



Nerves, Estrogen, Dr. Mikovits and Paradoxes: The INTiDYN Approach to Fibromyalgia and Chronic Fatigue Syndrome

by Cort Johnson

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Last year researchers associated with a company called Integrated Tissue Dynamics ([INTiDYN](#)) in New York discovered [excessive numbers of nerve fibers in the skin of the hands of a high percentage of Fibromyalgia patients](#).

A [recent update on their progress](#) from the President and lead researcher at INTiDYN, Frank Rice Ph.D, indicated that they, in collaboration with Frank Ruscetti Ph.D, Sandra Ruscetti Ph.D (formerly of the NIH), and Judy Mikovits, Ph.D (formerly of the NIH and the Whittemore-Peterson Institute) are also studying viruses in Chronic Fatigue Syndrome (ME/CFS).

We took the opportunity of the update to review a recent podcast by Dr. Rice and ask him about his Fibromyalgia and Chronic Fatigue Syndrome research.

INTiDYN, a for-profit company created in 2008, uses complex tissue analyses to understand the effects of disease, toxins, and drugs on the body. INTiDYN asserts that the integration of the nervous, cardiovascular, immune, and endocrine systems in the skin make it an easy-to-access and cost-effective portal that can help us understand many of the problems happening in the body. Their testing of small biopsies of the skin includes examining the vasculature, nerve innervation, immunohistochemistry, gene expression, and sensory function. Their integrated approach allows them to assess the effects of disease, toxins, and drugs on the morphology, biochemistry, and genomics of tissues.

They used their ability to provide detailed analyses of microvasculature and the vascular sensory and autonomic nerves innervating the skin in their Fibromyalgia study. That study grew out of work they'd done with chronic regional pain syndrome (CRPS) patients.

First we cover a podcast interview with Dr. Rice [on Fibromyalgia and his work](#), and then go to our interview with him. (The podcast with Dr. Rice starts about seven minutes in.)

Dr. Rice's Podcast: A Personal Experience Flips Rice From Doing Basic Science Research To Doing Applied Research



During Dr. Rice's Ph.D studies in neuroscience at John Hopkins University he became interested in nerve endings in the skin. New methods had been developed that helped them see nerve endings in a way they couldn't before. He was doing basic science at that point; he was not focused on disease – he was simply determining how the nervous system and how nerve endings in the skin formed. But then after a minor accident a friend with four kids developed complex regional pain syndrome (CRPS), a “horrible condition” he said, he became interested in pain.

How bad does CRPS get? He noted the plight of two CRPS patients in one of his studies. Their CRPS was triggered by rotator cuff surgery and by a broken toe. Their pain became so bad that one's forearm and the other's lower leg were amputated. That – and the changes he saw occurring in their skin tissue – stunned him.

Hooking up with another researcher, Howard Fields, he began using techniques never before used in pain research to examine the nerves in the skin of people with a variety of chronic pain conditions.

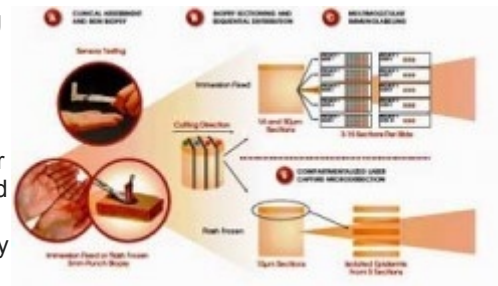
First came a study on shingles, then one on CRPS, and then last year a Fibromyalgia study. All revealed increased numbers of autonomic nervous system and, in particular, sensory nerves in the skin of the hands of FM patients.

How the Fibromyalgia Study Got Done

It took three years to get the Fibromyalgia study done. They'd noted that the serotonergic and noradrenergic reuptake inhibitors (SNRI) approved for Fibromyalgia affect the nerve fibers in the skin – in particular, the nerve fibers that converge on and regulate the blood vessels that control the flow of blood to the skin. Two types of sympathetic nerve fibers – one that constricts and one that dilates the blood vessels – are found. Through the production of noradrenaline these nerve fibers also influence that activity of the sensory nerves in the same way that SNRIs are supposed to work. Using that information they got drug company money to help them complete the study.

Study Results

They found ten times the number of nerve fibers expected surrounding the shunts that regulate blood flows into the hands of people with Fibromyalgia. This suggested blood might be readily flowing into the hands of FM patients but might be having trouble flowing out. The hands, it turns out, serve as blood reservoirs for the rest of the body. They fill up with blood when the body is at rest and send blood to other areas of the body when needed. Their findings suggested that reduced blood flow out of the hands of FM patients could result in low blood volume in, say, their muscles, when they attempted to exercise, thereby causing fatigue and pain. They suggested that sleep, pain, and cognitive issues could also be associated with this problem.



Cautionary Note

He cautioned that it was a small study (24 FM patients) and needs to be validated, but the fact that 75% of the FM patients in the study demonstrated the pathology was striking. That kind of consistent result, he said, does not often happen. He said he was 'very excited' about the findings.

Drug Effectiveness Poor in Fibromyalgia and Chronic Pain

One reason for that excitement was the huge need for better pain treatments. He'd received many emails from FM patients thanking him for his work. Lumping in Fibromyalgia with irritable bowel syndrome, CRPS, restless leg syndrome, and other mysterious pain disorders, he noted, "There's really nothing out there that can consistently and predictably work for a given patient. That's the frustration in chronic pain."

The best most pain medications do with disorders for some people with RSD and FM is drop a pain score from eight to about a four – a significant improvement – but since a score of three means you're in significant pain, they're still in significant pain. Of course many of these drugs can have severe side effects and work in a limited proportion of patients.

Possible Estrogen Connection

Dr. Rice's preliminary data, suggesting that under normal conditions women appear to have more of the sensory fibers that become a problem, could help explain the gender imbalance in Fibromyalgia. That suggests hormonal issues could come into play, and preliminary evidence from his lab suggests estrogen may play a role in these nerve changes.

Stress Connection

Because the sympathetic nervous system (SNS) fibers that go to the blood vessels are particularly activated by stress, he noted that it's possible that stress – triggered centrally in the brain – produces excess activity in the SNS fibers in the skin which then drives the pathological changes in the sensory fibers. Hormonally (estrogen) driven changes in the nerves in the skin could also trigger the stress reaction in the brain.

He noted that trauma (auto accidents) or infection (mononucleosis) or abuse can increase the risk for FM and suggested that the body's attempt to do stress management may tip it past some threshold (system reset) into disease.

Ketamine Reset Works – Sometimes

When asked about ketamine's effectiveness in Fibromyalgia, he noted that some patients with severe CRPS have been put into a ketamine-induced coma. When their system comes back or reboots, it appears to reset itself in some patients. In the right patients it can be very effective. Electroshock therapy can do the same thing for depression.

Staying Engaged Helps

"What we do know is that those who refuse to surrender to their pain and engage in activities despite the pain, those individuals generally fare better in managing their pain."

He also noted the importance of staying engaged. Rice acknowledged that it's easy for him to say that, since he's not the one that's in pain, and acknowledged the challenge of staying engaged when you're in pain, but nevertheless asserted that it's important to stay engaged as much as possible.

By producing pain signals, your body is essentially telling you to stop doing anything, but it's pretty clear that stopping doing anything makes it worse. Clauw has stated that his FM patients that go on disability tend to get worse.

Pain itself, of course, is very stressful and that stress is going to activate the sympathetic nervous system, causing more pain. (This is a key facet of Dr. Martinez-Lavin's hypothesis.)

Doing things that get you outside of the pain as much as possible is helpful. It's simply a management technique to use while researchers uncover the causes of and treatments for pathological pain.

The Dr. Rice Interview

In the interview Dr. Rice reported his team is engaged in a study examining the efficacy of a possible treatment for a similar kind of nerve fiber loss that occurs in chemotherapy patients. (An earlier Health Rising blog "[Could Cancer Treatment Improve the Treatment of Widespread Pain in Fibromyalgia and Chronic Fatigue Syndrome?](#)" revealed that cancer pain may be associated with mitochondrial problems.) Rice's statement that small fiber nerve loss is sometimes associated with pain – and sometimes not – also suggests there's more to SFN in FM than we know.

Your team explores a very wide variety of pain issues and you're also examining the intersection between viruses, immune factors, and chronic fatigue syndrome and fibromyalgia. That seems like quite a new direction for you. Can you say how this study came about?

Actually, we have long held a globalist point of view to our research which involves a multi-component approach to diseases involving peripheral tissues and their nerve supply.

We have a long publication record on a comparative assessment of normal innervation across a variety of species including mice, rats, gerbils, rabbits, cats, ferrets, African naked mole rats, kangaroos, manatees, raccoons, monkeys, humans, and recently whales. The reason for this is that there are variations among different species that help them survive in their particular environments.

Consequently, we often find something that is exaggerated in some species that draws our attention to it in others. For example African naked mole rats and manatees have some extremes in their blood vessel innervation that drew our attention to this in humans, which contributed to our discovery of pathology in this innervation in patients with Fibromyalgia.

We also have a long publication record in developmental neurobiology involving the impact of various molecular mutations of trophic factors and signaling molecules in tissue structure and innervation.

In all these studies, we have long taken a comprehensive multi-molecular approach to evaluating all components of the tissue structure and innervation, which, in skin, looks at epidermal cells (keratinocytes), hair follicles, sweat glands, blood vessels, and nerves.

This multi-species, developmental, multi-molecular, and multi-structural approach laid the foundation of our research on disease conditions and caught the interest of clinicians and the pharmaceutical companies.

Therefore, we have adopted a globalist approach of doing research across a variety of diseases where we look for differences and commonalities between diseases, and each disease teaches us something about another. So Chronic Fatigue Syndrome, PTSD, low back pain, etc., are a natural extension of our research.

The skin is particularly interesting in that it is a multifunctional organ that has a convergence of numerous body systems including nervous, vascular, endocrine, integument, connective tissue, and immune. We have mostly focused on the former five, so the recent addition of immune components and related virology was long overdue.

What viral infection and immune system factors are you, in collaboration with the National Cancer Institute, examining in the Chronic Fatigue Syndrome/Fibromyalgia study? Who are you collaborating with in the NCI?

Herpes zoster and retroviruses. The evolving new collaborations are with Drs. Sandra and Francis Ruscetti (who both recently retired from NCI) and a collaborator of theirs, Dr. Judy Mikovits. Their work on the possible contribution of retrovirus to some types of CFS is controversial but nonetheless intriguing and overlaps with some preliminary work that we have been doing with the Center for Functional Genomics here in Rensselaer. They have a new company called [MAR consulting](#).

[Herpes zoster causes shingles. Dr. Rice's work here and Dr. Pridgen's work with Fibromyalgia patients both seek to extend the herpesvirus connection in ME/CFS and/or FM beyond the usual herpesvirus suspects: Epstein-Barr Virus, HHV-6, and cytomegalovirus. Herpes zoster infection of the dorsal root and other peripheral ganglia in Chronic Fatigue Syndrome was proposed by Shapiro five years ago. Shapiro noted that varicella-zoster hides out in the dorsal ganglia, can cause severe disease, causes symptoms similar to ME/CFS, and could account for cases of rapid onset.]

Apparently the altered skin sites you found are only present in the feet and the hands. As laymen we're struck by the evidence of nerve problems found there and in the other parts of the skin in the small fiber neuropathy studies. One, if I understand this right, involves a buildup of nerves (hands) and the other the destruction of nerves in the skin (small fiber neuropathy). Is there any reason to believe that these two issues are related in

some way?

Yes, you understand correctly. The destruction you are referring to is a partial loss of sensory nerve fibers that terminate in the epidermis that was found by Dr. Oaklander's team at Harvard, and Dr. Claudia Sommer's team in Wurzburg, Germany. The later study was the better one.

A loss of nerve fibers in the epidermis (referred to as small fiber neuropathy) has been seen in several other pain conditions such as diabetic neuropathy, complex regional pain syndrome, and postherpetic neuropathy which has been described in many studies by others including us.

It is a paradoxical finding in that such nerve fibers were assumed to be a potential source of chronic pain, so it was somewhat strange to see them reduced in chronic pain conditions. However, a technique called "microneurography" (which actually records the electrical activity of nerve fibers using thin electrodes inserted through the skin) has revealed that there is excess activity among the remaining nerve fibers that supply the skin.

A group based in Spain headed by Dr. Serra confirmed that such hyperactivity also occurs among nerve fibers in Fibromyalgia patients. However, this technique cannot determine whether the nerve fibers are those whose endings remain in the epidermis or whether they might be the fibers that we found affiliated with blood vessels.

The Oaklander and Sommer studies looked at the epidermal endings in the arms and legs of Fibromyalgia patients. In our study, we also found that the epidermal endings were reduced in the skin over the back of the shoulders in a location of one of the "tender points" that have been used to diagnose Fibromyalgia. This finding did not get much attention in view of our finding of excessive fibers around blood vessels.

However, we did NOT find reduced sensory endings in the epidermis in the skin over the palms of the hands. Although, a reduction of endings in the epidermis has commonly been found in a variety of chronic pain conditions, it is important to note that reductions have also been found in conditions where there is no chronic pain. So a reduction in epidermal endings does not necessarily mean that there will be pain.

Likewise, we have found patients with severe postherpetic neuralgia who do NOT have reduced endings in the epidermis. So having chronic pain does NOT NECESSARILY mean that there is a loss of sensory endings. Oaklander actually provided very little data in her study. Sommer did a much better job showing her data. Importantly, the reduced endings was the AVERAGE over all her patients, but did not occur among many of them.

The "build up of nerves in the hands" that you are referring to was in our study, and refers to excessive nerve fibers associated with the arteriole venule shunts in the hands of the Fibromyalgia patients. This was a much more consistent and a more highly significant finding than the reduction of epidermal endings. We do not know if these two phenomena are related.

Will the expanded 'hands' study, if it is funded, examine the role estrogen may play in producing the increased levels of sensory fibers you found? (INTiDYN, in collaboration with the Center of Excellence for Pain Medicine at the University of California at San Diego, is applying for a major NIH grant to further explore their FM findings. We should know the grant's fate soon.)

That is part of the intent. At this point we already have considerable data on normal women and men of comparable age that shows women normally have about twice as much of the sensory fibers affiliated with the blood vessels as men. So there is clearly a gender difference. We suspect that women more often have Fibromyalgia because they start with more sensory fibers than men.

Since there is a gender difference, an obvious question is whether estrogen is involved. We now have preliminary data indicating that the sensory fibers do have a receptor molecule that is known to respond to estrogen. So one of our objectives will be to determine whether men with Fibromyalgia also have excessive sensory fibers affiliated with the blood vessels. So we will be recruiting men with Fibromyalgia as well as more women, and we will be measuring estrogen levels in blood tests.

What factors are you examining in the cancer/chemotherapy/pain study?

We are working on a project with the MD Anderson Cancer Center. It is known that Taxol also causes a reduction of sensory fibers in the epidermis in cancer patients who can also have reduced skin sensation and chronic pain. We are involved in research that attempts to prevent or **restore the lost innervation**. The specific details are proprietary.

Can you say how the new techniques for examining blood flows in fibromyalgia being developed will enhance your understanding of blood flow issues in FM? (Dr. Rice reported he is, in collaboration in UCSD and Georgetown University, using new techniques to study blood flows in FM.)

The discovery of the excess innervation affiliated with the AV shunts in the hands led us to an extensive literature search on the normal functional role of the shunts which is where we found indications that they play a key role in thermoregulation and metabolic vasoregulation.

But, there was really nothing that explicitly described the normal functional role of the shunts. What we wrote in the discussion of our research paper and subsequent public summaries are a logical speculation based upon piecing together the available literature.

So first we need to enhance our understanding of blood flow issues in normal individuals to make sure that that the shunts normally work the way we think they do. Next we speculated what would be the functional consequence of the excessive innervation that we found. There was very little on this topic on Fibromyalgia patients in the literature. So once we have a better understanding of the normal function, we will then assess the impact of Fibromyalgia on that function.

An Unusual Company

Dr. Rice and INTiDYN have shown an unusual degree of compassion for a research laboratory. (They cannot recommend treatments, by the way – they are medical researchers, not medical doctors).

Recently they stated, " ... many of you have felt that your particular case is unique and unlike anyone else. That is not entirely true. We want to assure you, that among all the Fibromyalgia patients, there are others who share your story and pain. Regardless of the differences, nearly all of you share the devastating impact that Fibromyalgia has or has had on your quality of life, and the frustration of finding a treatment that works. Some have been fortunate to find improvement and others have not. Unfortunately, that is a major problem with almost EVERY type of chronic pain condition."

Finding a Pain Specialist Near You

INTiDYN is also interested in helping FM patients hook up with good pain specialists. To that end they stated: "Many of you are seeking specialists in your local area for Fibromyalgia and other forms of chronic pain. We will work with the NRPC and others to seek their recommendations for top pain specialists over as many areas of the country as they can cover. We will work with them to develop a way to disseminate this information. To do this, if you haven't already done so, we would appreciate it if you would visit our website and submit your information and where you live on a form that can be found on our home page."

In their recent update Dr. Rice reiterated:

"In some cases we have been able to make recommendations where you may find a well-regarded pain specialist if you are not already in good hands. Most University-based medical centers are more likely on top of the most up-to-date information. Most of you have sent us information about where you live to help with this, though we haven't been as systematic as we could about doing this. If you are not sure if you have provided us information about where you live, and you wish to do so, you can register this through a form located on the home page of our website (www.intidyn.com)."

About the Author: Cort Johnson has had ME/CFS for over 30 years. The founder of Phoenix Rising and Health Rising, Cort has contributed hundreds of blogs on chronic fatigue syndrome, fibromyalgia and their allied disorders over the past 10 years. Find more of Cort's and other bloggers' work at [Health Rising](#).

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