddC also inhibit mitochondrial functions when used chronically (usually for more than about 3 weeks). Because mitochondria are descendants of free-living bacteria, their machinery for protein synthesis, RNA synthesis, and DNA replication are susceptible to many antibiotics, and for reasons unique to mitochondrial DNA synthesis, they are also sensitive to antivirals. Chronic use of these drugs can do more harm than good if there is no longer good evidence for an active infection. When mitochondrial functions are critically impacted by long-term use of certain antibiotics, a ripple effect in metabolism and gene expression is produced that can further impair energy production by mitochondria, converting an active cell danger response that occurs during active infection to a hypometabolic survival response.

In the field of mitochondrial medicine we are particularly sensitive to these issues of iatrogenic toxicity because some of the drugs that inhibit mitochondrial functions are very commonly used in patients without mitochondrial disease. For example, statins, valproate, and metformin can each produce problems in patients with pre-existing mitochondrial dysfunction. Most doctors do not think about how some antibiotics, antivirals, and other common drugs can inhibit mitochondrial function when they are used chronically. Our patients with mitochondrial disease are often the ones who educate their doctors about the mitochondrial dangers of many common drugs.

I know this is a sensitive area for many people struggling with CFS. It is important to emphasize that individual medical decisions must be governed by individual responses to treatment. Medical decisions should be informed by science, but cannot be based solely on abstract scientific concepts without also considering the clinical variables that are relevant to the care of each specific patient treated as an individual. Some patients do better on drugs that we would consider to be inhibitors of mitochondrial function. This may not have anything to do with the conventional pharmacologic classification of the drugs as antibiotics, antivirals, anticonvulsants, antidepressants, neuroleptics, or anticholesterol agents. Most drugs have metabolic effects beyond their primary action. Because the field of metabolomics is so new, these "pharmacometabolomic" effects of drugs have not yet been studied well.

Q8. Since mitochondria have two main jobs in the cell—energy metabolism and cellular defense—is it possible the one function can be overactive at the expense of the other?

Yes. This is a key concept. Our lab classifies all complex chronic disease as being the result of either mitochondrial underfunction or mitochondrial overfunction. Each type has both genetic and environmental causes, but environmental causes outnumber genetic causes in the clinic 10:1. Only expert centers in mitochondrial medicine will typically see the many genetic forms of mitochondrial oxidative phosphorylation and metabolic disorders. Most academic centers will see more of the "ecogenetic" mitochondrial disorders caused principally by environmental factors. These disorders range from autism to asthma, depression and autoimmune diseases, to Parkinson and Alzhemier disease, and many more.

Mitochondria lie at the hub of the wheel of metabolism, coordinating over 500 different chemical reactions as they monitor and regulate the chemical milieu of the cell. It turns out that when mitochondria detect "danger" to the cell, they shift first into a stress mode, then fight mode that takes most of the energy-producing metabolic functions of mitochondria off line. Even normal exercise stresses mitochondria transiently and reminds the cell how to heal. Cells

"go glycolytic" under conditions of stress, using oxygen less and sugar more for energy production. Mitochondria are highly dynamic in the cell. They will fuse with one another and divide, moving about the cell, changing their location according to cellular needs. Sometimes mitochondria will proliferate so a cell has more mitochondria than normal. Other times they will become hypersensitive to minute changes in one or more chemicals in the environment, overreacting to a stimulus that would normally be undetected by cells that have a normal mitochondrial setpoint.

What does all this mean? It means that mitochondria don't do just one thing. Sometimes, when one function is overactive the other is decreased. This is experienced by athletes in training. Overtraining increases the energy function of mitochondria, but causes a decline in the defense function and they become more susceptible to colds and many other infections. On the other hand, in CFS, many patients report a surprising resistance to the common cold and many other common types of infection. This increase in the antiviral defense function of mitochondria comes at the expense of the energy function.

Energy production and cellular defense are two sides to the same coin—when you are looking at one side, the other side is temporarily hidden. Mitochondrial cannot perform both energy and defense functions at 100% capacity at the same time. Health requires a dynamic balance of both these functions. It is plausible that when a particular patient seems to benefit from longterm use of a drug known to be toxic to mitochondria, that the drug helps rebalance cell defense and cell energy functions by decreasing the over-activity of one function and permitting an increase in an underactive function. My experience is that this is rare in CFS, but exceptions occur and are important to understand if doctors are to get better at treating all patients. Both patients and doctors should carefully evaluate the pros and cons of long-term antimicrobial therapy if the signs of an objective infection have disappeared. Any drug has the potential to be therapeutic or toxic.

Q9. Does the fact that some antibiotics can inhibit mitochondria mean that treatments for Lyme disease that last too long might actually convert an acute Lyme infection to a chronic post-Lyme syndrome and chronic fatigue syndrome?

Yes. There may also be dangers of using long-term antiviral drugs for the same reason. Not all patients will respond the same way, but doctors should know of the theoretical risk and inform patients before continuing any chronic regimen that lasts longer than any objective signs of an infection.

Q10. If all roads lead to mitochondria in CFS, are there "mito cocktails" or supplements I can take now that could help me while scientists are working out more definitive treatments?

We have learned through hard experience that the answer to this question is not simple. Many patients with CFS have suffered for years or decades. Their metabolic reserves are severely depleted. We have found that if we give the same mito cocktails that we give to patients with genetic forms of mitochondrial disease, the jolt is too much for most people with CFS and they experience a paradoxical flare in their symptoms. Just a simple thing like taking just 25 mg of vitamin B6 and 100 mg of magnesium can send some people into heart palpitations and a feeling of being unwell for hours after a single dose, while a baby with a mitochondrial disease takes twice this much every day without difficulty.

The guiding philosophy to starting any new treatment for CFS is to "Start low, and go slow." A helpful analogy is to think of metabolism in CFS like a car that has not been used all winter and all the gas and fluids are gone or low. If you try to start the engine before the fuel tank and fluids are topped off you can do damage. I think that effective treatments for CFS will

ultimately require a 2-step process. First, we have to refill the metabolic tank, then we need to turn the key. The first step will be guided by personal metabolomics testing. The second step will be based on new discoveries in the lab that have focused on the role of mitokines that maintain the cell danger response in CFS and other disorders. Mitokines are signaling molecules that trace to mitochondria. They have metabolic functions inside the cell, and informational functions outside the cell.

Q11. Many ME/CFS experts have improved the symptoms in some patients by treating with antivirals and Ampligen (polyIC double stranded RNA). I think this proves that ongoing viral infections are causing our symptoms. It is not merely "tired patients" who are stuck in a lowered metabolic state because of a past trigger (which now is gone).

We devoted a section of our paper to this and related questions about infections. The section title was, "A Homogeneous Metabolic Response to Heterogeneous Triggers". It concluded with the sentence, "Despite the heterogeneity of triggers, the cellular response to these environmental stressors in patients who developed CFS was homogeneous and statistically robust." As background for this conclusion, I recommend reading our paper on this topic entitled, "Metabolic features of the cell danger response" (PMID 23981537).

The first response our body mounts against a viral, bacterial, or any kind of infection is metabolic. Yes, our chemistry is our first line of defense. Our chemistry reflects our instantaneous state of health. Innate immunity is coordinated by mitochondria and is an essential first step in developing adaptive immunity to any infectious agent. Without innate immunity there can be no antibodies and no NK cell activation, no mast cell activation, and no T cell mediated immunity.

In addition, all antivirals have metabolic effects that have nothing to do with inhibiting viral DNA or RNA synthesis directly. Many antiviral drugs inhibit the key metabolic enzyme SAdenosylhomocysteine Hydrolase (SAHH). Inhibition of SAHH causes an increase in intracellular SAH levels. SAH is a potent inhibitor of DNA, RNA, protein, and small molecule methylation. This affects both viral and host cell epigenetics, gene expression, mRNA translation, and protein stability. The inhibition of methylation reactions in the cell also affects neurotransmitter (dopamine, norepinephrine, and serotonin) and phosphatidylcholine membrane lipid synthesis, folate and B12 metabolism, and many other reactions. So by giving antivirals, doctors are not just inhibiting viruses, they are also inhibiting many host cell metabolic functions. Sometimes the inhibition of host cell functions can attenuate ME/CFS symptoms for a time, but in other cases, using potent antiviral drugs inhibits mitochondrial and methylation reactions and can delay a full recovery from ME/CFS.

You also asked about Ampligen. Ampligen is a form of double stranded RNA called poly (IC) tempered with one U for every 12 Cs. We have studied the action of polyIC extensively and have published this in our studies of autism and virology. PolyIC and Ampligen act by binding to an innate immune receptor called TLR3, creating a simulated viral infection. If you expose a pregnant animal to a single dose of polyIC at the beginning of the second trimester, she develops a 24-hour flu-like illness then completely recovers. However, her pups have social and cognitive abnormalities similar to autism for life. If you look at their brains, you find that they have activated microglia and brain inflammation for life. In adults, Ampligen also binds the TLR3 receptor, and activates an incomplete antiviral response characterized by activation of interferon and other cytokines. Long-term use of polyIC carries a risk for toxicity because of chronic innate immune stimulation. In certain clinical situations like cancer or Ebola virus infection the toxicity is actually part of the therapeutic effect. Chronic interferon release causes flu-like symptoms, and the inhibition of mitochondrial protein translation. This can lead to secondary mitochondrial dysfunction. As I noted in an earlier Q&A response, sometimes the inhibition of mitochondrial function can make some people with ME/CFS feel better

temporarily because some symptoms can come from unbalanced overactivity of some of the hundreds of functions mitochondria perform. However, in the long term, any pharmacologic inhibition of mitochondrial function will delay a full recovery.

Third, latent and reactivated viral and bacterial infections can occur, but in the case of ME/CFS that has lasted for more than 6 months, this may be the exception rather than the rule. Some doctors and scientists have not done a good job at educating patients and other scientists about the difference between serological evidence of infection in the form of antibodies like IgM and IgG, and physical evidence of viral replication like PCR amplification of viral RNA or DNA, or bacterial DNA. We have learned in our autism studies with Dr. Judy Van de Water that supertiters of antibodies do not mean new or reactivated viral replication. Supertiters of IgG antibodies mean that the balancing T-cell and NK cell mediated immune activity is decreased. This is a functional kind of immune deficiency that causes an unbalanced increase in antibodies. This is like the famous figure-and-ground illusion that shows the silhouette of two faces that also create the form of a vase. Both things happen. But which is cause and which is effect? Increased IgG antibodies to CMV, EBV, HHV6, Coxsackie, etc. are not good evidence of a reactivated viral infection. While Coxsackie is an RNA virus related to poliovirus, antibody titers can increase to this virus too, even though it cannot establish a chronic or latent infection. This can be proven in most cases by trying to measure viral DNA or RNA by PCR in the blood or swollen lymph nodes. In most cases, supertiters of IgG are PCR-negative. There are exceptions to this generalization.

Chronic PCR surveillance studies in healthy humans are showing that little waves of viral replication happen periodically throughout our lives. We have been, and are regularly infected by hundreds of viruses over a lifetime. Sometimes this is obvious and causes a symptom like blisters or an ulcer around the mouth. However, most of the time these waves of viral replication are silent and produce no symptoms at all because they are handled in the background by the innate and cell-mediated immune system. Even the deadly poliovirus infected 150 to 1800 people, producing only mild or unnoticed infections, for every one person who developed paralytic disease. In most of the cases of ME/CFS that I have seen where IgG antibody titers have been measured before, during, and after antiviral therapy, the antibody titers remain high after treatment, even though the patient may report symptomatic improvement. I believe the symptomatic improvement after antiviral treatment may have more to do with the metabolic effects of antivirals in ME/CFS than their action on viral replication. The good news is that this hypothesis can be studied scientifically and put to the test easily using the tools of PCR and metabolomics.

Good science needs to remain open, ask the questions without bias, design good experiments, take careful measurements, then have the courage to follow the data wherever they may lead.

Q12. I read that your study shows that diet can cure ME/CFS. I have suffered and studied this disease for many years. I've tried every diet under the sun. You are categorically wrong.

Please refer to our paper in PNAS, which is free to download for anyone. Or go to our website at: naviauxlab.ucsd.edu and click the CFS button. You can download the paper and this Q&A from the website.

Our studies show that metabolism might be the final common denominator for ME/CFS. It is important to remember that "diet" and "metabolism" are not the same. Diet is what we eat. Metabolism is the performance state of the matrix—the dynamic state of flow in the network that constitutes all the biochemical reactions that our cells use to conduct the business of life. Doctors in the field of biochemical genetics have been treating inborn errors of metabolism for over 50

years. Correct treatment of metabolic disorders is complex and takes advantage of both the resource and the signaling functions of foods, supplements, vitamins, cofactors, and metabolic drugs. Mitochondria lie at the hub of the wheel of metabolism. Because mitochondria are also the concertmasters of innate immunity and inflammation, it makes them uniquely positioned to help the cell decide whether to devote energy and resources to “peacetime” metabolism, or cellular defense. We have several ideas about how to approach the treatment of CFS. We will be testing these in carefully designed clinical trials. For more thoughts on treatment, see the answer to Q10 above.

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