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EVALUATION & MANAGEMENT OF AUTONOMIC DYSFUNCTION IN EDS (Transcript)

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Video https://youtu.be/6pmv_Pt2u1Y

A. Pockini Okay, so hopefully you guys have seen this logo enough times that it doesn't need more introduction. One of the taskforces I was honored to participate in was to review what's known about the evaluation and management of autonomic dysfunction in Ehlers-Danlos syndromes. I'm going to review, present much of what is published in our paper, which is in this guide here. I have no financial conflicts of interest. I have no – I think you guys all know, we get no remuneration of our time for doing this and I'm certainly not here to promote my practice. In fact, my office manager texted me during this morning's talks saying, "Please tell people you're not accepting new patients." It's one of the reasons I make the effort to come here, so other people can listen and hear some of what I have to say, and hopefully, there's some of you who take some of it back to their physicians.

Autonomic nervous system basically is that part of the nervous system that regulates all the body processes that go on automatically. So, while you're sitting here your autonomic nervous system is regulating your heart rate, your blood pressure, your breathing, your digestion, your body temperature – all of those things, fortunately, without you having to think about it. The job of the autonomic nervous system is to maintain those things in fairly stable ranges. Autonomic dysfunction is very common in Ehlers-Danlos syndrome and related hypermobility syndromes and underlies many of the symptoms.

The autonomic nervous system is a pretty simple system, probably because evolutionarily it goes way back. Basically, you have your sympathetic nervous system – that's the fight-or-flight. That's your stress response. That's adrenaline. And, on the other side, you have your parasympathetic nervous system, which generally slows things down. That's here referred to as rest and digest if you've eaten, or you're getting ready to go to sleep, you want to take your foot off the gas and apply the brake and you slow things down. Autonomic dysfunction in Ehlers-Danlos syndrome is associated with instability and the failure to respond to stresses appropriately. If you sense that you're a little bit chilly in this room, your body will warm you up a little bit. But, if you have body temperature problems, like a lot of Ehlers-Danlos patients do, then in a few minutes from now you may be feeling too hot, and then a few minutes later you might be feeling too cold again.

This, what I call the autonomic roller coaster, is a very common feature of autonomic dysfunction in Ehlers-Danlos syndrome. So, typically, the other feature is what I call over-response – that your body overreacts to minor stresses. Also very helpful, and you guys heard Jason who gave a great presentation on "The Spoon Theory." I use the fuel tank metaphor, same idea. You've got a tank full of energy and the paradox, the

central paradox of autonomic dysfunction in Ehlers-Danlos syndrome is that as that energy reserve gets more and more depleted, instead of getting tired, more and more tired and needing to rest, you actually get more jittery. Your body starts overacting to minor things, and it's just wasting the very energy that you're trying to save. So minor stress comes along, your body overreacts to it then it says, "Wait a minute, that was too much adrenaline, better slow down." And, "Whoa, that was too much slowing down, speed up again." That up-down-up-down is shown very well here.

A lot of you have asked me, this is a software developed by a company called ANSAR. It's very simple compared to what autonomic specialists have in their labs. Basically, it measures sympathetic nervous system activity on the basis of what's called heart rate variability and it measures parasympathetic activity based on minor changes in respiration. I'll show you. Typically, in a test, what we do is, there's a rest period and we have people doing slow, deep breathing. That generally will stimulate the parasympathetic response. If you're stressed, upset, some people say, "Calm down and take a deep breath." Taking deep breaths stimulates your parasympathetic nervous system. Then there's a break. Then we do what we call Valsalva, where people clench and strain to simulate acute stress. So then, I think most easiest to see here is the standing portion. That's why we ask people to stand.

You'll see a healthy person: their blood pressure drops when they stand up, but their body makes a little bit of extra adrenaline to raise their heart rate and raise their blood pressure so they're not dizzy when they stand up. But then, very quickly, the body does things like constrict blood vessels and move blood in from other parts of the body so that within literally seconds, they don't need this extra adrenaline. Now this person is having autonomic issues, stands up and has this over-response. They get too much adrenaline in response to the small drop in blood pressure and then almost immediately the body recognizes, "Whoa, that was too much adrenaline. We better hit the brake." And slams on the brake even harder. That's how a lot of people faint. In this case, the person's body quickly recognizes, "Whoa, that's too much brake. Better hit the gas again. Nope, that's too much gas. Better hit the brake."

She's been standing for four minutes and her body is still struggling, trying to get her heart rate and blood pressure regulated. And in terms of energy, look at how much energy this person is wasting going up and then up and down, compared to this. This is how she could spend most of the day on the sofa and still be exhausted because your body is wasting energy regulating basic body processes. These are just other similar ways of presenting the same data. It's hard to see the normal. There's a shaded gray area here in the middle that's normal, but this reflects the baseline sympathetic

and parasympathetic activity at rest. This person is chronically ill. Their tank is low, what I call depleted. They're not expending much energy. Their autonomic nervous system has kind of downregulated. They're just trying to keep everything going at a slow level. If this were your car, your car would decide that we can't afford to burn too much fuel if we run all eight cylinders, so let's just run on four.

Then, if you're trying to fall asleep and you want a nice big parasympathetic response to slow things down so you can fall asleep, can't do it. Just not there. What if something stressful happens and you need to kick it up a notch. Again, you don't have the reserves to do that. What happens when you stand? Your blood pressure drops. You don't make as much adrenaline as you should. Yet, even when you make a little tiny bit, your body senses that's too much and overcorrects. Generally, this is a sympathetic stress. You should be increasing your sympathetic activity. You should not be increasing parasympathetic activity. This is a very similar patient that I just saw recently who one of her major complaints was persistent nausea. I tried to explain to her that if you're nauseous all day and eating doesn't affect it one way or the other, then the odds are pretty good that's an autonomic symptom and not a GI symptom. What happens when something's stressed? She makes a little bit of adrenaline and then slams on the brakes. In fact, I just saw somebody Monday who I asked her if bright lights and loud noises startle her. She said, "Yes." She gets nauseous. She gets sudden nausea. She doesn't even feel the initial adrenaline response to an unexpected sound. She just so rapidly gets a big a surge afterward.

Our paper was mostly about cardiovascular autonomic dysfunction and specifically, mostly, about orthostatic intolerance: problem with regulation of blood pressure when you're standing. Temperature intolerance is another major problem. Your body has trouble regulating your body temperature. You have trouble going in somewhere it's cold, trouble where it's hot. Reynaud's phenomenon, I think, is often an autonomic problem. You get cold, your body generally constricts your blood vessels to maintain heat to your brain and vital organs, but it's relatively less concerned about your hands and feet. Only, it shouldn't cut off all the blood flow to your hands and feet. That's what happens in Reynaud's. This fluctuating, rapid cycling of sympathetic and parasympathetic activity often is a trigger for migraine.

You can extrapolate this kind of autonomic roller coaster to almost every other organ system. Clearly, your digestive system should run fairly smoothly, and not from one extreme to the other. If your bladder acts like this, then you're going to feel like you have to go way too often, and then other times you may not feel like you have to go when you should. Your breathing patterns may be erratic. Lots of other things that an

autonomic dysfunction can affect. And then, some of you heard my other talk; most of the sleep disorders I see here I think are related to autonomic dysfunction and the problem of too much sympathetic activity and not enough parasympathetic activity overnight to get a restful night's sleep.

We try to summarize literature on cardiovascular autonomic dysfunction in Ehlers-Danlos and surprise, surprise, there isn't really very much, and the literature talks about there's some studies on joint hypermobility and others on Ehlers-Danlos in general, and not much about Ehlers-Danlos hypermobility type specifically. We do know, just from talking to our patients, as well as some studies, that some people have symptomatic tachycardia, their heart rate is either beating too hard or too fast and it really bothers them, and some of them are symptomatically hypotensive. They stand up, they get so lightheaded that they feel like they're going to faint. Their vision blurs out. They have to sit back down. We know, again from our patients, that these symptoms can be highly debilitating. There's some people who can't stand for more than a couple of minutes.

Why does this happen? We don't know. Various mechanisms have been suggested and the odds are there is more than one mechanism at play in most people. A lot of people have talked about venous dilation, what we call blood pooling. If your tissues are too stretchy then, like everything else, your veins are going to be too stretchy and blood that should be going back to the heart to be recycled, instead is sitting in veins and your body has a bunch of what we call capacitance veins, whose job is to store extra blood just in case an emergency, but these tend to be overly full and too much of your blood is taken out of circulation. Combine that with standing and the tendency of the veins in your legs to fill up blood, and that's two strikes against you. Of course, management of this is keeping your feet up and wearing compression hose and things like that.

Paradoxically, I think high levels of catecholamines are chemicals like adrenaline: if you're constantly cranking out adrenaline and that's usually because you're in pain and/or you're exhausted, that further compromises your autonomic dysfunction. Basically, you're walking around with your accelerator all the way to the floor. You not only can't kick it up a notch if you need to, but that's another scenario where your body may tend to make you nauseous to try to get you to slow down. Various reports of antibodies that get directed against receptors for catecholamines, some studies have found that. Other studies have not. I think that I will leave it at that. Certain medications that we use for treatment can make orthostatic intolerance worse. The one that comes to mind most often are the tricyclics, things like amitriptyline and nortriptyline, that we use because

they pain effects and they have sleep enhancing qualities. Usually, the doses we use for that don't seem to make lightheadedness worse.

Histamine is a culprit. Histamine is one of the major things released by mast cells. One of the major physiologic effects of histamine is it makes fluid leak out of your bloodstream into the tissues. Again, if you have an allergic reaction to something and this, at the extreme, it is anaphylaxis where blood rushes out of your circulation so quickly that your blood pressure drops and that can be life-threatening. Histamine in any degree of allergic reaction can aggravate autonomic dysfunction. For some unfortunate people problems with Chiari: with the brainstem being compressed, with the cervical spinal cord being compressed, seems to cause or at least be an important factor in autonomic dysfunction. Over the years I've seen a few patients whose autonomic symptoms got dramatically better after surgery to fix their cervical spine problems, but that's certainly not always the case.

We talked about this, and you saw this over-response idea. This was first reported in the fall of 2003, and I remember it well because in June of 2003 I tried to explain some of this at a meeting NIH and Peter Rowe of Hopkins and David Goldstein were the only people in the room who had any idea what I was talking about. Fortunately, just a few months later an Israeli group published this paper where they showed this over-response when they stimulated people's adrenaline receptors and exaggerated heart rate and blood pressure response.

What we do know about causes? Well, as I mentioned, we know that histamine causes blood pressure to drop and heart rate to increase. That implicated mast cell activation disorders in some patients. Now we know that mast cell activation has been associated with Ehlers-Danlos. In general, populations, meaning not specifically patients with Ehlers-Danlos; in patients with Chiari malformations, as I mentioned, there's some autonomic dysfunction that can be associated with that.

This is probably the most important slide, maybe besides the roller coaster slide—now you have a patient with autonomic dysfunction. It seems rather obvious but the place to start is thorough history and physical examination because what you want to see is the forest and not the trees. You want to look at what's going on with this patient, not why does this patient's heart rate go up too much when the stand, but what's underlying autonomic dysfunction in this patient. You specifically would look for things that we know are causes of autonomic dysfunction in Ehlers-Danlos like pooling, dehydration, poor sleep, chronic pain, things like that. Recognizing patients have lots of other comorbidities and keeping in the back of the mind that

lots of other things besides Ehlers-Danlos cause autonomic dysfunction. You hate to see somebody who's already got a lot of medical problems or that they might have something else, but every once and a while that will be the case.

This is a slide I have to include, but frankly, I would just as soon skip it. Basically, make the point that there are strict diagnostic criteria, which by now most of you have learned to hate, for all these different things. Most of the patients I see who come to me with a diagnosis of POTS, don't really have POTS. Some of them had tilt table tests and were diagnosed with POTS and their tilt table test did not show that they had POTS. I saw somebody recently who was diagnosed with orthostatic hypotension on a tilt table test, in fact, she had no significant drop in her blood pressure. It's kind of frustrating when somebody who had an autonomic testing lab wouldn't even know these things.

The bottom line is, whether you meet criteria of one these things, or you just have orthostatic intolerance, your management is going to be the same. Your treatment is going to be the same. You have autonomic dysfunction. It's really not – again, the label is not that important. POTS is based on heart rate increase. You could meet the criteria for POTS today and not meet the criteria for POTS tomorrow. If you decide on purpose you're going to dehydrate yourself, then you might get a false positive tilt table test. Further evaluation: well, I think, pretty much if you're having significant symptoms, then we're going to obviously make sure you're not anemic. We should do some blood tests to make sure you're not dehydrated, an EKG and maybe a 24-hour monitor if there's something that suggests you might have a more serious arrhythmia like atrial fibrillation or something like that, which is an irregular heartbeat rather than just rapid.

Blood pressure monitoring is nice. It's nice to do 24-hour ambulatory blood pressure monitoring. That's not available in most places and insurances won't cover it, so most people don't use it. Nowadays you can get a blood pressure monitor at home fairly inexpensively and check your blood pressure at various different times and even healthy people are surprised how much their blood pressure varies during the course of the day. An echocardiogram, but an asterisk because this is somewhat controversial. Basically, we looked at the literature and said there's really no evidence to suggest that people who have autonomic dysfunction need to have an echocardiogram unless there's something else about their history that suggests that they might have a structural heart disease.

Unfortunately, now that mitral valve prolapse in our group notation, are among the diagnostic criteria for hypermobile Ehlers-Danlos, a lot of people are going to have an echo anyway, which is fine. But it's probably not necessary for evaluation of

autonomic dysfunction. I could say in some cases, in a small number, tilt table testing can be helpful. Generally, you don't really need anything as fancy as a tilt table test. You can do a test in the office where you lie down for a while and then you stand up for ten minutes and have somebody check your heart rate and blood pressure and watch and see what symptoms you develop.

Rarely, and not specifically if you think that there's really significant damage to the autonomic nervous system, that referral for some of these more specific autonomic nervous system tests may be useful. Here I would just take a minute to try to explain some terminology. The reason I tend to use the words dysautonomia and autonomic dysfunction are to make the points that the autonomic nervous system is intact. There's nothing wrong with it. It's just not working properly, whereas I hear the term autonomic neuropathy, that's suggests to me that the autonomic nervous system has been damaged. So those are very different. If you have autonomic neuropathy, then you do warrant a little more extensive evaluation for other medical conditions because Ehlers-Danlos syndrome itself is not associated with neuropathy.

Sorry, this is my only cartoon; frankly, this is the way I feel about tilt table testing. Asking someone who says they get really dizzy and spacy and feel like they're going to faint when they stand up, say, "Okay. Let us strap you on this table and we're going to tilt you up and we're going to leave you there until you either throw up or pass out." It's kind of like asking somebody with vertigo to go around a revolving door a few times. It's really not necessary and frankly, I think it's cruel. Some of you may have had to experience the tilt table test, can leave people in bed for a week or two and it can really wipe you out.

What do we know about management of autonomic dysfunction in Ehlers-Danlos syndrome? Surprise! Not much. Really, nobody has done any clinical trials and, frankly, a lot of us who manage these patients wouldn't want our patients to have 50-50 chance of getting placebo. Not sure when that's going to change. We base our management on a few small cohort studies, expert opinion from people who manage patients like this for a long time and who have sort of figured out what works and what doesn't. And then, what we call pragmatic approach. We don't have a lot of information on Ehlers-Danlos syndrome in particular, but there is a fair amount of data published on management of dysautonomia. Blair Grubb has written a lot of papers on POTS and evaluation and management of POTS, so a lot of that is applicable to the Ehlers-Danlos patients as well.

Not surprisingly, as with everything else, pain, fatigue, everything else that I've discussed – usually, several different treatments are going to be needed to get things to work more appropriately. Education is a big thing, and basically by education we mean trying to educate patients so that you will understand what's going on, so that if you're sitting quietly and then all of a sudden your heart starts pounding, you're not going to rush off to the emergency room to make sure you're not having a heart attack. Instead, you're going to stop and say, "Okay. My autonomic nervous system just cranked out some adrenaline. I wonder why. Am I dehydrated? Am I overtired? Am I in more pain than I realize? Something is going on that is stressing me out? Maybe I've just been sitting or standing in one place for too long."

Non-pharmacologic treatments are things like dehydration, getting enough salt and fluid. Most people who are lightheaded are told to eat lots of salt, drink lots of water are not getting enough salt. Releasing venous pooling with some kind of binders or compression garments, very helpful, helps a lot of people. A lot of them are very reluctant to try them. A lot of them are very reluctant to admit that they help. A lot of people remember the compression stockings that their grandma or great grandma used to wear and say, "Forget it! I'm not doing that." But nowadays, fortunately, compression garments like Spanx are cool and you can get compression hose in fashion colors and patterns and everything. They look like leggings, so it's an easier thing to do than it used to be.

For people whose symptoms are pretty significantly impairing, we're going to have to consider medications. The standbys, unfortunately, in the field are fludrocortisone/Florinef and midodrine. I say unfortunately because fludrocortisone is a synthetic hormone that kind of tricks your kidneys into holding onto more salt and fluid. What I've found is that most people, their kidneys are working fine, they're trying to hold onto every bit of salt they can because they're not getting enough. So I have very few patients that need Florinef. Most of them just need more salt and when you get them on an adequate salt/fluid balance they don't need Florinef. Florinef can have some steroid side effects. The other issue with Florinef is you lose potassium. And there's a problem because most of your potassium is not in your bloodstream. It's in your tissues. I hear people say, "Oh yeah, no. I don't take a potassium supplement on Florinef, but my doctor checks my potassium regularly and it's fine." The problem is, as you lose potassium out of your bloodstream, your body takes potassium out of the tissues to replace it. You're slowly leaching potassium out of your tissues. You can check your blood test and it's fine. That's another problem with using Florinef.

Midodrine is a vasoconstrictor. It raises your blood pressure. If you're going to stand up and then your blood pressure is going to drop, it raises the floor so you don't come crashing down as far. Different people have different approaches. There are good autonomic specialists who know a lot more about this than I do, who use midodrine a lot and swear it's helpful. I'm not a big fan of midodrine because it only lasts a few hours. It kind of kicks in and wears off and then you take the next dose and it kicks and it wears off and that roller coaster is exactly what you're trying to avoid. Ivabradine is a relatively new chemical block. It works by reducing heart rate without dropping blood pressure. Particularly in the case of POTS, your blood pressure tends to be low-normal and you have this really rapid heart rate, medication with light beta blockers might lower your blood pressure as well as your heart rate.

I have a few people who are finding this helpful, and most people who have tried it haven't found it helpful. Sorry, I'm going to hold questions till the end, okay? I'm a beta-blocker person. I think it makes more sense to block the up, so you don't get the drop, instead of taking this thing so that you just don't drop quite as far. What we said here is that lower doses tend to be better tolerated. This varies tremendously. In general, start with very small doses because just the way patients can be very sensitive to little bits of adrenaline their body makes, they can be very sensitive to blocking. But other people can need surprisingly large doses. I just heard from one of my patients who's on a rather huge dose. Basically, 25 years of chronic and poor sleep has left her at the point where walking up a flight of stairs makes her blood pressure go from 100/70 to 190/110. We actually tried a couple different beta-blockers before we hit the right one. She's on something called nadolol and most people take about 60 or 80 mg of nadolol a day. She's on 600. And on 600 mg of nadolol, her blood pressure is 130/80 and her heart rate is in the low 60s. The last time I asked her, "How's your blood pressure doing?" She said, "I don't know. I stopped checking it because every time I check it it's normal." Naturally, we've already started reducing her dose.

There are other medications that sometimes are helpful, especially in adolescents and young women, birth control pills for reasons I don't understand, reduce orthostatic intolerance symptoms. Pyridostigmine works primarily by increasing parasympathetic activity. Again, lots of autonomic specialists, rather than prescribing beta blockers which block sympathetic, prescribe pyridostigmine to increase your parasympathetic activity. Different strokes for different folks. Clonidine works primarily, rather than blocking adrenaline you've already made, it gets into your brain and keeps it from making it in the first place. It can make fatigue worse, but sometimes it's the perfect thing to take at bedtime to just shut down the adrenaline. Serotonin drugs can be helpful if there's

anxiety, if there's pain, if there's other things going on. I mentioned earlier that I'm not a big fan of the serotonin drugs because they tend to make your sleep worse.

Stimulants and some of you may have heard me mention this in the other talk, so low doses of stimulants for people whose pressure is too low and their heart rate is always low. It can raise their heart rate and raise their blood pressure and keep them from feeling lightheaded – can be very effective, but that's very different from taking stimulants because you're exhausted, to try and keep you going.

Desmopressin reduces how much urine you make. It's something we use primarily in kids who get up too many times at night to pee.

This is just a reference to very old studies showing that if we take somebody with these symptoms and dump a liter or two of saline into their bloodstream then, surprise, they feel better. They're less lightheaded. They're less tired. Their brain fog gets better.

This is a reference to the alternative medicine literature: butcher's broom is an herb that's been around for centuries that's putatively a "venotonic" that helps constrict veins and reduces venous pooling. I don't know that I've known anybody who has taken it and found it was really helpful, but we included that for the sake of completeness.

To come back to this slide, really, the take-home point here is to not lose sight of the forest for the trees, to not get lost in the details of, "Gee, my heart rate only went up 26 points and I need to go up 30, so I don't really have POTS. I must have something else." Really, the point is that there's autonomic dysfunction and you need to look at all the comorbidities and address them. In evidence for management, we don't know; I put this slide in again because we're left with this pragmatic approach. This is my pragmatic approach to management of autonomic dysfunction in Ehlers-Danlos syndrome. Most people come to me with their tank almost empty. They're exhausted. Sometimes they're tired but wired. They're so tired they can't sleep, "I'm exhausted. Every little thing seems to bother me." The goal is to replenish their reserves. How do we do that? Well, we have to try to get them on a more restful night's sleep because most of them don't sleep well.

Pain management is critical. Most people underestimate how much pain they're in. Pain is sucking up energy. Pain is disrupting your sleep. It's a major factor in perpetuating autonomic dysfunction. Every time you're really tired but you suck it up and plow through it anyway, you're further depleting your reserves and making everything worse. Sometimes people just need to understand that to sort of give

themselves permission to rest when they're tired. Dehydration, again, a surprising factor. A lot of people are chronically dehydrated. Trying to convince people they are dehydrated from drinking too much water is not an easy sell. If some of you heard my other talk, it relates to other factors and, basically, you need less plain water and more salt. Recognizing that cognitive efforts draw from the same energy pool. Emotional stress is draining. I could have another thing here for autonomic dysfunction, another thing here for mast cell dysfunction. I could keep adding things.

In conclusion, cardiovascular dysregulation is found, I would say, in many patients, not just some. There are some mechanisms that we think may play a role and probably multiple mechanisms involved in each patient. Diagnosis is based on history and examination to look for, not specifically issues of complication, but more general causes like pain and fatigue and poor sleep. Simple clinic room tests like having people stand is often very helpful. People don't need a lot of more exotic sophisticated tests. And then medications may be helpful or may be needed for some people; should always do the non-pharmacologic stuff first. On looking at medications, first, we want to reduce or get rid of any medications that might be making those symptoms worse. Medications that we have tend to work through volume expansion: that's the fludrocortisone, vasoconstriction, drugs like midodrine, and then modulators of autonomic tone like beta blockers.

"Prognosis remains uncertain" is what we put in our paper. I've added most patients improve with treatment because I don't like seeing such negative stuff published in the literature. Of course, lots of questions remain because none of this has really been studied at all. Why do I say most people get better with treatment? Well, you remember this slide. This is the before and after, to make the point that this in balance. This is dysfunction of an intact autonomic nervous system, and that with treatment function can return pretty much to normal. This was a patient who was totally exhausted, couldn't function, could barely sit up, couldn't think, couldn't sleep, couldn't do anything and took a long time for a us to get her depression under control, her pain under control, her sleep under control, stabilized her autonomics, but at the end of a year and a half of doing this, she went back to work recently with a normally functioning autonomic nervous system.

How did she do that? Just by doing this. Here I always think of my colleague Pradeep Chopra making the point that if you can find five different things that are each contributing 10% to your feeling badly, and you can do something about all five of those things, then suddenly you're feeling 50% better.

Thanks to Ehlers-Danlos Society for inviting me and helping to spread knowledge and understanding of these things. I always thank Peter Rowe and David Goldstein for coming to my rescue when everybody else thought I was nuts. And Clair and Dr. Henderson for encouraging me to learn about Ehlers-Danlos and see how many of my hypermobile patients that that [inaudible]. And then I always thank my patients because, obviously, none of this is in the literature. I learned this from my patients having faith in me and being willing to let me experiment on them and say, "Hey, I think this might help you. Are you willing to try?" Thanks for your attention.

Transcription by Christina Cole