On March 16th, the MEAO recorded a phone interview with the Pacific Fatigue Lab (PFL), in the Department of Sport Sciences at the University of the Pacific in Stockton, California. PFL is a research, clinical and teaching laboratory focused on the functional aspects of CFS/ME and other fatigue-related disorders.

Staci Stevens is the founder of the PFL. She is the current Vice President of the International Association of Chronic Fatigue Syndrome/ME, which is planning a national conference in Ottawa this September (see separate notice for this event in Reaching Out). She is also the developer of the test-retest protocol for CPET (Cardio-Pulmonary Exercise Testing) evaluation for ME patients.

Christopher R. Snell, Ph.D. is a Professor and Chair, Sport Sciences at the University of the Pacific. He is also the chairman of the Chronic Fatigue Syndrome Advisory Committee, which was chartered under the public health services act of the US.

C: It's interesting for us how much interest we're actually getting out of Canada. I've gotten some comments from Canadian Reader's Digest a couple of weeks ago. They were doing a piece on Chronic Fatigue Syndrome up there. It seems to be of interest up there, perhaps even more interest up there than down here.

Ralf (MEAO): I have on the phone Staci and Chris of the Pacific Fatigue Lab (PFL). It's part of the sport sciences department at the University of the Pacific in Stockton ,Northern California. They also have roles beyond the pacific fatigue lab. For example, Chris is the chair of the chronic fatigue syndrome advisory committee, which was chartered under the public health services act of the US. Staci is the current Vice President of the International Association of Chronic Fatigue Syndrome, which just happens to be organizing the conference in Ottawa this September. Let's start by asking for their thoughts on this upcoming event.

S: Thank you Ralf. We're really excited to be here with you and your listeners. I'd just like to give a plug for the upcoming conference. This year it'll be in Canada. It's the first time the International Association of CFS/ME has had a conference outside of the US. So we're really excited to be coming to Ottawa on September 22-25. There will be a one day patient conference and a clinical and research conference that follows. For all your listeners, I would encourage you to come and please invite any clinicians that you know or researchers that may be interested. We would love to see you there.

R: Great. I'm looking forward to saying hello to you in person. That'll be the first ME conference that I'm going to attend. I'm curious – how do presentations to the public compare to the ones to fellow researchers?

S: Every conference that we have has a patient day that is geared towards patients. So there will be a number of both researchers, clinicians and our board presenting to patients on a variety of topics. The clinical day has a number of workshops geared directly towards clinicians from diagnosis to treatment and management of the illness. Then the research conference we have a call for papers and people submit research projects that are accepted. We see their presentations over a two day period.

C: There are a variety of presentation formats from oral platform type presentations to posters.

R: Is the PFL going to be represented and presenting at this conference?

S: I will be there as the Vice President but also as a member of the PFL. Our group will be attending and I think we plan on having a couple of presentations at the conference. We really encourage that since it's in Canada that you get the word out and encourage people attend.

R: I think it's a great opportunity for us.
In descriptions of ME/CFS we are accustomed to hearing that there is no diagnostic laboratory test or biomarker for it. But in a recent letter to lancet, Kimberly McCleary, President of CFIDS. Said that it's biological basis has been objectively demonstrated. She gave a number of citations and then wrote "Using exercise testing, researchers have identified physiological responses that persist for days or weeks." As a person with ME I really prefer the second description over the first. So we ask S and C, if Today we can describe ME as having an accepted diagnostic? Are we there yet?

C: We get a lot of similarity in terms of the measurements we get from a number of patients. Whether we are at a point of having an algorithm that diagnosis CFS I don't think we can say that. But the similarities are very striking and we also see that in testing done at other labs along similar lines to ours. The classic post-exertional detriment in performance up to this point appears unique to CFS. The idea that people are unable to repeat their performance on consecutive exercise tests seems to be a hallmark of the illness.

S; I would add to that that cardiopulmonary exercise testing in general is a great diagnostic tool. It's been used for 50 years for the diagnosis of cardiac disease, pulmonary disease and metabolic disorders. So it's not a new test. In terms of CFS/ME it's a great diagnostic tool because it excludes cardiovascular and pulmonary disease. And allows to look at metabolic function from day to day. I think it's a perfect evaluation tool because ME is a diagnosis of exclusion at this point.

R; Okay, so at this point it has to be part of a mix. It's not ready to be stand alone yet but it can be part of the compliment.

S: Absolutely

R: Describe the assessment and interventions that go on at pacific fatigue lab.

S: What we do is a two day evaluation. This started out as a research project and patients started to find out about it and started to contact us to ask if they could use it for disability evaluation. The test consists of two days on a bicycle. We have a number of tests that surround the actual exercise test. We do resting EKG, resting lung function testing, and a reaction time test as well. The actual exercise test itself only lasts about 8 minutes. It starts out with a resting phase of 3 minutes. We do a minute of unloaded cycling with just the movement of the legs. Then it goes into a very gradual ramping protocol that gets harder and harder throughout the test until the patient can no longer peddle. And then we ask them to come back and do the test again the next day.

R: And some of them are pleased to do that? I can't imagine.

S: We'll tell you about the client we had yesterday. I asked Chris to come down and have this discussion with the patient. Because She did the test on day 1 and showed severe functional impairment, which means that she didn't have to do it the second day. But she wanted to do it anyway.

C: As researchers we're very interested to see what happens. As human beings we're resistant to putting people through more pain than really is necessary. The key thing is we don't always need the second test because there's a floor effect. They're sick enough on the first test to demonstrate disability, so we don't expect to see a decrement on the second test. There's nowhere further that they can drop to so generally we won't require the second test. This person was really willing to put herself through the second test just to learn a little bit more about the illness. We find that with a lot of patients, that they really just want to learn more about what's happening with their bodies. And they'll put themselves through all sorts of torture to get that information.

R: Especially if they're worried about a disability claim.

C: And certainly it's counter to the accusation of malingering when people are attempting to do the least amount of work possible. There are people that will knowingly make themselves sick just to validate that this really is an illness of some significance.

S: Our problem is not getting patients to do the 2 day exercise test. Our problem is often trying to talk them out of doing more harm to themselves if they do not require a second test.

R: I guess you can see the big crash coming.

C: But we also recognize that there are patients that are too sick to even leave the house which are never going to even be able to do the test. Unfortunately we have nothing to offer those people at the moment. It's beyond our capability to do the sort of testing we do with people that are not able to at least achieve a minimal level of function.

R: I want to get back to that particular point later. I wanted to ask, do you have a specific mandate for your research?

C: Could you just clarify mandate for me?

R: I'm thinking in the corporate world – a mission statement, a reason for being?

C: Well we're housed within a University so that's our day job and that's part of what we do. As a University professor I am mandated to conduct research. This really came about as an accidental consequence of the research we were doing. It seemed to meet a patient need and so we expanded our research protocol to include the disability assessments that we do. Certainly we would not do it if there wasn't a research component because that's what we're expected to do at the University. To a certain extent being housed within the University subsidizes what we do in terms of the disability testing. We probably couldn't afford to operate as a commercial enterprise because we would not make sufficient income to be able to run it as our only business. It's one of the beauties of working at a University, they do allow you the time for public service and research and we can justify what we do here based upon those grounds. Have a salary that we know we're going to get every month. The lights will come on in the morning when we get here and the heating works most of the time.

S: In terms of a mission statement or a mandate the focus of our research is really on the functional aspects of CFS/ME. Because that is our area of expertise. We're from an exercise science department and we're approaching the illness from that area. We also have collaborations with other departments on campus. We've recently started working with the school of physical therapy, one of the professors there, Todd Davenport.. Which allows us to expand a little into research in the area of rehab and bioengineering. We can branch out a little bit from our physical function to these other departments to collaborate with them as well.

R: How would you summarize the main findings of your research to a fellow exercise scientist or physiotherapist?

S: I'll take you through a little story of how this all evolved. Dr. Snell was my graduate thesis advisor. And our very first presentation, I was working with CFS patients and prescribing exercise. So we presented at a little conference on 'The impact of an exercise program with a patient – a single case study'. I went off and I happened to be involved in

clinical trial with Ampligen and was doing testing at multiple sites in the US ended up doing 1200 tests. I came back and asked Dr. Snell if he'd look at the data and publish it. As I was traveling over the six years, what came up over and over again was that the patients could do an exercise test on a single day but rarely did they recover from it immediately or even days later. So I came back to Chris and said we're not asking the right question. The question isn't what can someone do on one day, but how quickly do they recover from it. After looking at that original data set of 200 patients we found that half of them were moderately to severely functionally impaired. But the other half looked like they had no impairment or just mild impairment. And even though they were all disabled according to their physicians, it wasn't being captured on a single exercise test. And that's how the two-day test protocol sort of emerged. We weren't capturing the post-exertional malaise and the delayed recovery response with a single test, we started the second test and what we found was a decline in metabolic function on the second day. And this doesn't happen – at least in the literature – in heart disease, in lung disease, in late-stage renal disease patients can reproduce exercise test results from day to day, but our CFS patients could not.

C: Two things came out of that: one of them was obviously our test-retest protocol. The other was we became strong advocates for using an exercise challenge to precipitate symptomology because a lot of the other research in CFS is equivocal. One set of researchers will get one set of results that find one thing and another set of researchers will get another result that seems to contradict that. It seemed logical to us that if a primary symptom of the illness was, this post-exertional exasperation of symptoms, that people might want to start looking at patients when the symptoms are present. That that might be the best indicator of what's going on. And over time we've actually convinced a significant portion of the CFS research community to include an exercise challenge in their research protocols. Essentially what they're doing is looking at the person downstream of an event designed to induce symptoms. We're quite proud of that along with our test-retest protocol. That's where we're working now, is to get the idea of using multiple tests and to get the protocols involved in cardiopulmonary exercise testing.

R: Were multiple CPET tests ever used before for different purposes?

C: They have been used for cardiac patients and one of the reasons that they do a test-retest protocol with heart patients is that they generally improve from test one to test two. So if you're designing rehabilitation protocols based on someone's performance on an exercise test you actually want the best that they can do and so it seems ironic that when you've got people recovering from heart transplants they do a two day exercise test protocol and actually improve on the second day. And we have CFS patients that clearly don't and we get up to 40% decrements in performance within a 24-hour period on the exercise test.

S: What's interesting Ralf, one of the studies that we looked at was published in Chest looked at patients with pulmonary arterial hypertension that were very, very sick. And the reason that they did the two-day exercise test was to determine if it was valid and reliable. What they found is that there's no need for a second test because it is indeed, even in people that are extremely ill it's very reliable and so there's is no need for a second test. Largely, in the literature, a two-day test will be done to ensure reliability in different disease states.

R: You didn't need jargon to get your points across.

C: Most patients understand it because they've actually done it themselves. They've got a family party coming up so they rest up and they function perfectly well for the duration of the party and then they're in bed for the next two weeks.

R: This has been so intuitive to me in the 7-8 years that I've had ME. It was very frustrating seeing some of the specialists, like cardiologists. Then trying to say, no look it's the reaction afterwards and they just want to take a look at how everything's working at the moment that you do the exercise. Then they say good-bye to you. I couldn't get anyone to believe that you need to pre-exert me. I was trying to explain that in my own words unsuccessfully.

C: Mostly, it's only very close family members who ever get to see the person when they're sick. Their public face is the best face they can put forward. So it's hard to convince people when they only ever see you when you're functional that you actually have an illness.

S: I think actually, even from a scientific perspective, our patients have a far greater understanding of this than most physicians or researchers that don't have any personal experience. Ours patients, like Chris said, they all get it. Our challenge is educating our providers.

R: You've published a number of studies, at least 10-12, does it occur that one study comes to some conclusions that automatically lead to questions and elements of the next investigation?

S: I think almost all of our studies lead us to the next step. We always ask ourselves, "What story is the data trying to tell us?" And then from there continue with the research and look into what we think are interesting areas.

R: What are you planning for future research studies?

S: Certainly, I think, the symptom of post-exertional malaise is so important in this illness. And no one understands what it even is. To further characterize that is one thing

we would love to do. Chris and I have been talking about the importance of hypothesis driven research and I'll let him comment further on that.

C: Two things, 1) One bandwagon that we've been on is the idea of sub-typing for chronic fatigue syndrome. Often the patient groups, or subject groups in research, are not very clearly defined. We would either like to clearly define groups by the results from the exercise testing that we get and then look at other parameters. Or we get groups that are defined by another parameter, be it a virus or a particular symptom complex and then we look at the exercise test data. So we start to test some hypothesis for what might be causing the fatigue and the other symptoms. And you really need a very clearly defined population. So all the hullabaloo about XMRV, if you want to look at that further, you need a subset of CFS patients that have evidence of XMRV to determine how important that is in the etiology, you know, the sequence of the illness.

R: Have you seen any hint yet that possibly there might be an overlap with the sub-groupings you're getting on the exercise with things like being XMRV positive?

C: We don't have enough data on that to be honest. We have the same problem as a lot of people in CFS research, and that's that we don't have any money (laughs).

R: There was a study a couple of years ago that seemed to show five sup-groupings of ME patients based on *genetics* and they seemed to group up nicely with the type of symptoms that they also had. I don't know if you recall that or if that has some potential for a future study for you as well?

C: Yes, if somebody could provide us subgroups of people typed by whatever they chose to type them by and we run our sequence of tests, then we could look at similarities and differences between those groups. They're large scale studies with large sample sizes, which is a problem with CFS research, is getting enough numbers in each subset that are accessible, that you can do the testing on. It's expensive to do that sort of testing.

S: Another area of research, Ralf, just to go back to future directions, is we'd love to do research into rehabilitation protocols for patients. We're actively working on educating the physical therapy community about what to do with patients that come into their practices. Because they are seeing patients and that's who patients often seek out to help them function better or if they have an injury, to rehab that injury. So that's an area that we're actively pursuing and would love to do more work with.

R: Diagnostic criteria – if you have patients that are CFS based on the Canadian Consensus, or the more general CDC definition – I'm just curious if you're seeing a pattern there. Are you less likely to get non-post-exertion malaise patients with the CDC definition?

S: I think it depends on who's doing the patient selecting. When we're involved in research studies we certainly make sure that all the patients have the symptom of post-exertional malaise or a two-day test really won't be helpful for them. I think Leonard Jason just published a natural history study of CFS, and found that the symptom of post-exertional malaise best differentiated the CFS group from the others. I think that's not only the focus of our research, but where we need to stay. And in terms of these definitions it will certainly differentiate the Canadian from the other two.

C: We don't really pay a lot of attention to the definitions. In part because we know that a lot of physicians don't. They'll diagnose CFS based on their experiences without any reference to any definition. And it's fairly easy to fit large groups of people into most of those definitions. There's enough variability in those definitions that you can slot somebody in there particularly given the way that you access the information. We're much happier with our objective exercise test data for categorizing patients independent of diagnosis to be perfectly honest. Because we often get a diagnosis of convenience when we get clinical patients come to us.

S: But we are finding a difference in symptom expression post exercise test in our questionnaires that differentiate patients from controls. Which is an interesting area of research. But patients are having symptom flare ups and fatigue, pain, sleep problems and immune problems are apparent after an exercise test in the post-exertional state and the controls have all recovered. That sort of diagnosis from the other end as a result of a standardized stressor. And we've just had a recent publication on that, looking at the diagnostic accuracy of symptoms in post-exertional malaise.

R: And did it show that it was a good predictor? Was there a strong correlation?

S: Yes, it was outstanding.

C: We could really easily separate patients from controls. We didn't do a great deal, since the sample size was probably not large enough, to look at people based on all the different diagnostic criteria. Some studies have attempted to categorize patients post-hoc by looking at the Canadian or Oxford or whatever and see whether they're different in terms of their performance. We've never really had the inclination to do that.

S: Nor the information necessarily. From the clinical trials we did not have access to all the intake data just the outcome measure of the exercise test. I think one of your questions was in terms of severity – can we identify sub-groups? We wrote a paper on sub-classifying CFS patients through exercise testing. And we certainly can functionally characterize them in the four different categories that the American Medical Association uses from severe to no impairment. It's none, mild, moderate and severe that are the four categories.

C: And they're primarily developed for cardiac patients, but there's a long history of use of those for categorizing. Social security use them, most of the government agencies use those criteria, to determine level of disability. And with our testing it's relatively easy to indicate a level of disability for a patient.

R: You say symptom severity - I'm kind of assuming that the actual specific symptoms for each individual, from the experiences of those I've met, they end up being quite unique and different.

C: We sort of don't find that. There's a lot of similarity between the self-reports we get from patients following an exercise test. Ranging from immune related symptoms to muscle soreness and aches and pains. Certainly brain fog comes up consistently. We've attempted to objectify that with our reaction time testing but we've not been terribly conclusive with that. We think it may manifest itself in a number of different ways.

R: What are the main benefits that the PFL can offer to patients that visit them?

S: I think the main benefit – when I sit down and go over results with a client – is that it offers them hope. I can tell them two things: I can tell them objectively what is going on and then give them hope for functioning better based on the results of the exercise test. And for the first time, often patients have never had any objective results or any positive findings. They're quite relieved when I can sit them down and say, "You've got metabolic dysfunction, this is why. Here's your heart rate at your anaerobic threshold which will allow you to pace your activities because when you exceed that heart rate, it's the beginning of the end." That's where fatigue and pain will set in. Most patients are exceeding their threshold just doing their daily activities. So knowing that this occurs is an extremely useful tool for management.

C: So when we can quantify why having a shower can wipe you out for a few hours then patients realize that there is an underlying biological cause for the symptoms and for their performance.

R: So this suggests that it is possible to manage ME using CPET. Is it good enough to just have the CPET doing it once or is it something that will require repeated checking?

S: Well we're just putting together a publication that we're hoping to have out in the next month or so that asks that question specifically. Is one test good enough?

C: The problem with one test is that it really doesn't take into account the effects of activity. The symptoms are cyclical and they may depend on a variety of different things including how much you've exerted yourself. But there's probably other factors that determine how sick anybody is on any given day given that it's a multi system illness. Even if we look at just one aspect of the immune system, your immune system varies just

in terms of its functionality from day to day and also your exposure to external pathogens. Like everybody else, people with CFS are susceptible to illness from outside so it's extremely variable. What we can tell them with the two-day test is, this is what you'll look like at your worst. And if you avoid going into that territory, if you avoid things that are guaranteed to make you feel sick, then your life should improve. You should see less instances of symptomology and you should be able to function. We've even had people that have been able to function in a work environment given certain guidelines. Surprisingly, a lot of people with CFS don't want to give up their jobs. They actually enjoy going to work, they like having and income, they like responsibility. So if we can do that, that's a win-win situation all around. And certainly the home life, as you're aware, that is devastating for people when they can't bake a cake with their kids and you provide them with some tools to help them do that. And it's life changing.

R: Have you been able to track patients like that after the visit and been able to see the improvements? Is it something on which you could publish statistics at some point?

C: It's mostly, what we would call, anecdotal from a research perspective. We don't have the means to track large groups of people that we've provided advice to. We also don't have a guarantee that they'll follow the advice – and very often they don't. Sometimes the things that you need to do are going to exceed your limits and then people make the choice that they do them or don't do them. When we give you a limit it may not enable you to do everything. It's not an answer, but will give you an indication of what you're capable of doing and how long you're capable of doing it.

S: And it's not a cure. That's probably the first question that every patient asks me is: can I exercise and will it make me well? I have tell them, no, it won't make you well but will improve your quality of life. It's not a cure – it's a coping strategy. It allows the patient to make an educated choice about how much payback they want, and when to stop to avoid that payback.

R: What services are offered and what are roughly the costs? How would a patient sign up and qualify for doing a visit to your lab?

S: Right now we are only offering disability evaluations as a service with a stipulation that we are allowed to use that data for research purposes. Unfortunately at this time we just don't have the personnel to do anything beyond that. The costs are $2000 for the two-day tests. It includes a 10-page report that gets sent to the referring physician as well as to the patient.

R: Do you need a reference from a Doctor?

S: Yes. The paperwork is available on our website at www.pacific.etedu under the PFL. We require a physician referral. We do a cardiac risk stratification – we want to make sure

that patients are at a low risk for a cardiovascular event. We have a medication list and a few forms that need to be filled out a returned to our office before we can set up an appointment.

R: Can you describe how CPAT is used as a biomarker for prognosis, diagnosis, for disability evaluation, for diagnosing post-exertional malaise and outcome measures? We've kind of touched on some of these, but what are your thoughts?

S: I'm really excited about it as a diagnostic tool, as a potential biomarker for CFS. There isn't a single test for CFS – yet. There are a lot of abnormalities, and a number of different viruses that are potential biomarkers. I don't think we can say it's THE single diagnostic for the illness, but certainly metabolic dysfunction is a biomarker that is unique to CFS/ME. In terms of prognosis it tells us the severity of impairment, where a patient is. The more functionally impaired a patient, the less likely they will recover quickly. The higher functioning a patient, they'll have a higher quality of life and a higher chance of recovery. As an outcome measure, for any clinical trials that we do it's ideally suited and has been frequently used in heart disease studies and lung disease studies.

C: In simple terms we're looking at the patient's capacity to generate energy. We see that that is compromised. It's the ultimate outcome measure – can this person function, can they generate energy to do work? And if they can't then that has numerous implications for their life. You would expect that not being able to do that is the main reason that CFS patients are unable to function normally. Plus we get all of the symptomology precipitated so that you can also look at other aspects of the illness. So if exerting yourself generates a whole symptom complex we don't always look at that because we don't always have the means to. So if it's causing an aberration in immune function then that should be apparent by looking at various immune measures post exercise test. And there are a number of researchers that are starting to look at that now. They're looking at a number of biological functions and markers and seeing how they differ post exertion between CFS and control. We just wish they were doing a better job of controlling the exercise challenge. Some people have taken it a little too liberally and think that any challenge is going to be sufficient for scientific purposes and they're not always as objective about the level of the challenge as we are.

R: What would you say are the most significant agreements and disagreements with other research papers on the subject?

C: We don't have a lot of people that are doing our test-retest protocol. There are some people in Europe that are doing it and their results seem to replicate ours. They have fairly well defined samples and fairly large groups. So we find that encouraging. What tends to happen if people are using very small groups of people that are not clearly defined in terms of the illness you may lose the effect and not see it.

S: That's tremendously encouraging. With all of these potential biomarkers, very rarely do you see them replicated and they're not readily available in labs around the world. Cardio pulmonary exercise testing as a tool has been around for 50 years – it's nothing new. And if done properly it can potentially be replicated in the Netherlands. A study that was done was replicated by the Vermeulen group in the Netherlands. And that's exciting. We expect that it potentially could be replicated anywhere if done well.

C: And the protocols are clearly defined by the American Heart Association and the American Thoracic Society and they have pages and pages on the protocol so it's relatively easy for people that know what they're doing the test to duplicate the test exactly. So you know that patient A in Holland is doing exactly the same protocol as patient B here in California or C in Ottawa.

R: I thought Nancy Klimas was doing something with multiple snapshots, looking at all kinds of blood tests at multiple intervals post exertion?

C: Nancy is onboard with the exercise challenge. Our main reservation is that a lot of people are not doing a maximal exercise test. And if you don't do this you can't equate the level of challenge. There's a body of literature on the effects of exercise on the general population and it's extremely variable in terms of the level of stress that you put somebody under and that person's level of initial fitness. What we do is we can equate the level of stress across individuals and we can say that person A who does not have CFS was put under the exactly same level of stress as person B who does have CFS. Therefore any differences downstream of the exercise test are not due to different levels of exertion. So if you don't do a max test, you don't know how hard someone was working to achieve whatever your goal. So let's say you're exercising two people for 8 minutes – even in the general population there will be differences in how hard those people work to achieve an 8-minute exercise cycle. And so that's our reservation, it's about the criteria. And you may well get results and certainly a lot of people are seeing things that they didn't see prior to using an exercise challenge. What it makes difficult to rule out are what are just the normal effects of an exercise challenge that you might expect to see in just anybody and what effects are specific to CFS. Is it the illness or is it the level of exertion that the person has to go through to get to the end point?

R: We've all heard about Dr. Paul Chaney and Dr. Peterson describing the diastolic dysfunction in ME. Do you corroborate that with what you see? How does that all fit in?

C: Sometimes we see heart rate anomalies. Sometimes we don't. It's a plausible hypothesis, and one that would be nice to test. Let's take a subgroup of CFS patients that have diagnosed diastolic dysfunction with a group of patients who don't. Lets look at a variety of different measures post exercise challenge.

S: One of the problems with diastolic dysfunction is that there isn't agreement within the medical, or exercise science community on what is normal and what is abnormal. Even for athletes. I went to a session at the American College of Sports Medicine on diastolic dysfunction and there was a great degree of controversy about what was normal and abnormal for healthy, athletic individuals, which makes it difficult to see what's abnormal or normal for CFS patients.

C: There's a lot of undiagnosed cardiovascular disease. And it's not unreasonable to expect that a subset of people that have been diagnosed with CFS really have undiagnosed cardiovascular disease.

R: I guess the diastolic dysfunction they describe is not something that would clearly show up in the CPAT test.

C: We do an EKG but we don't do a stress echo and we do it primarily for safety reasons. So if we do get someone who clearly has a heart problem then we don't complete the test.

S: We often see orthostatic intolerance that shows up during the exercise testing. An abnormal blood pressure response from lying down during the EKG to being in a seated position on the bike. Sometimes blood pressure will actually drop instead of continuing to rise. That would indicate that a patient should follow up with a tilt table test but we don't have access to that in a clinic so we'd recommend them to go see a cardiologist to follow up.

C: Certainly orthostatic intolerance is either a symptom or co-morbidity in a number of CFS cases. We see it often enough to substantiate that but we don't see it all the time.

R: Are you able to provide advice in terms of exercise to those who can't come to your center?

S: Only really in broad strokes. Unfortunately we are not at this time doing individualized exercise or activity management consultations. We've got two lay publications that we can make available to patients that are interested; "When working out doesn't work out" and "A realistic approach to exercise and CFS." There are some resources for patients that we have developed and we hope in the future that we will be able to offer more services in this area.

C: We have the knowledge to do it but we don't have the capability to do it.

R: Would you see a potential to one day be able to extrapolate the CPET findings to something more readily available? Something cheaper and faster?

C: We've been dreaming of that for a long time and you can actually do it with a normal population because people function pretty much the same way when you give them an exercise test. People with CFS don't. So it's very hard to extrapolate without getting the data that we need to get. The thing with a max test is that it allows us to equate a number of things. A key thing is something called the anaerobic threshold. This is the point at which anybody in the world, if they exceed their anaerobic threshold, the time that they can continue to work is going to be limited and there's going to be some payback. It's the use of energy borrowed against future supplies of oxygen. It's the emergency energy system used for fight or flight. It appears that a great many people with CFS rely solely on this emergency energy system because their normal, aerobic energy system, their long-term energy system, is malfunctioning and not working properly. If you can't find that point, that's where we think people precipitate symptomology. but unless you do a full test and then go back to see where that point was, you don't know for anybody where it is. You can guess for general individuals that it's going to be 50-70% of their max output so you can run somebody at a predicted 50% max test and look at that, but we can't even predict endpoint for CFS patients. A lot of people use predicted max heart rate, but even the American Heart Association say not to use it because it doesn't work. It's based upon a normal, healthy individuals max heart rate, 220-their age. We get blunted heart rates frequently that don't even approach 60% of predicted max.

S: Absolutely, and we just had that happen this week. You can't tell by looking at a patient, they look good when they come in, but looking at them and looking at their test results are two different things. We would love to find an alternative. We keep dreaming about it and talking about it but we've just not been able to figure that out because of all the abnormalities with patients.

R: I would love to have something to put on my wrist that says 'low battery'.

C: And we can sort of do that with a heart rate monitor, but we'd need to know your anaerobic threshold is to tell you the point where your heart rate is approaching that.

R: I guess the extra complexity with the heart rate, as a guide, is the typical lower heart rate that shows up for some of us on the second trial. So I guess you can really get fooled by just watching the heart rate.

C: Half the population is on heart medication now that blunts your heart rate and that's why the American Heart Association says not to use heart rate as an indicator of effort. And the standard rates are unreliable for the different sections of the population anyway. The numbers we use probably work fine for an 18 years old college student but not for a 40 year old sedentary office worker with no other pathology, let alone for someone whose central nervous system is messed up.

R: Other centers are offering exercise testing and therapies What would you look for from centers to make sure it was providing reliable results?

S: I think there are several things. 1) Personnel that are familiar with working with CFS patients and have an understanding of post-exertional malaise. What it's going to cost a patient to do this testing, having somebody who's sympathetic is extremely important. And having somebody that's competent. You need to have good staff that knows how to do this testing. Ideally having an exercise phyisiologist do the testing is the best case scenario. Other things to look at are 2) maintenance of the equipment and quality control. A mistake that often medical providers make is that they assume that if the equipment calibrates at rest then it's working properly. They may or may not be maintaining the equipment. Basic equipment quality control and maintenance is important but beyond that biological validation, which means having a healthy individual do three steady state workloads, so three workloads of 3-6 minutes at different work rates, and making sure that every other week they're getting the same results to make sure that their machine is reading appropriately.

C: And we've had experience where we've consulted with other entities on exercise testing in clinical settings where we've not been present during the exercise test and when we look at the results it's clear that the equipment was not calibrated properly or they didn't follow the appropriate ramping protocol for the patient. And essentially you've got to throw the data away. You've just put a sick person through 2 twelve-minute periods of purgatory and what you have is of absolutely no use. So it's got to be taken seriously.

S: We would say do it right or don't waste your time. Sadly, because it's an exercise test most researchers and clinicians just assume that they can go out and buy the equipment and they can do it because it's just a walk on a treadmill. This is an entire field that has manuals and textbooks on the proper ways to do exercise testing that you need to hire a professional in those areas to do that. And beyond that you need to have someone that can interpret the results. Most cardiologists don't know how to interpret gas exchange or may not use a metabolic cart. So you need somebody that's familiar with the gas exchange side of the equipment and isn't just looking for a cardiac abnormality.

C: We've had cardiologists working for insurance companies question our results because the patient did not achieve 80% of the predicted maximum heart rate. Now, a cardiologist should know better anyway, because the American Heart Association has come out and said don't use predicted maximum heart rate for heart patients, let alone anybody else, and clearly they don't understand cardiopulmonary exercise testing and gas exchange. Where we have the gold standard for maximum effort, which is the respiratory exchange ratio, which is another thing that is key for our disability evaluations. The sub max tests are not really good enough because we always get the "well is this person malingering?" argument. We can dispute that categorically because we have a clear objective measure of maximal effort or good effort as an integral part of the testing protocol.

S: Chris and I have been doing this for years and it still takes us at least an hour or more to do a good solid interpretation and write the report. I know that in most medical centers physicians just don't have that kind of time, they don't have that luxury to sit down and do a complete analysis. So those are the road blocks to doing this well.

C: A lot of people look for the simple explanation. If you're starting with the premise that this person is not really sick, and I've just got to show that they're not really sick, then you're going to approach the test very differently than from the idea that this person's got a definite diagnosis, that these symptoms are real and not imagined, let's see if we can shine a little more light on why that might be happening. If there's nothing there then we're not going to say that there is. If we don't get the results that you hope we get then that's what we're going to say, and we have to stand by that. We get a number of other conditions other than chronic fatigue syndrome where we don't get a clear disability based on the data that we use.

R: PFL collaborates with key groups involved in ME research. Are you seeing results and patterns of interest in the ME community?

S: In this last year with the discovery of XMRV there has been much more news associated with the illness and much more excitement within the community to find out what's going on. Other research groups with other findings like the group from New Jersey that has come out with their findings. There's a lot more news, a lot more excitement just in the last year, year and a half, about the biological basis for the illness.

C: We certainly have the ear of the under secretary, the problem is that government just doesn't have any money either. So there would be a lot to invest in new areas. We're getting a lot of positive interactions with the National Institutes of Health, that hopefully will be productive. We've beaten the drum of functional exercise testing and exercise challenge we've just got to convince everybody to do it properly now. A lot of people are looking to incorporate that into their protocols; they're just not willing to spend the money and put the effort into it.

R: On your website you describe collaborations with Whitmore Peterson institute and Stanford. Are you able to speak of your involvement with those? How are those studies progressing?

S: We have non-disclosure agreements and confidentiality agreements with those groups.

R: You also evaluated patients with other conditions. What are the similarities and differences between them and ME?

C: FM is an interesting - some people consider it a co-morbidity, some people consider it the same illness. We've had people that have had a primary FM diagnosis that look classic CFS. So clearly they have CFS with whatever symptomlogy is required to diagnose FM. That's another area where you need a large group of people and you need to separate the co-morbid FM from the pure ME/CFS and look at what those differences are. Why would there be such a large percentage of people that seem to come down with both conditions and another group of people that have one or the other. FM is just as serious a diagnosis as CFS. What if you have one less pressure point than is required, does the physician still put FM down? Lyme disease is another one that there's a lot of scientific literature out to show that there's a great many of Lyme disease cases that are misdiagnosed CFS, and it's both political and regional. You go in with a certain symptomology and you've come from New England and been out in the country where they know there's deer with Lyme ticks so even if they don't find hard evidence of Lyme disease you may well get that diagnosis.

S: But we don't do the diagnosis ourselves. In our research studies they've largely been in the area of CFS and we've worked with physicians that are very good at diagnosis. The patients that come to us for disability evaluations, we have to go with the diagnosis that they're given. Often patients will tell us that depending on the Doctor they see their diagnosis changes. One Doctor may diagnose the same patient with FM and they go see another Doctor and they're diagnosed with CFS.

C: If you go to a rheumatologist, they're going to diagnose you with FM.

R: That's a very important observation for some members of our audience.

C: There are certain diagnoses that are preferable to others. It seems the least preferable diagnosis is CFS.

S: You're asking about MS and HIV and I can tell you that with the patients that we have tested, both have reproduced their test results. And there's a wide range of disability for both.

C: MS is a "syndrome" so there are multiple manifestations of MS and not all MS patients look alike.

The MEAO is very grateful to Chris and Staci for this interview.