

# Community Spotlight

## Marti F. Wolfe, PhD



*Marti F. Wolfe, PhD is a toxicologist based at the Department of Biological Sciences at California State University, Chico. She has a bachelors in Conservation from UC Berkeley, a masters of science in Biological Science from San Jose State University, and a PhD in Pharmacology/Toxicology from Washington State University. Originating in animal toxicology, she took an interest in multiple chemical sensitivities and the organic mechanisms involved in multi-system illnesses.*

**Tell us a little about yourself and your background.**

My hometown is San Jose, California; I lived there most of my life until I ran away to graduate school. I've always been a science nerd. I had my first chemistry lesson when I was four and my brother was six. My mother used stuff in the kitchen, water and alcohol, baking soda and vinegar, and taught us to write a balanced chemical equation. I started college as chemistry major, but it didn't take long for me to be seduced by biology – and this is our time in the sun, no question about it – biologists rule! I got a BS in Conservation from UC Berkeley, then an MS in Biological Science from San Jose State; in those years my concentration was organismal biology, ecology, and evolution. I became interested in toxicology when I was working in industry, so I went off to get a PhD in Pharmacology/Toxicology from Washington State University. The divide between the two major arms of biology is about the size of the Grand Canyon, so it's rather unusual for a person to change from one to the other. But I think it's been helpful to me – I can look at diseases from an evolutionary perspective, and ecosystems and cells share many features, just at different scales. The more ways you have to view a problem, the greater your chances of solving it.

**How did you become interested in MCS?**

First, I need to say that I don't view MCS as a unique disease, but rather a one member of the family of diseases and syndromes for which Claudia Miller coined the term "multisystem illnesses". The core group of MSIs are MCS, CFS, FM and PTSD, but there are other candidates and evidence for their inclusion is accumulating rapidly. MCS and I go back to the mid-80s, first when I was still working in the semi-conductor industry, and then when I was working for an industrial hygienist while I was in graduate school at San Jose State. I have a BS in Conservation from UC Berkeley, MS in Biological Science from San Jose State, PhD in Pharmacology/Toxicology from Washington State. That's when I first got into the MCS literature, which was really in its infancy then. I partly supported myself in graduate school by writing briefs for attorneys who handled worker's comp and toxic tort/chemical injury cases. My PhD dissertation work was on interspecies and age-dependent differences in toxic response to organophosphorus insecticides. I wasn't specifically working on MCS directly, but it just continued to pop up in my life; when I was working for another industrial hygienist in Seattle, when I was at the EPA, and at National Pesticide Information Center. CFS came into my life when my best friend Rini,

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also a toxicologist, developed it so she and I got into that literature while I was trying to help her out. I think even that early, Rini and I had some conversations about some correspondences between CFS and MCS. Then my daughter developed fibromyalgia, and I while I was in Corvallis I became friends with a psychiatrist whose specialty is PTSD. And about that time, the first GWS articles started coming out, so there were hints at mechanism there. I was intrigued by the underlying commonality and annoyed by the articles proposing a psychogenic mechanism. I just knew that eventually an organic cause would be found, but it was always peripheral to whatever I was doing, so I didn't do much more than glance the literature.

In 2003, I was diagnosed with interstitial cystitis and mastocytosis, so plunged into that literature and joined patient support organizations for both diseases and I was struck, and I mean *just bowled over* by the degree of co-morbidity with CFS, MCS, FM, and I thought "There it is

*again*, I really have to look into it, try to figure something out", but felt out of my depth, and also I was really sick. And of course, by that time the literature had just mushroomed. But, if you are marooned on your sofa with fatigue, you have lots of time to read.

So in the spring of 2004 I was PubMed crawling and what pops up but

*Pall, M. L. 2001. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. Med Hypotheses 57: 139-45.*

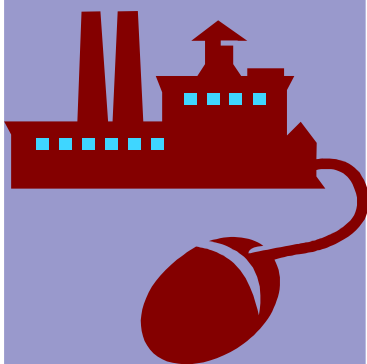
People use 'jaw-dropping' as a metaphor, but my jaw really did drop! I was just dumbstruck! It was just an absolute eureka moment!!! I mean, here was this idea that had been nibbling at the edge of my consciousness for 10 years or so and there it was AND it was accompanied by a mechanism which I found extremely compelling. AND, I saw immediately that it had potential links to IC and masto. AND then I saw who wrote and I nearly fell out of my chair!!! Because Marty Pall was my biochemistry professor when I was in graduate school. It was just such a funny coincidence.

I didn't make any real contact with Marty for another year, but spring 2005 was my last semester of teaching, so I sort of invited myself to work for Marty. I did sort of a post-doc with him for two years, helped him with his book and so forth. And learned tons!

And, I continued to accumulate and read articles, which you have a lot of time for if all your mitochondria tell you Adios and leave you velcroed to the sofa. After I'd been working with Marty for about three months, I



**“Oxygen is dangerous stuff, so the cell handles it with utmost care.”**



started on his protocol, and it produced an almost miraculous effect. That awful fatigue that makes you feel like your bones have turned to lead just lifted. It was very dramatic, I've always been an energetic person, so fatigue made me feel like I was trapped in someone else's body and when the NO/ONOO- protocol banished my fatigue, I felt as though I'd gotten my life back.

**Do you believe toxicology plays a role in MCS and what, in your opinion, is the most likely cause of MCS?**

Of course toxicology plays a role! Toxicology is simply the study of the adverse effects of xenobiotics on organisms. I have heard folks state that MCS doesn't belong to toxicology because toxicology is confined to effects that have a discernable dose-response relationship. In fact, some of the old guys were still saying that when I was in grad school. Some dose-response relationships are just more complex, but as more sophisticated statistical tools become more widely available, toxicologists are getting braver about tackling those tougher relationships to. And MCS is definitely one of the more challenging ones, no denying that.

Institutionally, toxicologists haven't contributed much to the task of unraveling MCS's mysteries, but it isn't so much a rejection, or official resistance as we see in some of the other professional societies, it's more like benign neglect. I submitted a proposal for a Special Session on MCS at

the 2008 Society of Toxicology meeting – SoT is the largest organization of professional toxicologists in the country with 6000 attendees at the 2007 meeting. We just have to raise the profile of MCS among toxicologists.

And causal mechanism is the area in which toxicologists potentially have the greatest contribution to make to MCS. Of all the MSIs, MCS is the thorniest one to tackle, because there are so many odd features that any mechanistic model must account for. All the mechanisms currently under consideration – oxidative stress, free radical damage, redox disruption, NO/ONOO- vicious cycle, can be thought of collectively as Oxygen Behaving Badly.

Oxygen is dangerous stuff, so the cell handles it with utmost care, passing it gingerly from enzyme to enzyme until it can be reacted with something that will hold onto it. Because if it gets loose from the cell's careful controls, it acquires a charge – this is sort of like handing a juvenile delinquent a gun – and goes on a rampage in the cell, raising hell with various cell structures, including the very ones evolved to make oxygen behave itself. When you look beneath the proposed mechanisms, neurogenic inflammation, neural switching, long-term potentiation, etc, the front-runners share in common an impaired ability in the cell's handling of oxygen.

One of the most vexing mysteries of

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MCS – and the one that may mislead people into thinking that MCS lies beyond the domain of toxicology – is that the dose-response relationship is so obscure. Another conundrum is the latency phenomenon, the lag-time between exposure and the appearance of symptoms. Latency can make it difficult to connect the disease to the exposure that launched it. And the fact that symptoms may persist even after all contact with the initiating exposure has ceased was another factor that challenged investigators looking for the etiological mechanism.

Marty Pall’s NO/ONOO- vicious cycle model ties these observations together into a coherent explanation. There are other vicious cycles in medicine, and certainly the role of free radicals/redox disturbances in many diseases is well documented. The NO/ONOO- vicious cycle draws on both those bodies of knowledge and is both explanatory and **predictive** – that’s the part that makes the model so compelling. The model predicts a therapy; in the last two years or so, MCS and other MSI victims on this therapy are enjoying an improvement in their health and a return to normal life. So this is a very exciting time to be working on the MCS and the other MSIs.

**What do you feel is the biggest block to MCS being recognized as a biological illness?**

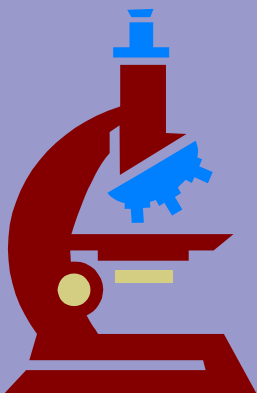
I’ve described what I call the ‘natural history of emerging diseases’ in which a syndrome when

first described is almost automatically ascribed to psychogenic causes, especially if all its victims are mostly women, so both the patients and the doctors who care for them become marginalized. Then someone, often someone working on a completely different disease, or on some aspect of basic cell physiology, discover a key to a mechanism, more experiments are done, which ideally lead to a clinical test that’s conclusive, and at that point the syndrome ‘graduates’ to the status of a disease and work on treatment accelerates. The unique and biggest challenge of MCS is the huge body of resistance against its recognition – for most diseases maybe a few academic reputations are on the line, but not multi-billion dollar industries pouring money into opposing the recognition of the disease. It’s a David-and-Goliath battle; it scares me if I let myself think too much about the odds. Another barrier is that no clinical specialty ‘owns’ MCS, and some professional organizations actively oppose it, such as the AAAAI. It has helped fibromyalgia emerge from the shadows of psychogenesis, for instance, that it belongs to rheumatology; interstitial cystitis was always understood to be a urological problem even before all urologists believe it was a real disease. This is one reason I’m trying to raise the profile of MCS among toxicologists – it is a chemically-induced disease, we should embrace it as *our* disease and start doing our share.

Another challenge is the lack of a specific biomarker or clinical test. When you can identify a factor that is present in all or almost all of your



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affected cohort and completely absent from your control population, you've got a biomarker you can take to the bank. But associated with that challenge is the frustrating fact that we have many assays, tests, potential biomarkers that are used in research, but that just aren't being made available to the clinician or other end-user. We discussed that problem at this year's meeting of the International Society of Environmental BioIndicators and decided it is so important that we need to devote an entire session to it at next years meeting.

**Do you think that MCS should be renamed?**

Ouch! You can really tie your synapses in knots thinking about this! There are many proposed names, with arguments for and against, as well as for and against retaining MCS. What makes the problem so gruesome is that almost all the names and arguments have merit from someone's quite valid point of view, so a universally acceptable name will continue to elude us, I fear. I think I'll stop there, because I'm on the case definition team, and our deliberations are embargoed for the time being.

**Where do we go as a community of researchers and patients from here?**

Well, of course we need more research funds, that's so obvious it hardly needs mentioning. But I think we hamstring ourselves if we think money will solve all our problems. What really solves problems is good thinking. Marty Pall didn't have a grant to work on the NOI/ONOO- vicious cycle model, he sat in his office for a couple of years using only his brain. Activists and advocates like you and Cynthia Wilson of CIIN didn't wait around for big grants, you rolled up your sleeves and got to work. And physicians who have stuck with MCS and

other MSI patients often take a financial hit to do it. Money is great stuff, but it doesn't take the place of dedication and brains.

So for researchers, that means keeping your mind open to new ideas. If you come into this field as an outsider, as I did, you can discern a pattern in which investigators come to conferences and present the latest development on one part of the problem and they do that year after year, but no one steps back and says "How do all these fit together?" And I say that to clinicians, as well. Stay up with the literature, don't keep doing the same things. And PUBLISH. I've been discovering that there are physicians who have been helping MSI patients with protocols they've worked out themselves, based on their reading of the literature on oxidative stress, free radical damage in cell chemistry. We need to have some system that makes it easier for practitioners to share these experiences, something more flexible and nimble than the traditional refereed journal approach that takes a year to get an article into print,

Collectively, I think we need to make common cause with the organizations supporting the other MSIs, to exploit the strengths that come with the recognition that these diseases are all connected in a very fundamental way.

And lastly, I think your word community is key. If we are a community with a common cause, then we need more cooperation. Many of the resources we need to solve the problem of MCS are already within reach. What's needed now is creative thinking and sustained cooperative, coordinated effort.

Thank you so much for inviting me, Sal. I'm always happy to answer questions on the toxicology aspects of MCS:

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