ACTTION - CONCEPPT/IDNC MEETING ON DIABETIC PERIPHERAL NEUROPATHIES

December 12, 2017

A Matter of Record
(301) 890-4188

ACTTION

CONCEPPT/IDNC MEETING ON
DIABETIC PERIPHERAL NEUROPATHIES: EVIDENCE BASED
TAXONOMY FOR DIABETIC PERIPHERAL NEUROPATHIES

Tuesday, December 12, 2017
8:01 a.m. to 6:01 p.m.

W Hotel
Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Welcome and Overview of Action

DR. FREEMAN: Good morning. This is a meeting I did not think would take place for another couple of years, and it's very exciting that it happened quite so quickly. I think what we have over here is a combination of groups that typically don't interact or don't interact much, and I think it's just the right size for us to go around and introduce ourselves very quickly.

I'm Roy Freeman. I am a neurologist from Boston.

Doug?

DR. WRIGHT: I'm Doug Wright. I'm a basic scientist at the University of Kansas Medical Center in Kansas City.

DR. TESFAYE: I'm Solomon Tesfaye, endocrinologist at Sheffield University.

DR. ZIEGLER: Dan Ziegler, endocrinologist, diabetologist, German Diabetes Center in Dusseldorf, Germany.

Page 5

DR. GIBBONS: Chris Gibbons, neurologist from Boston.
DR. SINGLETON: I'm Rob Singleton. I'm a neurologist at the University of Utah.
DR. HARATI: Yadollah Harati, neuromuscular specialist from Baylor College of Medicine, Texas.
DR. DYCK: Jim Dyck, neurologist, Mayo Clinic, Rochester, Minnesota.
DR. SMITH: Gordon Smith, neurologist in Utah.
DR. MALIK: Rayaz Malik, endocrinologist, Cornell, Doha, New York.
DR. POP-BUSUI: Rodica Pop-Busui, endocrinologist, University of Michigan.
DR. RUSSELL: James Russell, neurologist, University of Maryland.
DR. JARPE: Matt Jarpe. I'm a biochemist at Regenacy Pharmaceuticals in Boston.
DR. HOKE: Ahmet Hoke, neurology at Johns Hopkins.
DR. BENNETT: Dave Bennett, I'm a neurologist at the University of Oxford.

Page 6

DR. BRIL: Vera Bril, a neurologist from the University of Toronto.
DR. BRUEHL: Dave Bruehl, psychologist and pain researcher at Vanderbilt University.
DR. HERRMANN: David Herrmann, neurologist at University of Rochester in New York.
DR. GEWANDTER: Jen Gewandter, University of Rochester, clinical trialist in pain.
DR. KOLB: I'm Noah Kolb, a neurologist at the University of Vermont.
DR. CALLAGHAN: Brian Callaghan, neurologist, University of Michigan.
DR. FEDLMAN: Eva Feldman, neurologist, University of Michigan.
DR. ZOCHODNE: Doug Zochodne, neurology, University of Alberta.
DR. FREEMAN: And Amanda?
DR. PELTIER: You already introduced me. Amanda Peltier at Vanderbilt University, neurology.
DR. FREEMAN: Why don't we get going? As you see, this is a unique meeting. It's a combination of CONCEPPT, which I'll talk a little bit about, and the International Diabetic Neuropathy Consortium, which my colleague Chris Gibbons will talk about in just a second.

Page 7

There are some housekeeping matters, which I can let you read through quickly on your own. Restrooms, I guess, located outside to the left. The rest is somewhat self-explanatory. Checkout is 12:00 noon. Feel free to refer to these at any time.
What I'd like to do now is give a brief introduction, overview, and set the stage for the proceedings that will follow. This meeting is, I think, a somewhat unique one, and you'll see why in just a few moments.
Now, typically at this point, I would introduce Bob Dworkin, who some of you met yesterday. He is the director of ACTTION, and he would give this talk. I'm going to talk through his slides, not do it nearly as well, nor with as much authority as he would have done, so bear that in mind.
Personally, I think ACTTION has really been

Page 8

a remarkable achievement. You see the mission statement over there: "to identify, prioritize, sponsor, coordinate, and promote innovative activities with a special interest in optimizing clinical trials that will expedite the discovery and development of improved analgesic, anesthetic, addiction, and peripheral neuropathy treatments for the benefit of public health."
The achievement of ACTTION and IMMPACT, which preceded and now is under the rubric of ACTTION, has been quite remarkable. Since the existence of ACTTION over -- I'm not quite sure how many years. Since 2010 and IMMPACT just before that, I think around 100 publications, all of which have been really important publications in major medical journals have occurred, and really it's made an enormous and I use the word impact with respect to those features that relate to neuropathic pain, pain in general, addiction, anesthesia, and many other aspects of the related disciplines.
ACTTION was born initially out of a

Page 9

collaboration with the FDA, who felt that there were deficiencies, that there were deficits in the neuropathic pain trial. The organization has grown since that initial time, and as you see, a number of partners, FDA, Department of Defense, Department of Veterans Affairs, NIH, American Chronic Pain Association, Chronic Pain Research Alliance, professional societies, you can read the list, industry, again, read the list. And industry has provided support for meetings such as this.

Now, there have been a number of activities. These are all organizations that fall under the rubric of ACTTION. IMMPACT was one of the first and, in fact, preceded ACTTION.

Bob has a number of strengths, innumerable strengths, but one of his major weaknesses is this addiction to acronyms.

(Laughter.)

DR. FREEMAN: And they are all misspelled acronyms, and in fact, somebody once looking at this said, "What's wrong with this guy? Does he have a sticky key on his computer?"

Page 10

Here you see IMMPACT, and I think many of you in the audience are familiar with the role IMMPACT has played in the clinical trial methodology for pain in very spheres. You see some of the more recent publications.

One the points, I think this is a good opportunity to make, is from meetings such as this there are always one or more publications. They are spearheaded by individuals who are in attendance. All of the members of the audience, all of the participants are contributors and will be authors, but only all of the members of the group. So this means nobody outside of this meeting with the possible exception on this occasion of somebody who made an attempt but could not make it because of inclement weather.

These are two of the more recent publications. "Evidence Based Diagnostic Criteria for Major Acute and Chronic Pain Conditions," and this meeting was really borne out of the initiative as far as acute and chronic pain is concerned. Here, you see two of the publications from those

Page 11

meetings and initiatives. "Addiction, Anesthesia, Sedation in Peripheral Neuropathy," and "Peripheral Neuropathy," which I'll talk about in just a while.

CONCEPPT, double P of course, is one of those initiatives, another one on sedation, and another obviously really important these days on addiction.

Outcome measures are a major initiative, and this will, I think, be part of the process that we will embark on in future meetings, but more about that briefly later. Here you see, QUALITE, PAACT, development of validation of a novel patient-reported outcome measure for pain. Lots to talk about, but not now. Validation of an accelerometry-based outcome measure, and all of these are done in conjunction with the FDA.

Then there is an ongoing process on the analysis of clinical trial data that has been submitted to the FDA; again, a really important and interesting initiative, no time to talk about that now.

Then finally, number 6, education and

Page 12

dissemination, and there are number of ongoing educational initiatives focusing on pain, pain treatment, and clinical trials.

I now want to move on to talk a little about CONCEPPT, which is the axonal peripheral neuropathy initiative. Now, a couple of years ago, the previous division director of the FDA, Bob Rappaport, made the observation, the obvious observation, that there is no drug approved for axonal peripheral neuropathy, despite the prevalence and thought that we should begin to address this in similar ways to the neuropathic pain, chronic pain, acute pain initiatives within the rubric of ACTTION.

That was really how CONCEPPT was born. It is the Consortium for Clinical Endpoints and Procedures for Peripheral Neuropathy Trials, but much bigger than that. And I think that title just allowed the CONCEPPT acronym to emerge.

So far, we've had a couple of meetings, the first of which took place in 2015, and you see one manuscript from that meeting, lead author you'll

Page 13

see at the back, Jennifer Gewandter, published this year, another manuscript in preparation, and Chris will be talking a little bit about that.

A second meeting took place earlier this year on chemotherapy-induced peripheral neuropathy, and one manuscript from that so far and another manuscript, which is circulating among the members of that meeting.

We have also a meeting planned for later this year on small fiber peripheral neuropathy, and there is a systematic review that is currently in progress.

That brings us to this meeting. Now, as you see or may have noted, the initial activities, the primary initiatives were in chemotherapy-induced peripheral neuropathy and small fiber neuropathy, and these are ongoing processes.

I had decided that diabetic peripheral neuropathy would be third in line for a number of reasons, which I'll begin to talk about in just a while.

The background to that is really as follows:

Page 14

I think all of us have in our collection -- I think the last time I saw one of these slides was just a couple of weeks ago in a presentation by Rayaz Malik. We have the slide, which lists in very small print in five columns the number of failed clinical trials in diabetic peripheral neuropathy.

The list has actually, unfortunately or perhaps fortunately, stopped growing just because there's so little interest now in diabetic peripheral neuropathy, and I speak not neuropathic pain in diabetic. I speak about disease modification.

These failed clinical trials have been of multiple drug classes, multiple targets, and multiple mechanisms of action. I ask myself, as I'm sure you all have asked yourselves, is this because the disease is just too complicated, or is it because the drugs are just not good enough, or perhaps we need combinations of drugs? Or is it because there is something wrong with our clinical trial methodology?

Is it that the architecture of our clinical trials

Page 15

is not adequate for the disease.

Now, 1 and 2 is not in our power, perhaps with one exception, to change. We can't change the disease. We can't change the drugs. But what we can do is examine intensely the clinical trial methodology, and that is what I hope we are going to be able to do over the next year or two, and this just the start.

I had put this third in line, but following the meeting of the International Diabetic Consortium at Sitges, there was such a degree of enthusiasm for looking at ways to develop the field, expand the field, grow the field, and enhance the clinical trial methodology that I thought that I would harness that enthusiasm, enthusiasm on the part of so many members of the audience, and move it up on the agenda. We were fortunately able to have this meeting very quickly after that meeting earlier this year in Sitges.

There is this quote that I think is apocryphally attributed to Einstein that "insanity is repeating the same thing over and over again,

Page 16

making the same mistakes over and over again, and expecting different results." My view is that is where we are with clinical trials in diabetic peripheral neuropathy.

On a personal note, I think I prefer the Tallulah Bankhead quote, "If I had to live my life again, I'd make the same mistakes only sooner," but I think scientifically, probably that's not appropriate. I think what we do need to do is deconstruct the diabetic peripheral neuropathy clinical trial and rebuild it from the ground up. That's really what I want to talk about a little, the deconstruction of the diabetic peripheral neuropathy clinical trial.

What that means is looking at the inclusion and exclusion criteria; the assessments; the instruments; the scales; the outcome; and bring it into the modern era; looking at assay sensitivity; looking at scalings; looking at reproducibility and validity; and trying to assess the placebo response, which has become a really important issue in disease modification trials in diabetic

Page 17

peripheral neuropathy, as important as it is pain. But we haven't adopted the same scientific rigor with looking at the placebo response in these trials.

Now, this is all work in the future. What we are going to do is start today and at this meeting at the basement, begin to look at the clinical trial and its taxonomy. What I want to talk about now briefly is taxonomy and why taxonomy matters.

I understand that perhaps with the possible exception of a few neurologists, it's hard to get too excited about taxonomy, but it is absolutely critical. What the aim is, to have a widely accepted, consistently applied evidence based, and I emphasize evidence based, taxonomy using standardized, reproducible evidence based criteria.

The aim is really to standardize so that when we are talking about the same disease, we are talking about the same disease, so commonality of terminology and language. What we want to do is to build a taxonomy that is suitable not just for

Page 18

randomized clinical trials for interventions, but also for cohort studies, case control studies, and even case reports, observational studies, interventional studies, and prevention strategies so that we have something that is evidence based; where it can't be evidence based, consensus, expert opinion, and that in the long run, the hope is that this will facilitate research, education, clinical practice, and allow, for example, meta-analyses to take place. When we are looking at different clinical trials, we understand that we are speaking about the same disease with the same criteria. The long-term goal, of course, is to develop treatments for this devastating disease.

This is really prompted by the success that this endeavor has had in psychiatry and in headache, and I'll talk a little bit about those. Psychiatry, the DSM-III has transformed, possibly even revolutionized, psychiatry and has resulted in a number of evidence based treatments for psychiatry. In the same way, the classification of the International Headache Society has done that

Page 19

and even more.

These are two different approaches to taxonomy. The DSM-III is more syndromal. It has its axes or as we are going to use over here, its dimensions, whereas the International Headache Society has a hierarchicalist approach in their classification, and I'll elaborate on that. What I'm hoping that we will do is have some merger, some fusion of both of these approaches.

Why I think that we should use the dimensional approach is that I think our disease, diabetic peripheral neuropathy, is more of a mosaic, and that allows us to, for example, integrate the neurobiology, the biopsychosocial, and it allows us to encompass a precision medicine based approach where we can look at genetic factors, environmental factors, lifestyle factors within that set of dimensions.

What I think of is a major taxonomic success is the headache classification, and let me talk a little bit about this. This is the International Classification of Headache Disorders, and I'm going

Page 20

to show you, if you'll bear with me, their approach to a couple of headaches. And I'd like as we move forward to use this as a model within our dimensions because this, as you, I'm sure, are aware, has probably revolutionized but perhaps transformed the way headaches are approached and headaches are treated.

They classified primary headache, secondary headache, and painful cranial neuropathies and other facial pains. Primary headaches, migraines, tension headache, trigeminal autonomic cephalgias, and other primary headache disorders. Migraine, migraine with, migraine without aura, chronic migraine, complications from migraine and so on.

Pay a little attention to this because this is the kind of approach that I think we should have when we speak about our individual diabetic peripheral neuropathies. This forms the basis of every clinical trial in headache so that they are talking about the same disease in the same way.

For example, at least five attacks fulfilling criteria B to D. What are B to D?

Page 21

Headaches lasting 4 to 72 hours, untreated or unsuccessfully treated. Headache is two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, two of those five. During headache greater than one of the following, and then not better accounted for by another IHD-3 diagnosis.

A couple of notes, clarification notes, which I won't go through in detail, and then the last criterion for every headache disorder: consideration of the possible diagnosis. Here you'll see, we'll talk about the differential diagnosis of diabetic peripheral neuropathy.

Migraine with aura, typical aura, brainstem aura, hemiplegic migraine, retinal migraine, and the hierarchical structure you see, 1.2.2.1, 1.2.2, 1.2.3, 1.2.4. Migraine with aura, very similar approach, but greater than one of the following fully reversible aura symptoms, 1, 2, 3, 4, 5, or 6. Greater than two of the following four

Page 22

characteristics, and you see the four. Aura spreads gradually over to 5 minutes, each individual aura symptom last 5 to 16 minutes, greater than one aura symptom is unilateral, aura accompanied or followed in greater than 60 minutes by headache.

Migraine with typical aura, and here you see it. Typical aura with headache, so fulfills criteria 1.2.1, migraine with typical aura. Headache with or without migraine characteristics accompanies or follows the aura, and typical aura without headache, so aura occurring without the headache. A migraine is migraine.

Then it brings us to our approach, and that is a model that obviously has been very successful, very successful from a clinical trial approach and very successful in terms of understanding the phenomenology of the disease and the basic science of the disease. It has been incorporated in a widespread fashion.

As I mentioned, I chose a dimensional approach because I wanted to in a way mirror what

Page 23

had been done with acute and chronic pain, but I thought it was really ideally suited for diabetic peripheral neuropathy because of this mosaic. It doesn't really fit the hierarchy that the headache classification incorporates, but within what we are looking at, I think there's a lot of room for that hierarchical approach.

What are the dimensions? I know I sent stuff around, and I know also when you send stuff around, nobody looks at it. So I want to go through this very briefly just to give you the overview.

There was this series. Somebody proposed that you never send more than three articles to read because the people you send them to then read none, and I know I sent more than three. So let me go through this.

(Laughter.)

DR. FREEMAN: First, the core diagnostic criteria, and this really is the hierarchical classification of migraine. These are the inclusion criteria, the exclusion criteria,

Page 24

perhaps. This is the disease. The basis for the diagnosis, the symptoms, the signs, the investigations and test results. And if applied in consistent manner, provide the standardized decisions -- "standardized" is the operative word -- for determining whether an individual fills criteria for that specific neuropathy.

As part of this in the manuscript, at least in the pain manuscripts, the major differential diagnoses under consideration, I actually feel -- and I want to make this point right now -- I in many ways with some exceptions mirrored what was done with acute and chronic pain. But I actually think we could restructure this, and I want you to be mindful of the possibilities that these dimensions are somewhat fluid.

I, for example, think the differential diagnosis is actually best positioned under two, common features. This provides additional information regarding the disorder helpful in describing the disorder.

These features may or may not be present in

Page 25

all cases, but this provides the full dimension of the picture. Variations common and uncommon not used as part of the core diagnostic criteria. Epidemiology is part of this, and life span considerations are part of this. Pediatric and geriatric issues; common medical comorbidities, very obvious.

Dimension 4, and this is where I think this differs a little from what has happened in the past because here we want to begin to look at the neurobiology, the underlying mechanisms, genetic, environmental, lifestyle, other potential etiological factors, the risk factors, the protective factors, and psychosocial factors; stress, allostatic load, mood, affect, anxiety, mood, coping and so on.

Then finally, Dimension 5, functional consequences, and going back, personally, I wonder whether psychosocial might be best positioned under this: functional consequences, falls, physical functioning, interference with activities of daily life.

Page 26

That's the structure. Bear those all in mind as people give their talks, as you sit on panels, think about how you can fill in the gaps.

I want to now make some acknowledgements, first of all to Andrea, who I don't think is in the room any longer, and Jill and Valorie, who is not here, who played a major role in the logistics, organizing this, making all of this happen so smoothly. I want to thank them at the outset and thank them at the end.

I also want to thank my co-director of CONCEPPT, Jennifer Gewandter, who did a lot of behind-the-scenes work for the meeting and has been and will continue to be enormously helpful.

I also want to make it clear that this is not designed to replace the ADA guidances initially in the 1990s most recently that Rodica put together, which are major contributions to the field but do not address this issue specifically; does not replace the NEURODIAB consensus statement that Solomon put together so well.

I would view this as in parallel and in the same way that those are not overlapping with one another, they all address diabetic peripheral neuropathy from specific and different vantage points. So will this do.

Page 27

I also want to say that this is iterative, that this is the foundation. As the evidence changes, this will change, and I view this as being a working document and a document that will hopefully endure with modifications as the evidence changes.

I mentioned the manuscripts. Typically from -- and we can discuss this in a little bit more detail, but I want to introduce the notion now. Typically from these meetings, there is at least one manuscript. Everybody contributes.

My vision for this is that there will be one primary manuscript which will address only the core diagnostic criteria and that I together with Chris and Jen will take the lead on putting that together. And then there will be multiple individual manuscripts that will be the individual talks that take place. Whether we combine them or separate them, we can discuss. I think personally, they could easily be stand-alone manuscripts.

Page 28

I'm hoping that all of these will go into high level journals, whether it be Annals of Neurology, Neurology, the diabetes journals, Muscle and Nerve, General Peripheral Nerve Society, all of those are options.

I'm sure there's something else I wanted to say, but I do not remember.

(Laughter.)

DR. FREEMAN: I want to finish with this conclusion, which is taken from the cephalalgia paper on the International Classification for Headache. Every patient entered into a clinical. This was the hope, their ambition, their plan. And I'd like this to be our plan following this meeting. "Every patient entered into a research project, be it a drug trial or a study of pathophysiology or biochemistry must fulfill a set of diagnostic criteria." I would add common diagnostic criteria.

I now hand over I think to, I think, Chris,

who will give the International Diabetic Neuropathy Consortium perspective on this.

Presentation – Christopher Gibbons

DR. GIBBONS: We'll move to the next set of slides.

It's already been a morning of revelations, so I discovered that the IDNC has already been taken by Troels Jensen, so we are going to have to as a society come up with a new idea for our title. But outside of that, we'll move on.

In any case, put on your thinking caps. I'm going to give you an introduction today of some of the discussion we've had that's gotten us to this point, hopefully where to go forward, and what this essentially means.

As you heard earlier from Roy and for most of the people in the room when we met in Spain this summer at the Peripheral Nerve Society, we had a dedicated session, and it was, I think, really impressive that, first of all, we had our first essentially session dedicated to this through the PNS, which has really been important because we

haven't had a foundation or a place at the table.

These were the topics that were covered. The bottom one here, the Diabetic Neuropathy Consortium, is now the time? This was what I think the main point that was raised at the meeting, and thanks to Eva for really making that happen. I think Eva put forward a great idea and got a lot of us very enthusiastic about this and started the process moving.

It is now the time, and I think based on that enthusiasm and work with Roy and getting things going here, obviously we're now six months later all at a meeting here in Washington, DC, and I think it's a really remarkable time frame to think about how much has actually happened so quickly. This is fantastic, and really want to thank Eva for getting the ball rolling on this.

Conceptually, where are we going to stand? The Peripheral Nerve Society, again an umbrella organization, and it exists already with two other consortiums, the Inflammatory Neuropathy Consortium and then the CMT and related neuropathies. I

really see that this potential has -- again, we will fit as the third major consortium as part of the Peripheral Nerve Society.

I think there's an enormous potential here, but there are a couple of steps we need to take in order to actually make this a reality. That's a little bit what I wanted to introduce today, which will be followed up by this afternoon, but these are the steps that are required.

So in discussion with the Peripheral Nerve Society, there are a couple of details they would like us as a group to address. First of all, they would like us to have a constitution, including things like missions, aims, goals.

Get some board members. We need to have chairs, vice chairs, ultimately past chairs, but secretary, treasurers, the executive committee, and then board members. So these are things that we need to have in place before the Peripheral Nerve Society will recognize us as an independent group within their purview.

I drafted a couple of things which I want to

introduce, and for those of us you interested, we'll discuss this in more detail later. But here's a draft of a mission statement that I hoped we could work on during this meeting to actually get us really step forward to nearly completing all the tasks assigned to us in preparation for the next upcoming Peripheral Nerve Society meeting.

As a draft concept, the mission is to improve the life of patients of diabetic neuropathies by promoting clinical and basic science research, educating clinicians, basic scientists, and other health professionals with the goal of improving clinical care. It's really going to be focusing on three areas, and this will be research, education, and clinical care.

These are going to be the sub-goals, and we kind of go through these targets, I think these are broad and some of this is important to be fairly broad and encompassing, again, not knowing how long and how far off in the future this will really be targeted.

The research is going to be both promoting

Page 33

both clinical and basic science with a goal of understanding that both the pathophysiology of the diabetic peripheral neuropathies at a mechanistic level and advancing human subjects research with an aim to prevent or reverse the complications of neuropathy in the setting of diabetes.

Education will be again training both the basic scientists, the clinicians, and other health professionals in the related neuropathies. Again, we're not talking about diabetic peripheral neuropathy. It's really the neuropathies. And then really to provide a continuing discussion and education between these groups so that we can facilitate progress.

So basic science and clinical researchers in isolation, we're not going to make a lot of progress. We really need to integrate this information, so as much as we can, provide a bridge between these groups.

Then finally, care, to promote standards of care and quality of care internationally, developing guidelines, outcome measures. Again,

Page 34

we've heard a lot about the taxonomy of this process and how it will really form a foundation. Again, this is not really meant to supplement or alter existing guidelines but really to build on the knowledge that we have so that we can continue to move forward.

Conceptually from a board membership standpoint, this is all idea generation stage. I imagine six board members, four executive board members, and these would be the rough outline. We could certainly alter that number based on people's input here, but this would be a concept to start with.

This is going to move us to this afternoon's discussion. The interest group, for anyone who's interested and hopefully if not all, almost all of you will be in this group today from 4:30 to 5:30. I really want everybody to participate. We're hoping to generate a lot of information and ideas on this. Certainly consider yourself for board membership, if you're interested, enthusiastic, we want you, and self-nomination is encouraged.

Page 35

One of the key tasks I'd like to really address this afternoon is that we've been able to secure two afternoon sessions at the Peripheral Nerve Society meeting, and I want to really establish an outstanding series of lectures based on what we can generate from an idea and outline this to the board, so the Peripheral Nerve Society will really see that we're successful, we're serious about this, and that we can really make some progress very rapidly. So I'd like just to have that as one of our major discussion points this afternoon.

These are all points to think about between now and this afternoon. We'll continue to discuss throughout the meeting, but please, feel free to generate ideas, approach me offline, online. We'll have lots of discussion, but this is really again the foundation of hopefully what will be a very successful consortium.

That's essentially all I want -- Doug, did you have a question?

DR. ZOCHODNE: I didn't know if you wanted

Page 36

us to interrupt you at all.

DR. GIBBONS: Please, feel free.

DR. ZOCHODNE: Two or three slides back when you had the aims, we've been their advocacy. Other than Lyrica research, still really under the radar with the public, I wonder if that shouldn't be a goal.

DR. GIBBONS: Yes, I think raising awareness of this would be critical. We're certainly a massively underrepresented physician group of interests. Considering the magnitude of the disease and the numbers that we're dealing with, the interest in this by physicians is woefully underrepresented, and in part, it relates to advocacy and recognition more broadly.

So I think that's an outstanding idea, and we'll have potential time for reiteration and modification this afternoon of these statements. So keep these ideas coming, so this will hopefully be something else.

Vera?

DR. BRIL: To follow up, I would say

Page 37

peripheral neuropathy in general is very poorly recognized and that the PNS has really not moved forward recognition of this disorder in the public the way MS is recognized or Parkinson's or Alzheimer's.

So it's not just this subgroup, but the entire organization should be much more dedicated to raising public awareness, so you don't have to explain what the disease is every single time you have a patient with it.

DR. PELTIER: I think that goes back to not having a real dedicated patient advocacy group. So a lot of the major diseases that have done a lot of work as far as getting research funding and pushing through Congress like attention have had a lot of patient groups. We've not done a very good job of organizing our patients, either, and getting them to or inspiring them to work with us, either.

DR. GIBBONS: So that was my final slide. This was just a taste of what's to come, so again, we'll have further discussion this afternoon and hopefully really get some juicy details organized.

Page 38

Thank you.

DR. FREEMAN: The next speaker is Stephen Bruehl, who many of you may not know. He's a professor of anesthesiology at Vanderbilt University. His scientific work is multivariate, but I think if there's one encompassing aspect to it, it's the psychophysiological aspects of pain.

With respect to this meeting itself, he was one of those -- he was the spearhead, I think, behind the Budapest classification of complex regional pain syndrome, sometimes called, in fact, the Bruehl criteria. He's going to talk to us about the development of a taxonomy for a condition, and he does this in a very beautiful and stimulating way.

Stephen.

Presentation – Stephen Bruehl

DR. BRUEHL: No pressure to make taxonomy beautiful and stimulating.

(Laughter.)

DR. BRUEHL: I do apologize in advance. It is difficult to make this very exciting, but I will

Page 39

do my best. I think that the reason I'm here is because I was brought into the parallel development of chronic pain diagnostic criteria in a systematic way that is an effort ongoing still, and also more recently, trying to do the same thing for acute pain conditions.

The idea is that we would end up with a consistent taxonomy for each of these general classes of conditions where within each of those, every individual condition is worded in the same style, the same kind of format, the same dimensions. The idea is make some consistency. The whole point of taxonomy is to make order out of chaos. That's what our task is here today.

Diagnostic criteria should help you lead to a dichotomous diagnostic decision. That's the whole point, and you will notice something -- or after I point it out, you'll notice something subtle about this.

So implied in this is when you create diagnostic criteria, you are defining the condition. In everything you do in trying to come

Page 40

up with a taxonomy, remember 20 years from now, what you come up with is going to be the de facto definition of what that disorder is. This is why my suggestion is you put some thought into this and come up with a systematic way to make sure you're doing it right.

The idea is that if you've got a set of disorders that are potentially confusable and they're overlapping criteria, but you indeed believe they are different things, you want to have diagnostic criteria that will force you to pick one of those so that one person cannot have two similar disorders.

It is very important that you use the right wording in these because otherwise, you'll get a person -- take an example person, if you can take those diagnostic criteria and apply three different diagnoses to the same individual within the same class of disorders, that is not a very useful taxonomy. So they do need to be mutually exclusive.

The whole point of putting effort into the

Page 41

wording of the actual criteria is that when you take a person who's not familiar with them and you hand them a sheet of paper that says here's the diagnostic criteria, go see your patient, and I want you to try to make a diagnosis using these criteria, you want to make sure if you give that to 10 different people, that they will all come up with a similar diagnosis. That really is contingent on how well you have created the wording and the decision rules implied in there.

I will say that one thing that I found surprising when I worked on the AAPT criteria, this is the chronic pain effort, I assumed that everybody in the room was thinking about things the same way that I was. I was trained as a clinical psychologist, and from literally the first year in graduate school, we started learning how to apply diagnostic criteria in the DSM for psychiatric disorders. Back then, it was DSM-I think III-R, but it's still the same thing.

I assumed everybody thought about diagnosis this way. What I discovered in talking with a lot

Page 42

of the physicians -- and this is across a wide range of conditions and specialties -- a lot of them had no clue about this. They had never really thought about it before. They didn't systematically apply criteria.

This parallels what Roy showed in his talk, and this is for major depressive disorder. But just as an example, think about this like a Chinese menu. You get two from here, you get three from here, and that's how you come up with the diagnosis.

So in the DSM-V, you have to have five or more of the following symptoms during the same two-week period, and it has to be a change from previous functioning. At least one of them has to be depressed mood or loss of interest. Then you go through, and you've got a list of nine very specific symptoms that are each worded in a very concrete way to where it minimizes the amount of judgment required to decide whether the person meets it.

Some of these, I've done a better job than

Page 43

others, but significant weight loss when not dieting or weight gain, that's fairly objective. The person could report that, or you could observe it.

In DSM-V, one thing they add is symptoms cause clinically significant distress or impairment, and the episode is not attributable to physiological effects of a substance or another medical condition.

You'll see headache and in DSM-V and in most of the conditions, I think, in the AAPT chronic pain criteria, that last thing is always like you don't get this diagnosis if something else better accounts for the symptoms. That probably is something you would want to do as well. I just throw that out there to think about.

Just to show you that this kind of effort like you're embarking on here will produce something tangible, this is an example of one of the papers that came out which proposed diagnostic criteria for chronic central neuropathic pain associated with spinal cord injury.

Page 44

I have to say when I came out of that first AAPT meeting, I had serious doubts that it was ever going to produce anything at all because it seemed like too much work, people weren't being paid to do this, nobody was talking responsibility. It seemed like nothing could happen, but surprise, surprise, it has actually produced a whole set of criteria, some are still in the works, but this is one of them.

You can see they've got very specific criteria including things like pain duration of at least three months. The pain has to be in the area affected by the SCI. It's got sensory changes in the same neuroanatomically plausible distribution indicated by the presence of at least one positive or one negative sign.

Those are very concrete and easy to follow for any clinician, and if you're doing a clinical trial and you want inclusion criteria, that's the kind of thing you want where it's easy to follow that. No other diagnosis better explains the pain.

If you were trying to come up with

Page 45

diagnostic criteria, you really have to let the wording of those criteria be driven by two issues. One is validity, one is reliability, and I want to talk a little bit about what I mean by both of those and in practice what that actually plays out as, how do you make sure the criteria are reliable or valid?

I'm going to use the example of complex regional pain syndrome to do this because that is what my first experience with this was, was there a mass diagnostic criteria that everybody could meet that had an unexplained pain and they weren't specific enough. We embarked on an effort to systematically and empirically change those criteria to improve them and make it a little more narrow and harder to get the diagnosis.

Reliability and validity are both related. You have to have reliability, but simply making them reliable doesn't mean that they're valid. You could have criteria that everybody agrees on that are totally meaningless. So you really have to get both of these.

Page 46

The types of reliability, one is inter-rater reliability, and this is the idea that if you take two different clinicians who see the same patient, you would hope that they would agree on the presence or absence of the conditions. This can apply to both the individual components like the individual symptom items that are in the criteria, and it can also apply to the full diagnosis that you get when you apply the full set of criteria.

There's also test-retest reliability, and these are those criteria stable over time? So sometimes we call it intra-rater reliability if we have the same clinician see a patient over time and try to apply them and see do they meet the criteria each time. More frequently, we're talking about are these across multiple clinicians getting consistent diagnoses over time. Both of these are equally important.

If we're looking at the reliability of these individual bullet points within the criteria, so criterion 1, criterion 2, we want to figure out are they operationalized well. As an example from the

Page 47

old 1994 IASP criteria for CRPS, it said -- the wording was literally, "Evidence of changes in skin blood flow."

That sounds good when you first put it on paper, but when you talk about how somebody's going to apply that in practice, what does that mean? Does that mean I need to do thermography, Doppler measurements of blood flow? Is simply sticking my hand on there and saying yes, it feels cool, and that implies blood flow changes. There are a lot of ways to interpret that, and you don't want to have things in there that are too generic that can't be applied consistently.

A hypothetical example -- and this came up during the development of the AAPT criteria -- was if you say progressive distal sensory abnormalities. Well, what do you mean by that? You probably know what you mean, but you want to put that on paper if you have a specific idea there because does positive or negative apply? Does it have to be positive? You want to say things like that that are going to alter the outcome.

Page 48

We've got these bullet points. Here are the criteria. There's also an implied or not -- it's not even implied. It's an explicit decision rule for combining those. Let's say you've got five criteria. Do you have to meet all five of those? If you've got five criteria, maybe having three of those or three or more is really what you're talking about.

That is a decision rule. It's what the person is going to use. They tick through the list. See the person has these things. How do I combine that to make a decision as to whether the person has the diagnosis?

The wording of the decision rule can make a difference. So something that's really straightforward is you've got five things and you have to have three or more. Anybody can follow that. That's very easy. But if you look around at some of the criteria that have been developed, you will see very complicated decision rules like that you've got them broken out in the A, B, and C, and you have to have 2 of 5 symptoms for criterion B

Page 49

but you only have to meet criterion C if you've got less than four on this other one.

You start getting into things like that, it's hard to follow that. If somebody is busy and not paying attention, that could easily lead to a diagnostic error.

We talked about test-retest reliability. This is stability over time. Now, obviously, this makes no sense if it's a condition that you would expect to vary a lot from day to day, and there are conditions like that where the symptoms -- CRPS is even one of those where you can actually have changes in things on a fairly short-term basis. But let's assume that we have a condition that should be pretty stable because the underlying pathophysiology is stable. That makes it really easy, and you do want to see stability over time, especially shorter periods of time.

So if you have a set of criteria you've developed and you have, let's say, two different clinicians diagnose that patient and then a month later apply the same criteria, they should come up

Page 50

with exactly the same diagnosis between them and across time periods if you've got good criteria because things should not have changed in a month unless you've implemented some new super effective treatment.

How do you know if criteria are reliable? Well, you can focus on, again, the individual components of the criteria or the overall diagnostic decisions. And if you want a very cheap way to initially look at the wording of criteria, you can do what's called a vignette study. You have a hypothetical patient description, and you include in there things that would give you information about whether they meet the criteria. You throw in some red herrings, things that are irrelevant. And then you identify 100 clinicians, and then you mail it out to them or email it out to them, and you just say take a look at this, we're interested in whether you can take these criteria we're going to give you here and apply them to the patient described in this scenario and tell us does the patient have this diagnosis.

Page 51

If you can get in this kind of system, a lot of people coming back with the same diagnosis, you know you've probably done a decent job of coming up with the wording for those criteria. It doesn't say that it's going to work in practice, but at least gives you an initial hint about the reliability of the criteria.

Now, if you send this to 100 people and you get half the people saying they do meet the criteria and half saying they don't, clearly, you have to go back to the drawing board because there's something not right about the wording of the criteria that's making it hard to apply.

You can do field trials, also. This is something that DSM has always done is you actually have clinicians that are participating in multisite research projects where they're doing diagnosis of patients and then looking at some of these reliability issues in a real-world setting.

Statistically to bore you even further, there are ways to numerically capture whether you are doing a good job in getting reliable criteria.

Page 52

So kappa is a common one, and this is used for like dichotomous diagnoses. This is to say if you've got two raters, are they agreeing more than chance, and that's how kappa differs from a correlation coefficient.

Correlation coefficients you see in the literature in this context. They're wrong because they don't factor in whether you are going to have chance agreement. So kappa is correcting for chance. That's what you'd want to use.

There's another option called an intra-class correlation coefficient, and this is a little more flexible. You can look at ordinal variables, interval variables like a scale from zero to 10. You can also look at ratio variables.

Both of these are in the same zero to 1 scaling just like you see with the traditional correlation coefficient. In the literature, there's a number 0.60 that is pretty much accepted as this is adequately reliable. So if you do your criteria and you do a vignette study or a field study and you look at agreement and you calculate

Page 53

kappa or intra-class correlation, if you're below 0.60, it probably means you need to go back and revise that before you start getting that out to the literature and say you should be using this.

Do the criteria reflect what they are supposed to reflect? That is a very fundamental question, and that is validity. If a patient gets a diagnosis, does it really mean that they have this condition? It's a straightforward question, brings up a difficult issue, which is surprisingly difficult. What is X syndrome? What is peripheral neuropathy?

Give me an example of any diagnosis you can think of in this area, and you'll have to answer this question. What is it? Then you have to think about who's defined that, where did you learn that, is this something you've gotten from clinical experience, was this the way you were trained and somebody else told you this? Is this based on research in the literature? How do you assess it if you want to do that?

There are many people who say, well, I can't

Page 54

really put it into words, but I know it when I see it. That's great, but if you can't put it into words, you're not going to be able to come up with criteria to diagnose it.

The question is you may think that this set of things defines the diagnosis, but would everybody in this room agree on that? Do each of you have your own variants and things you may more or less attention to? So those are the things you want to think about with the question of validity.

For pain, it was a little different because these are all pain disorders. Pain is subjective. You can't go do a test that will tell you whether somebody is having pain and how intense that pain is, not really.

Definitive pathophysiology, in most cases, we don't really know. We know things that contribute, but we don't know the full picture. Because of those, that meant there was no real gold standard to use to say these paper and pencil criteria we've got here are an indicator of this underlying mechanism, so we know they're good.

Page 55

We didn't have that luxury. Now, I don't know in the case you're talking about, you can do peripheral nerve testing and biopsies and maybe see things that you would consider more of a gold standard, and if that's the case, your job is much easier.

You want to be able to have clinical criteria that don't require that elaborate testing, hopefully, that can do a good job of approximating that gold standard mechanism you can assess. That would probably be the task for you guys in determining the validity of the criteria.

There's also the issue of fuzzy boundaries, that you have a set of mechanisms that may be all in combination, you've got a set of clinical features, and where is the dividing line between conditions within that? Is it a continuum, and you'd say people down here, this is a different disorder than this group? Or are there particular features that would define a subgroup that's distinct?

There's no clear answer to how to make those

Page 56

decisions, but there are some ways to statistically test those and determine whether you're right when you come up with a guess. It's an iterative process of guessing and then looking at the data to see whether they support it, and if not, you modify it and then do the same thing again.

Construct validity is what we talk about. This is like are we measuring what we really think we're measuring. In pain, these are indirectly measurable, so we have a lot of problems, and all we're able to show statistically is relative validity because we can't really assess a gold standard. This is like the worst case scenario for what you might be trying to do, but I'm going to go ahead and walk through a little bit here.

Content validity simply means would a person who's an expert in the area and would a patient look at your criteria and say yes, this pretty much captures what I think are the most important aspects of this disorder. Internal validity, the way I use it, I'm talking about if you've got criteria that have subgroups under it of signs and

Page 57

symptoms, do those hang together in a way that matches the way they actually exist in the real world?

Concurrent validity is looking at your criteria relative to some gold standard, maybe a test of some kind. Convergent validity, I love the term "nomological net." I learned that in graduate school. It's basically saying if you have something that is inherently unmeasurable, you have all these other things around it that are related that should be related in certain directions. You want to make sure all of those interrelationships fit the construct that you're interested in.

Then you've got discriminate validity, and this is can we use these criteria to distinguish between groups that we think are distinct.

What gold standard do we use? So in the context of pain, we may have a current consensus based standard. So this would be something that a roomful of people like you would come up with, and at the end of the meeting, you say this is what we think the criteria should be. Now, that could be a

Page 58

gold standard.

It could be -- and this is based on actual literature -- usual method of diagnosis. This was used to develop the fibromyalgia criteria in 1990. DSM has used expert clinician diagnosis.

You also have and something that's a little bit easier, previously published diagnostic criteria that you can use as a reference point. That's talking about really relative validity or what we have coming up with better than the existing criteria.

Empirical validation, how do we actually test validity? It's nice that there are these statistical techniques that if you can get a large enough data set of patients and get systematically collected data on test results, signs, and symptoms, you can apply these techniques and actually get some good and meaningful information to help guide you in developing diagnostic criteria.

These would be things like principal component analysis, cluster analysis, got other

Page 59

options, but they're all basically doing the same thing. It's saying I'm going to give this data set to the computer and say tell me how many different subtypes of patients are in this group of patients, and it will come up with subgroups of patients. And then you can look at the profile of signs and symptoms associated with each of those empirically defined patient groups to say do I recognize any of these.

You go yes, this one right here clearly looks like X condition, and this one, the pattern of signs and symptoms clearly looks like this other condition. And if you've done that, you've done something really nice, which is you had kept your judgment out of this initially and let the computer based on the actual data identify the subgroups. Now, that's kind of the ideal situation if you were to try to figure out how many different conditions you should parse your data set into. And I'll show you some examples of these in a moment here.

So you want to identify groups of statistically similar patients that are based in

Page 60

the patterns of clinical features. So what you're doing is essentially defining empirically what the prototypic presentation of a condition is.

You also may want to identify at a lower level here, groups of signs and symptoms that may cluster together within a patient population. So if you remember those diagnostic criteria for the DSM-V or the ones that Roy showed for headache, you might want to decide are those specific signs and symptoms grouped together in a way that actually reflects the real world.

You also may want to show whether two conditions are distinct. Now, migraine versus tension type headache, I did this right after graduate school, but we happened to have a data set of really careful diagnoses of patients that met the IHS criteria at the time for migraine headache and tension-type headache, and we asked a simple question: Are these two different disorders, or are they basically the same thing? Are they really distinct?

We took the diagnostic information, and we

Page 61

did a cluster analysis. The computer said there are two different groups of patients in here, and we said well, show us what they look like. It gave the clinical features for each of the two groups the computer came up with, and that matched up with the IHS diagnoses.

It turns out it matched up quite well. The computer identified migraine headache and tension-type headache, and that supported the idea that they were really two different conditions that even a computer who doesn't know anything could distinguish. So that's the kind of thing you can do with this approach as well.

We frequently will ask, do proposed criteria have concurrent validity relative to whatever our current reference standard is, whether it's a test or some existing set of criteria. If we're revising criteria, do they improve on existing criteria in terms of being able to discriminate between known groups of patients?

If we're going to do this, we have to start looking at how you would be able to justify saying

Page 62

these criteria are valid. You would look at sensitivity and specificity, so that's true positive and true negative rate.

Probably more important conceptually is positive predictor power and negative predictive power, and that is how probable is it that a positive or negative diagnosis you make is accurate? That's your diagnostic accuracy. The problem with that particular statistic is that you have to know the base rate in the population to calculate it. Most of the time we don't know that. So another alternative is positive and negative likelihood ratio. So there's a statistic. You can get a number that will tell you how accurate you're likely to be if you apply the criteria in the real world.

We've got a diagnostic threshold that we have to set. So if you've got five criteria, how many of those do you have to meet to get the diagnosis? This will affect both sensitivity and specificity, and it affects them on opposite directions.

Page 63

So if you reduce the threshold, so instead of three, you say you only need two of these, what you're going to get is an increase in sensitivity. You're going to capture more people, but specificity is going to go down. You're going to over diagnose.

These are going to move proportionally, and your goal is to find the threshold for diagnosis that optimizes the balance between those two. You do this by using a receiver operating characteristics curve. This is plotting sensitivity versus -- it's actually one minus specificity, I think. But you do this, and you'll see this nice line. And you can see by the shape of the line where you get the optimal balance of sensitivity and specificity.

That's the theoretical basis for doing this. Now I want to walk through what we actually did with CRPS just as an example to show you an approach you might use.

In 1994, there was a room full of people in Orlando, Florida. These are all clinicians and

Page 64

research experts in complex regional pain syndrome. You may know it as reflex sympathetic dystrophy. But they all got in this room, and they as a group came up with a set of diagnostic criteria that they ended up getting reified by putting it into the International Association for the Study of Pain Taxonomy.

They defined it, published it. In theory, people were supposed to use this. It didn't get used, and you'll see why, basically because everybody could get the diagnosis or it was way too easy.

You had to have an initiating noxious event or cause of immobilization, right, but then if you read the fine print, it said you don't have to have this. Now, what use is it to include something like this in diagnostic criteria? It makes no sense to me.

Number 2, continuing pain, allodynia, or hyperalgesia that's disproportionate to the inciting event. Probably no way around the judgment involved in disproportionate, but it could

Page 65

be that you could have no allodynia or hyperalgesia and have only pain and still potentially meet this criterion.

Number 3, evidence at some time for edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain. Then you've got number 4, the exclusion criteria, if something else can explain the symptoms, you don't get the diagnosis. So just made the points I did.

Do the criteria adequately capture the core defining signs and symptoms of CRPS? This is a little more of the judgment call, but that's one issue we wanted to address.

Is the structure of the criteria optimal? So the 1, 2, 3, and 4, does that make sense what's included in each of those to break it down the way they're broken it down? Is the decision rule, you had to have all four of these, does that make sense?

Then this is going to determine our sensitivity and specificity. So sensitivity is how well do we identify CRPS positive cases.

Page 66

Specificity is if a person doesn't have CRPS, do we weed them out appropriately?

If we're going to look at the first issue of content validity, we had to go back to the literature. So you read the literature, there was this condition called reflex sympathetic dystrophy, algodystrophy, neurovascular dystrophy, a variety of names, but people were all talking about the same thing.

If you looked at the set of symptoms and signs that had been described in the literature to be associated with the condition, those criteria I just showed you did reflect four of those: allodynia, hyperalgesia, skin temperature and color, sweating changes, the sudomotor, and then you've got edema.

However, in the literature, you also very frequently saw trophic changes to hair, nail, and skin; tremors; dystonia; range of motion impairments; hemi-body hypoesthesia; you go on and on, a bunch of these things that were pretty odd features that were reported frequently that are

Page 67

totally ignored in the diagnostic criteria.

We decided to empirically look at some of these questions, and this is a really simple way to do it is we created a standardized form with instructions that go along with this for assessing all the clinical signs and symptoms that we felt the literature described were associated with the condition.

For the symptoms, this was self-report by the patient, and we also had objective signs seen by the examiner when they actually saw the patient. Then there were definitions for how you assessed each of these particular issues that were designed to be clinically useable, so it didn't require elaborate testing.

We had this form, and we did a multisite study. Ended up being international, so we had about 10 sites in the end who participated in this. Everybody used the same form, and what we were able to address was -- we ended up with about 123 patients. It took a year and a half, two years to get the data, but we ended up with 123 that met

Page 68

those diagnostic criteria I showed you. They all had the same evaluation.

The questions we asked was does it make sense to include objective signs and subjective symptoms in the same criteria. The criteria I showed you, you could meet it solely based on the patient telling you something. You didn't have to see anything at all in the clinic. And the question we asked was, is that appropriate, or do we need to require that people see objective signs as well?

What we ended up seeing -- and this is just looking at the frequencies -- is for those features that were both assessed in the clinic and the patient reported, if you look at the pattern of signs and symptoms, what you will see is that the features that were more common like color changes were common in both the symptoms and the signs.

Now, the numbers differ because the numbers are always higher for symptoms because the patient is going to have more opportunity to see it than you will in the clinic. But roughly, the

Page 69

proportions vary in a similar pattern across signs and symptoms. So the things that are very uncommon like fingernail changes are uncommon in both of those categories.

What this told us was that they're both probably providing meaningful information, but that maybe we should be assessing both and not just symptoms alone because clearly, you don't get exactly the same number in both cases.

Internal validity of the groupings of signs and symptoms supported by the data; this is the critical one, number 3, evidence at some time, meaning not even in the clinic, just by patient report, for edema; changes in skin blood flow, how defined, I don't know; or abnormal sudomotor activity in the region of pain. Any one of those three could meet this criterion. Maybe this is too low a threshold.

What we did is something called principal components analysis to look at the interrelationships between the signs and symptoms in that large data set that we got. And what we

Page 70

found was that they tended to cluster into subgroups of symptoms that were relatively distinct. So we had what we called a sensory group that was hyperalgesia and allodynia. Vasomotor group, this is the skin temperature and color changes tended to group together.

Oddly enough, the sweating and the edema grouped into the same cluster, we weren't exactly sure why that was, and then motor and trophic changes like range of motion, strength, tremor, dystonia, that all kind of clustered into the same thing.

You'll notice the motor and trophic factors are not reflected anywhere in those diagnostic criteria that the consensus group came up with. And then you've got overlap here for vasomotor and sudomotor. The computer says they're different things. The consensus criteria lump them together.

What we concluded from this was that the IASP criteria are really not internally valid and that probably is not justified to combine vasomotor, sudomotor, and edema all into one

Page 71

criterion because this could lead to poor specificity or over-diagnosis, which was the clinical problem we were having. It suggested a revision.

So how do we revise this? What do we do with this information? So we ended up with a sample of 117 patients meeting CRPS criteria. We had another group of patients that had pain that were clearly not CRPS. This was like diabetic neuropathy patients and a variety of other groups.

The idea is that we had a group that by diagnosis had CRPS and another group that we knew had pain from other causes, and they all underwent the same evaluation using this form that I showed you up there. What we found when we tried to distinguish between the CRPS group and the non-CRPS group was that those criteria we came up with were very sensitive. It picked up everybody that had CRPS, but it wasn't very specific at all.

Frequently, people with these other pain conditions would get misdiagnosed as CRPS using the criteria as worded, and it basically says that if

Page 72

you just base it on appearance, the non-CRPS patients, by this definition we had, looked very similar to CRPS patients.

That is going to lead to over-diagnosis if you're doing it in a clinical setting, and in a clinical trial, that's a problem because you're going to get a lot of people that don't even really have the condition you're interested in that are going to meet entry criteria.

I would say that all of those methods I just described there, you could easily apply to a study of any condition you wanted to pick in your area. You just have to be thoughtful and systematic about it, but it is something that is easy research to do because it can be done as part of clinical practice. It's a matter of coordinating and collecting the same data at all the sites using the same methods.

How are we going to improve diagnosis? Well, we thought that including objective signs was important so that you don't have a diagnosis that is solely based on the patient saying they have

Page 73

something because there are a lot of ulterior motives for saying you have features, especially in the chronic pain context.

Motor and trophic changes need to be included because they're clearly something distinct and they aren't reflected in the criteria. Also, splitting out vasomotor features from the edema and sudomotor features, that's clearly what that principal components analysis said is that they're two different things.

Then in Budapest, Hungary, we had some revised changes, a proposed revision of the diagnostic criteria that we looked at, so it was kind of expert opinion at to what needed to be further changed based on these empirically-derived criteria. We came up with this set, which is continuing pain disproportionate to any inciting event.

Now, based on the data, we've got four categories of symptoms, and the threshold for diagnosis, at least in terms of symptoms, is you have to have at least one symptom in three or more

Page 74

of the following categories. So you've got four categories; three of those have to be positive.

We also require signs. You've got the same four categories. Patient has to show at least two features out of these four. If they have that and there's no other diagnosis that can explain the symptoms, they get the diagnosis of CRPS.

This now is what CRPS is. We have defined what CRPS is. Not everybody agrees with it. You can't please everyone because they all have their reasons. The clinical criteria, we did something a little bit odd. I wouldn't necessarily recommend it, but we also had a different threshold for diagnosis for research settings. The idea was if we want to absolutely make sure we rule out people that don't really have the condition, if you apply this different criterion, you'll maximize specificity but still capture a lot of the CRPS patients.

We empirically tested it. So if you look at sensitivity and specificity, the old criteria -- this is in a totally different sample,

Page 75

by the way, from what I talked to you about earlier. So the old criteria, perfectly sensitive, but they're not very specific. Lot of misdiagnosis.

We used the Budapest clinical criteria we came up with. They're still very sensitive. You capture the people with CRPS, but now specificity has gone up by 27 points on this scale here. Budapest research, as intended, improves specificity a little more.

This is the justification for saying these new criteria are better than the old criteria. We can't answer the question of whether in the big scheme of things our criteria reflect reality, the underlying mechanisms, because we don't know the mechanisms. But it works better than the old criteria empirically.

We ended up going through a process with this then where these criteria, we published a couple of studies on this. We proposed it to the IASP taxonomy committee. They eventually voted on it. The IASP board voted on it, and now it is part

Page 76

of the official taxonomy.

The things out of all of this that I hope you take home are wording matters. The individual features, the wording matters. The decision rules you come up with, the wording matters. You want to make sure it's all operationalized, so it's worded in a way that somebody knows exactly what you mean by it. They know how to assess it.

Little changes can affect things a lot, especially if you're changing a decision rule from saying three of these to four of these are required to meet the diagnosis. That has an impact. Thank you.

(Applause.)

DR. FREEMAN: We will have plenty of time for questions during the moderated session. I want to emphasize that this is highly interactive, so feel comfortable interrupting the speaker, but don't do it too frequently.

(Laughter.)

DR. FREEMAN: But definitely during the moderated session -- the way the meeting will be

Page 77

structured is after each set of talks, there's a moderated session with panelists. Panelists will speak for a few minutes of their either impressions of the talk, their impressions of the topic, but it is a free-for-all. This must be highly interactive.

What I didn't mention, which perhaps I shouldn't mention, but there is a stenographer who you see at the back who is taking down all of your interruptions. So interrupt politely because this is part of the permanent record and could be viewed by anybody, so just so you know that. That will, of course, help us collate everything that happens at the meeting and will allow us to put together the work product.

Now, I think everybody knows Chris Gibbons, who is an associate professor of neurology at Harvard Medical School, who will talk about one of the projects that is ongoing with CONCEPPT, which is looking at the instruments for assessing the neurological features of disease, the signs that we use in diabetic peripheral neuropathy and other

Page 78

peripheral neuropathies.

Chris, why don't you go.

Presentation – Christopher Gibbons

DR. GIBBONS: Excellent. Moving on a little bit, so this is going to be, I think, an equal opportunity offender talk. I'm going to try and insult every single person in the audience before we're done, so hopefully, you'll really enjoy this and get something out of it.

But the point of this is I'll go through a couple of details as we're getting into this and how we just really heard a very insightful talk on how to think about taxonomy. Some of the things we need to think about, really review how we got to where we are. What is some of the background to the information of when we're doing an examination and we jot this down or think about research criteria, how do we get there? What are the current criteria? How do these exams fit and across spectrums?

Review some of the relationships between these examinations and the current criteria for

Page 79

complications of diabetes. What are the different neurological complications and how they fit the examination criteria.

Then I want to conduct a little bit of an exercise, going through why we want to think about this, why it's so important, then really again feeding forward to this what we're going to be doing for the rest of these sessions, hopefully pretty dynamically.

Historically, again, the neurological examination has been around for quite a bit of time. There's been a lot of development actually over hundreds of years now at this point. Thinking about how people grade reflexes, sensation, muscle strength has really developed over time, a lot of contributions from different groups.

Ordinal grading is one of the big steps forward. How do we ordinally grade in a numeric fashion muscle strength? That's something that was really done -- and Lovett introduced this, who was a Boston orthopedist, on a 6-point scale, which then really was converted to the current MRC scale.

Page 80

The numbers are reversed, but the concept of the MRC scale really came into prominence during World War II with the concept that war injuries and nerve injuries specifically, how do we predict if somebody's going to have any chance of recovery? Is there no strength? Are they completely paralyzed? Is there a flicker of strength?

This is where a lot of the data started to generate and come from when we're thinking about this scoring system. If you're interested historically, Peter Dyck actually had a really nice paper outlining some of the history of this in JPNS back in 2005, and it goes through a lot of the evolution of the examination and how we've come to where we are.

Historically, these are some of the things to think about, how we got to these systems, but the concept of the exam was frequently based on war injuries or major traumatic injuries and how we quantify that. I think moving forward to the concept of what we're talking about here with the diabetic peripheral neuropathies, we have to think

Page 81

a little bit about how that might fit.
Where are we now? If you peruse the literature and you're interested in finding your exam du jour for diabetic peripheral neuropathy, you have at this point at least 16 different examination criteria to choose from. There are more out there. I'm sure we didn't get everything, but again, these scales are really pretty widely different in scope, what they're trying to accomplish, weighting of the different systems.
Predominantly, they're based on the MRC criteria where you're looking at an ordinal system of grading from paralysis to full strength, not everything, but a lot of them are based on that. Again, looking at this as a pattern recognition approach to diagnosis, so that's a lot of the background to this concept.
These are some of the scales you can choose from, if you're interested, and Jen over there has done a remarkable job putting some of this together, and we've been working on this for a while. But if you're looking at these, here you

Page 82

pick your scale du jour. Some of the different systems that you can consider looking at here, whether it's vibration, reflex, pinprick, muscle strength, touch, joints, temp, allodynia, two-point discrimination where there's associated physician-recognized or patient- or clinician-recognized symptoms, nerve conductions.
You can really see that there are a lot of different options on this menu, and again, we heard about the menu selection criteria, how would you do this. Well, there are a lot of different options. You can see they're pretty widely distributed.
This only gives you one particular picture on the challenge that you're seeing. This is just whether this is included globally or not. If we dig into some of the details, this is going to look a little painful, and I apologize, but we'll walk through this. But this is a really important slide conceptually.
Again, you're looking at your scales here, and you're looking at different groupings, so muscle strength, reflex, and then sensory,

Page 83

vibration, touch, joint position, pinprick. What you're seeing are these bars across. A full bar means more global assessment proximally and distally. If you're seeing here, it's more distal to slightly proximal, and this is just distal.
If you're looking at that, you can start to see a distribution both of territory and of magnitude of what you're checking. You can see some check everything. Some are much more distally focused so that UENS is really again distally focused, but some of these are really checking every single muscle group or sensory group that you can possibly imagine across.
When you're looking at this, again, it gives you a very different perspective on what examination might be chosen for what particular scenario. But it's important to consider not just what the examination is measuring but what are the scoring assessments? So how relative is the weighting?
If we're looking at motor reflex, large fiber or small fiber sensation, it's important to

Page 84

recognize that if you're measuring a scale one way shifted or another, you can see some have no motor examination. This is INCAT's. This isn't really one we're going to be using for diabetic neuropathies, but some of these have no motor assessment where some are 90 percent motor weighted.
This range of weighting of motor from 0 to 90 percent and this similarly for the large fiber, small fiber, and reflex testing, really gives you an enormous difference in terms of an outcome of a particular study, depending on which scale you choose. So if we're thinking about this broadly, it's pretty critical to consider all of these options as we start to go through this process of taxonomy across these different specific systems that we're thinking about.
This, I think, creates a challenge, and this is one of the things we're faced with because all of these scales, with the exception of maybe INCAT, have been published in just the length-dependent diabetic peripheral neuropathy. You're going to

Page 85

get very different discussions depending on the result, and of course, if we can't have the same language or use of conversation, we're going to get into a lot of trouble. This may be some of the challenges we're facing.

The real question is why is this relevant. If we have a drug -- and maybe it's just because we haven't had a drug. Maybe we just haven't had a drug that's worked. But if we had a drug that worked, halted neuropathy progression or even reversed diabetic neuropathy in some way, shape, or form, does it really matter? Could we just pick any one and it doesn't make any difference whatsoever?

It's an important concept. Does this make a difference? Is this worth the effort?

Pulling to a side a little bit, some of our own data -- and this is again more recent data on a longitudinal study of diabetic neuropathy, trying to get at some of the questions, well, does it matter? What changes? What's going on?

This was just a natural history study

Page 86

looking at a little over 60 individuals with relatively stable hemoglobin A1Cs who were followed for three years with basically just every exam, every test. Lots of things done repeatedly just to understand what changed and when.

We really selected a group that was quite well controlled in terms of risk factors. They didn't smoke. Their blood pressure was controlled. Their hyperlipidemia was controlled. Triglycerides were under good control. Again, from a numbers perspective, this was a reasonably well controlled group of individuals with diabetes.

This is publishing one or reporting one scoring system. There was no change in examination over three years. Looking at this exam, this was a fairly balanced exam looking across motor, reflex, large fiber, small fiber symptoms. No change at all over three years, none. There were no change in symptom scores over three years either, none.

Then we looked at lots of other things as well. We looked at quantitative sensory testing. We looked at nerve conduction velocities and

Page 87

amplitudes. We looked at autonomic function, and a lot of figures here, some with type 1 diabetes, some with type 2 diabetes, repeated measures, basically, the result is over time, nothing changed at all of any sort. Again, from a three-year period, we were stuck with nothing changed in any measurable way.

But why bother? Nothing is going to change. Why bother measuring it? Are we just wasting our time? What's the point of all of this? Are we ultimately going to get somewhere from here to there if what we're doing isn't making any difference?

Well, this comes into an important concept as we move into this meeting, no pun intended here, but looking at this different topics that we're going to address today, diabetic neuropathy, neuropathy of the pre-diabetic state, treatment-induced neuropathy, lumbosacral radiculoplexus neuropathies, and then focal entrapment neuropathies. These are pretty different disorders if we really think about it, and we'll hear more

Page 88

about the details.

Maybe we need to consider these individually as we're trying to do today. Maybe these aren't the same problem even they all fall under the same heading of diabetes-related complications.

Ahmet, jump in.

DR. HOKE: Chris, you said nothing changed, but did you guys look at the skin biopsy?

DR. GIBBONS: We don't have data on skin biopsies on that particular study, no. So that's a good question, and you're getting at hints and details, yes, that I'm trying to throw out and hide for later. But yes, absolutely, but that's exactly the point.

Maybe there are ways we can get into that, and that's hopefully what we are going to do is generate what are the specific things we need to look at to get to that data.

Again, for these different diseases, they're not the same, and I don't think we should consider them as such. One size is clearly not going to fit all. If we have different exams, we have different

Page 89

ways of scoring, are they going to fit across all these different disorders we're talking about in the next two days? The answer clearly is no, and if we select the same answer, we're going to have a problem.

If I'm just looking globally at some criteria, whether it's motor, reflex, large fiber sensory, or small fiber sensory, what are the different disorders that we're talking about today and tomorrow, and how might we think about these? So you'll forgive my scatter plot efforts at drawing on a moving airplane with a mouse trackpad, but if I splat something across the top here --

(Laughter.)

DR. GIBBONS: -- and I call this diabetic peripheral neuropathy, this is maybe what some of us would think about.

Most of us almost never see motor neuropathy anymore. Is there some? Absolutely. Do we see it regularly? I would say not really. Again, not except in really advanced cases.

Is there reflex involvement? Of course, we

Page 90

see absent reflexes quite frequently. But large fiber, small fiber, absolutely, we see both. So if I was going to throw a splat on the screen, that's probably what I would imagine, and maybe that's one way of thinking about the conversation, our weighting systems.

What about neuropathy of the pre-diabetic state? Again, that's going to be a much smaller involvement. Would we see motor? I would say if we did, we probably wouldn't be calling this in this category. There'd be something else going on. But reflexes, maybe. Maybe we'll talk about that, but small fiber, certainly, and maybe a little of the large fiber touch in there.

These are the things we'd want to think about, and maybe this has a different perspective on this discussion for later that we want to think about.

Treatment-induced neuropathy, if I'm drawing another splat here, I'm thinking this is predominantly small fiber, maybe touching on large fiber, maybe some reflex. Really a hint of motor,

Page 91

but I would argue that that's a debatable issue. But that's a very different, again, overlap than these other conditions.

What about the lumbosacral radiculoplexus neuropathies? Well, again, we'd be looking at different conditions there, and yes, there'd be some sensory involvement, reflex involvement, no question. Again, it depends on which group or targeted nerve we're thinking about. Motor, that's where we're thinking most commonly. I think again, we may see some discussion about how much weighting that would do and where it would go, but just conceptually, these are different problems.

The entrapment neuropathies, of course, it depends on what's entrapped and where and whether they get to it, whether there's sensory, motor. I would argue you're really not going to see much of that unless you're having a major problem. But again, very different diseases, so something to think about as we're having this discussion moving forward.

DR. HOKE: Chris, why don't you have

Page 92

autonomic evaluation or autonomic fibers in that?

DR. GIBBONS: I do think about that. This was really thinking predominantly about the examination, which I think most of us would struggle a little bit more on the autonomic, which would be more physiology and symptom based. So if I'm just looking at exam, maybe I could get to autonomic with some measures, particularly orthostatic for bedside, but for the most part, I'd say that's going to be one that we have to think about, and particularly for the treatment-induced neuropathy, I'm going to highlight that later. Hopefully, we'll discuss that amongst the other neuropathies as well.

That's a little bit trickier to get at in terms of bedside testing, though. So that's where if we're focusing just on the exam, that's I think a little bit more of a challenge.

I wanted to do a little bit of an example in thinking about why this might matter. Many of you are familiar with this particular trial publication down here, but this is looking at the tafamidis

Page 93

trial on familial amyloid polyneuropathy.
As most of you are aware, this is a randomized controlled trial of tafamidis. It was an 18-month duration trial, and the primary outcome was a 2-point change in the NIS-LL. We'll talk about that a little bit more later, but the NIS-LL is a pretty comprehensive lower extremity examination looking at sensory, motor, reflex. This was the primary outcome.
Just showing a figure from the actual trial here at 6 months, 12 months, and 18 months, really what you're looking at is the decline or in this case, as the number went up, this is getting worse. The treated group was lower than the placebo group, so there was less of a decline, if you will, in the treated group. This was the primary endpoint looking at that.
Now, if we think about this, why this exam? Would it have mattered if we chose a different examination? If we look at the raw data and -- it's not always the easiest to get raw data when you're looking at change from a baseline score

Page 94

when you have to go to the various subtexts to find raw values, but the tafamidis group essentially changed from 8.3 to 11.1. The placebo group went from 11.4 to 17.2.
Their NIS-LL scores worsened, but again, there was a difference in baseline score, which always creates some challenge. But what you really found was that the worsening in the placebo group was predominantly motor based. So that's what we're seeing here. The placebo group got worse because of a motor decline.
Thinking about the NIS-LL score, this strength in lower extremities is rated based on a 0 to 4 scale. There are subdivisions for fractional in the 3 to 4 range, but the total score is 0 to 64 for motor strength. Reflexes, which are generally 0, 1, or 2 with some age adjustment, which wasn't really relevant in this population. They were generally younger individuals, so I don't know how many fell into an age-adjusted reflex scoring. But the score ranged generally then is 0 to 8 for reflexes.

Page 95

Sensory in the lower extremities was a 0, 1, or 2 at both great toes, and so that gives you a score of 0 to 16, looking at a variety of sensory measures. So this is your proportionate assessment in the NIS-LL.
If we went back in time and we selected a different examination, and we decided not to go with the NIS-LL, what might have happened? Back to our handy slide of all these details, if we look at their percent scores in the different scoring systems, again, we know that in this particular case, the study demonstrated that the individuals who got worse got worse from a motor perspective. So if we looked at who got worse, these are all the scales that would have detected no change.
If we selected any of the ones in yellow here, we would actually have had a failed clinical trial without any hint of a positive, potentially not moved forward. There wouldn't have been a hint of a change. We might have detected that in conversations that people were worse clinically, but if we're looking at a sensory exam and we saw

Page 96

no change, that might have killed the advent of that movement into a further study.
Those that did have more motor weighting are really all modifications of the neuropathy impairment score and the plus/minus. There are a variety of iterations of this, but those are more motor heavy scales. Those are ones that might have detected the change. These others would not.
This is one thing that says well, perhaps the selection of the proper examination is quite critical to this decision-making process. If we had those 18 potential exams, 14 would have had no clinical effect and really would have killed the trial or any future development. Four potential effective scales again were all variations on the neuropathy impairment score, and this again, I think there's really clinically relevant implications for what we're trying to do in selection moving forward. What is going to be appropriate, what is going to have a dynamic range of change, and how do we think about that.
Again, if we go through our criteria here,

Page 97

what we're selecting, what we're interested in, these different scales, we need to think carefully about our selection process because they are not the same thing, and we need to be very careful about how we're choosing.

I wanted to throw a little bit of a teaser for one of the other talks coming up on treatment-induced neuropathy of diabetes. So that's predominantly a painful small fiber neuropathy. You see pain here in red. Some people have it in gray, but progresses, this is the more severe looking case. But this is a distribution of severe neuropathic pain. Visibly, when we look at this, it's not complicated to see that this hurts, this is bad, and this is horrendous. Visually, this is quite simple to see.

If we chose the NIS-LL for this examination, what would we see?

DR. HOKE: No change.

DR. PELTIER: It wouldn't be any different.

DR. GIBBONS: No change. NIS-LL would be 4 in every single one of these cases, but something

Page 98

is different, but we're not measuring it with that particular scale.

DR. DYCK: I think your example is very good. In TTR amyloid, they made a modified NIS precisely for this reason because they thought it was overly representing motor. So they put in a lot more emphasis on sensory exam and a smart somatotopic so you could show changes throughout the entire body. They modified it precisely because of the disease exactly per the discussion we're having here.

DR. GIBBONS: I think that's a perfect example, I think, of how you can evolve general data and move on in terms of examination hopefully to fit what we're all thinking here.

It's interesting, I think was thinking back -- actually, I was having a discussion with Roy the other day. I remember learning in medical school amyloid neuropathy was a painful small fiber neuropathy. And if you go back in the old textbooks, you don't see much about the motor involvement. It was one of those that it was a

Page 99

painful small fiber neuropathy. If it's really painful, it's amyloid. Think about that. That was just the thing going on in the back of my head.

So as you're really thinking about this, the historical perspectives on some of these don't always fit. So that's where again the evolution and the motor data that we're really seeing in the amyloid story is particularly intriguing.

Again, for this one, if we don't have loss of reflexes or strength or other large fiber perception, again, you're not going to see any difference. Again, it's quite critical to select the appropriate scale for the appropriate process.

Clearly, choices of outcomes measures matter, and that's hopefully what we're going to accomplish moving forward is really having a pretty dynamic discussion about what is appropriate for each of these disease states.

Thank you very much, and I think we are on schedule.

(Applause.)

DR. FREEMAN: I think probably now is a good

Page 100

time to have the first break, and then we'll meet again afterwards to discuss the various talks that you've had.

I just want to clarify one of the reasons for having Chris give this talk was to provide a perspective of what CONCEPPT is actually doing, long-term goals, variability in the various diagnostic assessments. But I want to be quite clear, this is not a meeting about outcomes. I'm hoping we will be having that soon. This is a meeting about diagnostic criteria, taxonomy, inclusion criteria, exclusion criteria.

We are right at the very foundation of a clinical trial, and moving forward, as you see, there's a lot to think about and a lot to discuss as far as ultimate clinical trials go. So it's relevant as far as the exams themselves, the validity, reliability, reproducibility because these are part of our diagnostic criteria, but we still are at ground level. In the afternoon, perhaps tomorrow, we will talk more about next steps. Enjoy your tea.

Page 101

(Whereupon at 9:48 a.m., a recess was taken.)

Q & A

DR. FREEMAN: I view this session as more conceptual. Perhaps a heading for it, an alternate heading, is what are we talking about when we talk about diabetic peripheral neuropathy? I think the subtext of this session, which is going to be a moderated panel discussion initially and then with interruptions, interjections, comments from everybody -- the subtext is, as somebody said to me when I invited them, "Is this meeting really necessary? Hasn't it all been done before?" And I gave my views as to why it absolutely was necessary and that it has never been done quite this way before.

So topics that I think are worthy of discussion are going to be how reliable, how reproducible are the criteria that we use for diagnosing peripheral neuropathy in the various peripheral neuropathies that we're going to discuss.

Page 102

I think Stephen highlighted very clearly the continuum from subjective symptoms, to more objective signs, to more objective special investigations. I think we're all aware of the flaws in all of those and the challenges of incorporating all of those in a taxonomy where, for example, if someone wants to do an epidemiological study, they will not be doing, Ahmet's point, skin biopsies, nerve conduction studies, whereas they may choose to do signs and how valid, how reproducible are the signs.

Do we, for example, need to do the kind of study that Stephen did with complex regional pain syndrome, looking at the alternatives, various causes of foot pain, various causes of numbness, or are we pretty much where we want to be and it's just a matter of implement it?

Having said all that, why don't I start with Chris and any additional comments that you'd like to make.

DR. GIBBONS: I think having actually breaks in between provides some great opportunity for some

Page 103

offline conversations. So I'm going to pull Vera back into a conversation over here because actually, one of the points she made, which is really critical, was again as we think about diabetic peripheral neuropathies and examinations and why would we choose one versus another, particularly if we're looking at early scoring, it's pretty important to think about that concept and why we might choose one or the other.

If you just want to throw in your two cents on that, I think that was right on target.

DR. BRIL: The question really is what are you trying to identify. If you're identifying a person with diabetic peripheral neuropathy, for what purpose, and that helps determine what you need to measure a little bit. Because if you want early neuropathy, for example, in diabetes -- and this is the distal symmetrical sensory neuropathy, or sensory motor -- you actually don't want much motor involvement because that's a little advanced if you're enrolling patients for a clinical trial. So you focus elsewhere.

Page 104

This may be why the NIS-LL when it was used in diabetic peripheral neuropathy studies was not that helpful or the drugs failed. At the bottom of all of this, it could just be that all the drugs failed so far.

But you need to tailor what you use to identify the range of patients you want. It may not identify all the patients with that disease, so the sensitivity is different, but at least you will go to the earlier spectrum in some diseases. That was what we were talking about at the break, plus the fact that the TCNS does have reflexes.

(Laughter.)

DR. BRIL: And that was an error on the second slide, but I didn't want to bring it up in the talk. But I'll say it now.

DR. FREEMAN: Rodica, and then Solomon.

DR. POP-BUSUI: First of all, I'd like to thank you, Roy and Chris, for all your efforts in putting this meeting together. It is really great to be here. And I'd like to make just some initial comments; we'll talk some more.

Page 105

The first talk that you gave, Chris, regarding the mission and the aims of the consortium or whatever the name will be, I think that's also very important to identify because at some point, I feel that's saying we need to educate clinicians and we need to educate patients.

Perhaps this is a little bit of a problem because if we aim to educate all physicians, clearly the type of tools will have to very different than the tools that we are going to use to identify outcomes for clinical trials. If you want to establish diagnostic criteria that are going to be used by practicing clinicians, again, if we make them very complicated, they are not going to be used.

I think that as an endocrinologist, I am seeing patients with diabetes every day in my practice, and even us endocrinologists are outnumbered by the diabetes epidemic. It's even more so for neurologists because not all of you are interested in diabetic neuropathy to start with. So I think that we have to have very clear messages

Page 106

that we want to convey out of this meeting.

In addition, Amanda mentioned there are no patient support groups. I think that that's a little not quite true. Maybe there is not a very strong patient support group for diabetic neuropathy right now, but however, the American Diabetes Association and also the Juvenile Diabetes Research Foundation are very, very strong proponents of patients with diabetes and partnering with them. It's also going to be very helpful for us to succeed.

Again, I think that maybe one way to start this, we'll try to identify diagnostic criteria, and measures, taxonomy associated with that that can then be used to identify personalized type of diabetic patients or pre-diabetic neuropathy patients that we want to target in this intervention in a typical precision or personalized care.

Those are my initial comments.

DR. FREEMAN: Solomon?

DR. TESFAYE: Again, I'd like to thank the

Page 107

organizers, Roy and Chris, principally of this meeting.

I think also when we are thinking about an endpoint, we need to think about the mechanism of action of that particular drug and how it's going to work. Therefore, then we target the population that we're studying, depending on the proposed mechanism of action -- so one size doesn't fit all or one endpoint, so it depends on that.

The other thing, I hope this meeting will address is that we have incredible under-diagnosis of diabetic neuropathy in clinical care at the moment, certainly in the U.K. We tend to use a 10 gram monofilament, which diagnoses the condition, in around 14 percent of patients coming in to an unselected eye screening program, whereas if you even used a handheld device, a neurometric device, you'd diagnose the condition in 51 percent. It's a massive discrepancy.

I hope this meeting will address that we really need to do better, and actually, these patients have an incredibly false sense of

Page 108

security. They think they're doing okay. They're told your feet are fine, you don't have any problems until they present to clinic with a foot ulcer and they have an incredibly terrible outcome at that point with very high mortality rate.

DR. FREEMAN: Can I just pick up on a couple of these points and maybe reframe or frame the situation?

I think all three of the commenters raised the issues with respect to the differing phenotypes of diabetic peripheral neuropathy, and I think that's the challenge that is going to be in Gordon and Rob's hands, where I think they are going to need to incorporate the different phenotypes, mild, moderate, and severe, early, late, sensory, motor, autonomic.

I think these are all different phenotypes, and I think there is room in this kind of a taxonomic approach to the generalized peripheral neuropathies to include all of those. It may be that -- and my focus, the focus of this meeting and of CONCEPPT, is really the clinical trial. I think

Page 109

Rodica's consensus -- and I say Rodica, all of the people who contributed to that, her consensus statement guideline focused on the clinician, but I think there should be room for the clinical diagnosis as well.

The way I would view this as being successful is that if this is an enduring manuscript that provides criteria for somebody doing an interventional clinical trial but also a cohort study, also a case study, and even the clinician in practice, I think it is possible to do all things for all of those, and clearly there's going to be a difference in the level of investigation that goes into those criteria.

I think Stephen gave us an example of that when he spoke about the clinical criteria for reflex sympathetic dystrophy, CRPS, and research criteria. That possibly is one way that Gordon and Rob can do that in their approach. I think it's a little less relevant for the talks given by James and Chris, but it's probably very relevant for the talk that Vera is going to be giving on entrapment

Page 110

neuropathies.

Who was next? Yes, Stephen?

DR. BRUEHL: I just want to make a follow-up point with that. So what I didn't show up there is on the CRPS criteria, you've got the core set of criteria that are the same across all the patients that we consider to have CRPS, but there are two subtypes. There's a type 1 and type 2, and the difference is that type 2 is associated with evidence of a peripheral nerve injury and type 1 is not, and that's based on this historic clinical distinction.

The reason I mention that is because what Roy was just talking about is differing phenotypes. The question you're going to come up with is you have a basic set of diagnostic criteria for whatever condition and you think all the patients should have this, but that there are differences in severity or there are differences in particular subfeatures, what you could do is have one set of diagnostic criteria with a definition of what operationalizes the difference subtypes.

Page 111

If it is so different, the phenotype is so different that you would really consider it two separate conditions, then you need to have mutually exclusive separate sets of diagnostic criteria for the two things. So you have some flexibility based on what we've done before, and we have done this with some of the other chronic pain diagnoses in the AAPT effort.

DR. PELTIER: Well, like a perfect example is would you consider type 1 distal symmetric polyneuropathy different from type 2 distal symmetric polyneuropathy? I would posit that there is a difference in the phenotype, time that they present. Then do you have more negative or more positive symptoms in each one?

Also going back to Rodica's point, is that you also have to make whatever we do accessible to not just endocrinologists but also family practitioners and to make it relevant to them. Because one of the things that drives me nuts is when I hear diabetics say, "Oh, no one's ever taken my shoes off before," which you would argue that's

Page 112

all part of the practice guidelines, but yet, then why do people come in and say that's never happened to them?

Giving them a reason, talking about the mortality risks, the five-year mortality risk is higher with neuropathy, period.

DR. RUSSELL: Can we just perhaps conceptually understand what we're going to try to achieve here? In other words, are we going to come up with consensus criteria, which is what has been done before, or are we going to do what Stephen suggested, which is actually take those criteria and systematically test them in a rigorous fashion to determine whether they're reproducible, sensitive, specific, et cetera?

DR. FREEMAN: That was the question that I raised at the initial. Where are we at this point, and where are we with signs? Where are we with symptoms? Where are we with special investigations? Do we need to systematically, as Stephen did, compare the equivalent of complex regional pain syndrome, in terms of classical

Page 113

criteria, versus other causes of foot pain, plantar fasciitis, metatarsalgia, calcaneal spurs, or are we happy enough? And that's really to me is exactly is the focus of this discussion. And if we need to go in that direction, how do we go about doing that?

Or are we okay? We can just say okay, we are prepared to live with pain, dysesthesia, sensory distortion as symptoms when patients say as they do then, and Gordon can say one of five criteria in his talks, either this or that or the other.

I don't really know the answer to this, and of course, it depends on effort and resources and who's willing to commit their time to doing such a study. But I think that's a critical question, where are we now with those criteria?

DR. HERRMANN: One complexity that I was thinking about during the talks, it also gets to the changing criteria for diabetes, right? When we talk about the peripheral neuropathy and the neuropathy aspect, if you just look at symptoms and

Page 114

signs, we could investigate that and see how you differentiate symptoms and signs in, say, diabetic peripheral neuropathy and maybe subtypes from, say, those in HIV neuropathy or idiopathic neuropathy.

There may be considerable overlap there, but everything rests on the diagnosis of diabetes. As that changes over time and maybe others in the audience will say they won't change in the next 10 years, but if they do and as you make the definition of diabetes more inclusive, that will affect the specificity and the characteristics of the criteria and how we deal with that. Do we develop a continuum of glucose dysmetabolism? I just throw that out.

DR. FREEMAN: That I think will come up in the next sessions where Rob talks about impaired glucose tolerance.

I think Jen had her hand up. No, no yet.

Chris?

DR. GIBBONS: Just to get to a couple of these points and maybe step back a little bit from an overall perspective, so the focus of this

Page 115

meeting will be fairly tight. Again, we're working on taxonomy, defining things fairly specifically.

What we're also trying to generate here is this consortium where many of these other related activities are going to occur, whether it's clinical, whether it's research, whether establishing concepts. I think the consortium will be a much larger target of things to approach, and maybe many people here will be having different foci within this. But the current meeting will just be a small portion, I think, of globally what we're trying to accomplish overall.

DR. FREEMAN: Can I just before -- Vera, I'll come to you in just a second, and then to Stephen.

Just as a show of hands, I'd like to get a sense of who actually thinks -- let me ask this in three specific ways. Who thinks that with respect to signs, signs of diabetic peripheral neuropathy, we need to do a study like Stephen did, or we're okay? Who thinks we're okay? We don't need to do anything more as far as signs go.

Page 116

(Show of hands.)

DR. FREEMAN: Who thinks we're not okay, that we should actually look at this more carefully?

Okay. Slight majority.

DR. POP-BUSUI: I'd like to make a comment. So I think that we should not ignore the data that we have acquired, and in fact, we know we have so much wealth of information in the DCCT EDIC. We have acquired signs and symptoms now for 30 years, and we have also acquired the entire spectrum of information regarding diabetes history, control, risk factors, biomarkers.

There is no other study, and it's continuously -- it hasn't even mentioned. We do have a lot of data, and we do have these signs that have been, in fact, acquired through your help because every single site had a board certified neurologist who had acquired those signs.

So I think that we have a lot of information on signs already that we should include in our consideration.

Page 117

DR. FREEMAN: I absolutely agree. The problem is unless -- I agree with that, and I think we should look at that. I also think -- I don't know if you saw earlier, but as part of the ACTTION initiative, they are looking at all of the studies that were submitted for neuropathic pain to the FDA. I think we should do the same with disease modification for diabetic peripheral neuropathy.

However, until you do it in an objective way like Stephen did it, looking at -- and this requires a hypothesis-driven study, the equivalence of PHN, the equivalence -- I forget what the other neuropathic condition that you looked at -- and comparing those to CRPS, I don't think we are quite there yet.

Stephen and then --

DR. BRUEHL: Can I make a couple points?

DR. FREEMAN: Yes.

DR. BRUEHL: I think you're pointing out exactly what the issues are in mapping out how to do something like this. I was thinking it might be useful to have a visual here to conceptually think

Page 118

about this.

In Chris' talk, he had the four different areas, which in some ways, I might consider might be different mechanisms. Physiologically, we're talking about something different for each of those. When we define the diagnostic criteria, we are defining some variety of overlap across different mechanisms. In all likelihood, every one of these conditions may have different mechanisms going on.

It would be helpful, if you feel like the literature is strong enough, to keep in mind what the mechanisms you want to capture are. You have a list of those. Then you go for a given condition, where should that just -- based on what you already know, where should that blob go? How much should it cover? Should it leave out the motor or whatever it may be?

Then if you have mechanisms in mind, what you think is you got a mechanism, and then in some cases, you have an existing objective test that you know is a marker for that mechanism, a reasonably

Page 119

good marker. That's theoretically meaningful. So that's really nice.

Now, the point about clinical use, nobody is going to do these really elaborate expensive tests out in Dubuque or I don't know, randomly picking a name, but some small town somewhere, Bucksnort, Tennessee.

(Laughter.)

DR. BRUEHL: It's an actual place. They're not going to use this, right? So they need clinical criteria.

So you've got this theoretically meaningful objective test, and if you can demonstrate that any given sign or symptom or combination thereof is a valid and reliable marker of that objective test, that's what you want in your ultimate clinical criteria, because if you tie it backwards, it goes right to this issue. So kind of keep that in mind as you're doing this.

I think the other question that was brought up had to do with should we start from scratch or not, and you have to start somewhere. Now, you

Page 120

could be totally atheoretical. I don't recommend it, but if you've got an existing data set that has the right data elements, you could inquire and see what comes out using the pattern recognition approaches I was talking about and do it all based on empirical things.

It's nice, though, because we're not totally stupid people, and if you've seen a lot of these patients, you have an idea in mind theoretically of what a given condition is. So you can look at it in this incremental validity manner where you've got a starting point that may be consensus based, and what you're trying to do is then optimize that using the empirical approaches, which could be collecting a new data set across a variety of sites as in a consortium, as long as you can all agree on what the key elements of that need to be. And it doesn't take a ridiculously long time. If you see a fair number of patients and are willing to commit to this, it can be done pretty quickly, within a year, a year and a half, something like that.

Just keep all of this in mind. I'm not

Page 121

trying to steer the direction one way or the other as to whether you start from scratch or not. You could do either one of these, but I don't think you can totally ignore what you already know.

The other issue is do you feel like for any of these particular conditions, there is already a published set of diagnostic criteria that have been validated or represent a clinical standard that is pretty much widely accepted, and if it is, then you can use that kind of thing as a starting point.

DR. FREEMAN: I will come to the question, and somebody should make notes of this. Two things, first thing is that we are going to end this meeting with criteria. We're not going to end this meeting by saying, well, we just don't know enough at this point, we need to do a study. That's the one thing.

But the other thing is I think it'd be really good to have a research agenda, and Rodica has offered to look at the DCCT and the EDIC databases, perhaps do a cluster-type analysis on those, other databases that exist. I think we can

Page 122

then in a way make this iterative, make this flexible, and begin to then use data to modify this as time goes on. I think that will be a very useful research agenda.

There were some questions. I think Vera was next.

DR. BRIL: We're happy with our scale. We've validated it in a single center and trained the people, but the study that Peter did at the Mayo with many people in this room should really give us all pause because they did the signs. They were neuromuscular physicians mostly. They did the signs, and they made the diagnoses, and there was not good concordance.

We're talking now about reliability. That's like a specter that's hanging up there in the corner of the room that depending on how widespread we want this work to be, we have to realize the limitations. Even in the EDIC, it was neurologists in each center. Well, most diabetes patients are never going to see a neurologist, right? They're going to be out there in the community.

Page 123

There's many elements, but even if they do see a neurologist, that neurologist may examine differently than the next neurologist. There was standardized training in this particular study. It's a data set that is quite pure, and there was standardized training in our set. So what we published had to do with a small group of examiners and standardized training, but when we get out there and don't do it, you get this variability even in things like signs, which should be really easy to assess.

In our own minds, I think, we all think we can do it, and yet there was this variation that reminds us a little bit -- pain, when you describe pain and you describe a symptom, you can then more or less categorize what the patient says, but when you're looking, I wonder what the variation was really, and that weakness, and that limited range of motion, and how much variation there was in that particular category of your chronic regional pain syndrome because it's surprising.

DR. FREEMAN: I couldn't agree more.

Page 124

Eva, Doug, then Dan, then Rayaz.

DR. FELDMAN: I just want to make one point early on that Amanda made that I'd like to reiterate, and that is, while I am a big advocate, for example, of the DCCT EDIC database and work closely with Rodica on it, it is a type 1 database. I really do think that many of us who see hundreds and hundreds of these patients believe that the neuropathy in type 1 and type 2 may be quite different.

So I think we need to keep that in mind as we're doing our taxonomy.

DR. FREEMAN: You want for EDIC as well?

DR. POP-BUSUI: No. What I want to say is do we know for sure that the actual disease, it's different or the risk factors that contribute to the disease? And I think that's another question that we can answer.

DR. FELDMAN: I think it's something that we need to ask and answer.

DR. FREEMAN: Gordon is nodding. Gordon will address this. Doug?

Page 125

DR. ZOCHODNE: I'm going to say, Roy, that in terms of this meeting, I actually like these microphones with the lights that come on. It's sort of like optogenetically activated neurons that pop up and down. I think it's quite neat.

(Laughter.)

DR. ZOCHODNE: My relevant point was that Stephen mentioned mechanisms and Amanda brought up type 1 and type 2 and Eva did as well. I think we've moved on. This was Anders Sima's idea, that there were differences, and we pushed that aside. No, no, we're not going to think about differences, but it's emerging. The insulin resistance of neurons, the insulin sensitivity in type 1.

I think it might be a good strategy to keep them separate at this stage.

DR. FREEMAN: Rayaz, Dan, Teresa.

DR. MALIK: The reason we're all here is because things aren't working. So if we just say, you know what, we don't really need to look at this objectively, as Stephen has said, and we just carry on as we're doing, then I think we're going to come

Page 126

back in 10 years' time, and we're going to say same old problems.

I honestly advocate an objective approach. Just do it properly, look at the symptoms, look at the signs, look at whatever tests you want to use, and address them objectively as opposed to opinion.

Chris, your data, I think, highlights the fact that probably when you did this study, you wanted to show that there's going to be a change. You didn't see any change. Three years. Okay. They were well controlled or whatever, but that data speaks for itself.

I disagree with anybody who says we just need to carry on doing what we've been doing for the last 40 years.

DR. FREEMAN: The insanity advocate.

Stephen and then --

DR. BRUEHL: I'll make an response to what's been said just a second ago. The type 1 versus type 2 example is the perfect prototype of exactly how this approach could be applied.

What you do is you have a set of signs and

Page 127

symptoms that you think encompass all the meaningful features of both type 1 and type 2. You do clinical evaluations with standardized instructions for how you assess everything. Assessing all of those in patients whether they're type 1 or type 2 in your clinical belief.

You get a large data set of at least 100 people. You do cluster analysis, and using this two-step cluster analysis, what it will tell you is it will use the Bayesian information criteria to tell you how many clusters there are. If it pops out two clusters and you look at the features and see the patients in those, what you should see, if type 1 and 2 are meaningful, is that it should fit basically what you'd expect clinically. You can match that up statistically, if you wanted to.

That's the type of thing I'm talking about, is that is a perfect use of this type approach when you've got a clinical question that is easily testable. You don't even have to know the mechanisms to do this. That's the cool thing, is you can do it totally not theory driven but just

Page 128

let the computer tell you this.

DR. FREEMAN: Just to editorialize for a second, one of the hopes of this meeting -- well, one of the interesting things to do then would be, as I suggest to Rodica, we look at both DCCT and EDIC.

One of the problems is that the entry criteria for the study are different. One of the hopes for a successful meeting would be that in the future DCCTs, future *EDICs, similar criteria will be used so that we can make these comparisons going forward.

I think it was Dan next, then Teresa, and then Rodica.

DR. ZIEGLER: I would just like to come back to what Vera said. I think the problem in practice is that there is no standardization at all, and there is no way -- I agree with you completely that we need something to dichotomize the diagnosis.

The problem is that if you come back to all these test, bedside tests, and the 16 different suggestions of scores, everybody is doing it in a

Page 129

different way. There's no way at all of standardization. If you ask the people, what is the normal cutoff for vibration perception threshold, you will hear 20 answers here, even here, among the experts.

We're starting from scratch. If there is no way to standardize this, these simple tests, there will never be an accurate and reliable diagnosis.

So the question really is historically, those people suggesting all these different tests, why didn't they get together 20 years ago and try to figure out which of these tests would be the most appropriate one and come back with a consensus on what would be a reliable approach of bedside testing using appropriate cut points and dichotomizing and defining the diagnosis? I think those years are basically lost so far.

DR. FREEMAN: My vision is to -- and one of the reasons why I delayed this meeting is I believe that that is absolutely necessary. It's enormously challenging, and it also requires people who have their own instruments being flexible as far as what

Page 130

we give and take from those instruments. But I couldn't agree more with you.

As a matter of interest, Jen, Chris, how many of those instrument scales that you looked at actually do give some standardization instructions?

DR. GIBBONS: This will probably be best answered by Jen, but I think as we went through, part of the challenge is everybody has their own recollection of exactly what they're thinking when they wrote their instrument. When we tried to recreate that -- and it's important to step back. As a neurologist, I have my own perception, so I came into this with some degree of recognition of what people were expecting. When Jen comes at it from a different perspective, a non-neurologist with clinical trial expertise, she looks at the language the way it's written.

The standardization was severely lacking. You could assume what we all thought we meant, but you could not find the definition in most cases. It was extremely difficult to come down to a really clear answer. We had to go back and query authors

Page 131

about what they were meaning or what they thought, and even then, I would say we frequently still got into dicey -- we weren't sure what exactly was going on despite many people using this, not necessarily in the same way.

DR. FREEMAN: Teresa, and then David.

DR. JONES: First, I'm really thankful. This is a fantastic meeting, and I really appreciate all the work that's going into it. It's really nice to think about these things.

Just as far as your aim statement, all of it's great, but I wish I'd seen the words "cure" because that's so powerful. From my perspective, seeing research out there, I'm hopeful. I see things that look very promising, so I don't think that's so far away.

I'd like to just have my comments more on the research module aspect, which I thought was great as I was listening to Stephen's talk. I have a question about how it's actually been used in practice, but I think it's -- I'm wondering and the door's closed, so this can kind of be in here. I

Page 132

wonder if we should work backwards and somewhat game the system a little bit, and think what drugs are out there, what are they going to be acting on. What are some of the mechanisms? What would be the patients that you would want to see in these trials so that we could finally get a drug that would be disease modifying? What would set the thing up in the best way?

Of course, it has to be valid. It has to be choosing the patients, but then work backwards. And then for this research module, which doesn't have to include primary care physicians but just for doing a research study would be your inclusion-exclusion criteria. That's all.

DR. FREEMAN: Let's track David, and then Rodica, Rob, Yad, Gordon.

DR. HERRMANN: Related to the point that Vera and Dan made about clinical criteria and practicing neurologists and precision, I wonder whether one way you could construct it is in your taxonomy, you have your starting set -- let's take symptoms or signs -- where you think of the signs

Page 133

as just elements, and so you define the elements that need to go into the diagnostic criteria, so maybe vibration or position sense, whatever the sign is.

That's the starting point, but then to get to the precision, which may be what you need is greater for a trial or for research than you might need for just broad clinical practice, there can be a separate component to how to or best practice around how to measure that element. Because I think if we get to the measurement too quickly and the precision, I think we will never really get there, but if we can define the elements in the diagnostic criteria and then move to best practice around precision of measurement, I think that might be more manageable to approach it that way.

DR. FREEMAN: Bob, Rodica, Gordon, and then that's it. There will be plenty of time.

DR. SINGLETON: I wanted to thank Teresa for opening this piece of the discussion because I think we will inevitably be talking about this neuropathy in the context of its spectrum of

Page 134

disease from metabolic syndrome, from pre-diabetes, to diabetes.

I really like the idea that we might have two different criteria, one that is diagnostic and another that is designed for research with the goal of finding a criteria that allows us to select participants who would best respond. I think that all of us -- I certainly think that we want to find a set point that is early in the disease progress at a time when it's reversible.

So choosing definitions that allow us to, at least for research, recognize the disease very early in its course means that we have a better chance of reversing that disease when we apply whatever treatment we're going to.

DR. FREEMAN: Again, to editorialize, I think that line of thinking, get it early, has been so prevalent in all of our thinking, not just with neuropathy but with many diseases. And I took something else from Teresa's point, and that is that it may be that a specific drug is not effective at that early stage of the disease, and

Page 135

its mechanism will only be effective at a later stage of the disease.

I had the view that we really do need to look across various phenotypes. This will come up during the course of the discussion. But I do have that concern that we've always focused too early in the course of the disease and maybe the drug may not be working at that stage.

DR. SINGLETON: I would disagree with regard to especially the clinical trials of the late 1990s, early 2000s. Those were studies where we applied very strict criteria to diabetic neuropathy to assure that patients had diabetes, and by doing so, probably chose patients whose disease was too severe.

DR. FREEMAN: Rodica, and then Gordon, and then I'm going to ask the panel if they have any comments, and then we will move on.

DR. POP-BUSUI: First of all, I'd like to say that I completely agree that we are all here because whatever we've been doing so far doesn't really work to advance the field.

Page 136

I also agree with particularly what you said, that the only way to move this successfully forward would be that we all have to look very objectively at some measures and may need to agree that whatever we consider that might be what we like to use may not be the best way to move forward. I think that's actually a very critical component of this meeting.

In addition, based on what Dan has said regarding all these signs and symptoms, if we are going to use this as a tool to define taxonomy and diagnostic, we will have to use those databases or trials where these criteria were most applied in the most organized fashion. Those are the clinical trials that looked at diabetic neuropathy because I completely agree that they are in the community the way that a particular sign or symptom is being assessed varies from one provider to another, but there is a little bit of consistency that that is in clinical trial.

When I gave the example of the DCCT, I didn't say that we have to continue to do that, but

Page 137

that we can use as a tool to define whether our diagnostic criteria meet sensitivity, specificity, and all the validity type of thresholds that Stephen has outlined because we do have resources that we should use constructively.

We cannot reproduce everything. We are not going to reproduce another 30 years' trial or study or epidemiological observation because there is no time and there are no resources. That's what I said, and I think it's very important to consider.

DR. FREEMAN: Gordon, and then the panel.

DR. SMITH: I want to reflect on two different comments. I think the first is Steve's, and I think our situation is particularly complex because we're dealing with a phenotypic disorder, really a syndromic entity that is largely indistinguishable from other clearly separate disorders, so HIV neuropathy, chemotherapy-induced neuropathy, and so forth.

I think it's certainly quite likely that a patient with type 1 diabetes and neuropathy phenotypically may look indistinguishable from a

Page 138

patient with type 2-related diabetic neuropathy, yet the physiology and mechanism is different. I think we have multiple different axes of chaos that we have to deal with, including metabolic pause, metabolic risk factor, disease stage, diabetes criteria, phenotypic variability.

To transition, I really loved Dan's comment, and I'm glad someone's writing it down. I'm not going to try and restate it, but I completely agree. To channel my inner Vera Bril -- which is something I like to do all the time, and I rarely succeed --

(Laughter.)

DR. SMITH: -- but hopefully, I'll approximate that now.

I think the signs are not uniformly applied well, and even if one looks at the way -- like the MRC scale, it's a terrible scale. How do we assess vibration?

I think using existing data sets, we're a hostage of this imprecision that has been talked about. And I am going to talk a little bit about

Page 139

Peter's study at the Mayo Clinic, which I think is instructive in many ways.

DR. FREEMAN: I like the notion of a meeting in Washington in which the term "axis of chaos" is used.

(Laughter.)

DR. FREEMAN: -- which is different from axis of evil, of course.

(Laughter.)

DR. FREEMAN: Anything from the panel?

DR. GIBBONS: Sure. I have been frantically jotting down lots of thoughts about everybody's comments, which have been outstanding. I think we're really getting some juicy bits of things to work on here as we move forward.

One of the things -- as I was hearing the comments about how do we decipher and the axis of chaos, as Gordon and Roy just put, but certainly, the criteria that we can think about, and we haven't really discussed, but the definitions possibly of possible, probable, and definite and some relation to whether that is clinical research

Page 140

based or how we loosen or expand our criteria to include that, particularly as going on to Stephen's discussion about how we want to frame the core diagnostic criteria. There is definitely some flexibility in there.

DR. FREEMAN: Jen, anything to add?

DR. GEWANDTER: Yes, I think a couple of things as someone who is not a neurologist or even a clinician listening to you guys talk about this, I would encourage you to think about the two different sets of criteria, clinical and research, and experimenting on how well they mirror each other for specific items, kind of like what Steve put up there. Because I think even from my perspective as a researcher, I might not have access to a neurologist for my inclusion criteria for my effectiveness study or my cohort study, and if there was a good level of reliability between the two entry criteria, it would be really helpful for me. Also, when it comes to generalizing the results of your clinical trials to the real world, it would be useful top have that. So if there is

Page 141

time, I think that would be really useful.
Then the other thing, when Roy said to try to standardize the individual items, some of us would have to put our feelings aside because there are so many different measures, I didn't see a lot of standardization at all in the measures in terms of the individual items. So I'm not sure that that necessarily would be a barrier in saying, oh, this scale doesn't do it right or this scale doesn't do it right because there wasn't that much standardization, so maybe that's not as much of a barrier as you think it might be.
DR. FREEMAN: You'd be surprised.
(Laughter.)
DR. BRUEHL: A couple of points here. With the reliability issue and the idea that nobody measures things the same way, something I didn't mention in giving the presentation about the CRPS criteria is those were all dichotomous intentionally because it was our impression from reading other things that it is much easier to get two people to agree on presence or absence than it

Page 142

is to get them to agree on some scaling. So if you've got a 5-point scale and reliability means you've got to agree on where on that 5-point scale they are, that is much harder to achieve than yes or no, is it abnormal.
Now, that's cheating, honestly. We're hoping that the error in measurement washes out across people and we end up with some meaningful information in that dichotomous decision. But I would recommend, given the circumstances, you consider not confining yourself to measures that are too fine grained where nobody is going to be able to agree.
Also, the idea of working backwards from drug targets to come up with criteria, I don't really see that as backwards because if you think about it in the bigger picture, these drugs were developed because they thought they affected a mechanism that's relevant to the disease. So really what you're saying is we should be working from the presumed mechanisms, creating the criteria, and that's exactly what I'm saying.

Page 143

If you wanted to look at it like what mechanisms should we be focusing on, if you wanted to look at drug targets that are being tested, now, that might make perfect sense because these companies have invested a lot of money in trying to identify meaningful clinical targets that are modifiable. Maybe not restrict yourself to that, but that might not be a bad starting point where you'd want to identify the mechanisms that you could assess clinical features that might be reflective of those.
DR. FREEMAN: Thank you, panel. Thank you, audience.
One of the pleasures of this meeting is that you don't need to introduce most of the people because just everybody knows everybody, and the next talk will be given by Gordon. It will be the last talk before lunch, and I think this talk is the critical talk, and there will be a lot after lunch of similar kind of discussion.
Before doing so, two quick points. One, I said that if you send out more than three articles,

Page 144

nobody reads them. Stephen criticized me for not sending out another article, which I'm sure would not have been read, either. This is, I think, very relevant to the discussion we've just had on reliability and validity, and he's going to email us or give it to Andrea, who will email us, so that we are all aware of another article. But this time I think after this discussion, you really should read. That's the one point.
The other point is we need to take the obligatory photograph, and what I'm asking is did anybody -- this is Washington. It's the nation's capital. It's the axis of chaos.
Did anybody come here with a good camera?
Yes?
DR. POP-BUSUI: I have a good camera.
DR. FREEMAN: A good camera, great. Because I was going to ask if not, is there any early adopter who has an iPhone 10? Yes?
DR. POP-BUSUI: I have the iPhone 10.
DR. FREEMAN: Have both. Whoa! Well, on that note, let me introduce Gordon.

Page 145

I think we should have the photograph -- Jim is leaving. I think we should do it today before he leaves, and I think before lunch, if you can hold out, that would be a good time to do it.

Gordon Smith.

Presentation – Gordon Smith

DR. SMITH: I sure wish that I had listened to this morning's discussion before making my slides. I'm not going to have a taxonomy at the end, I'm afraid, but rather what I hope to do is go through the taxonomic process, as it were, and bring up issues for discussion.

It's actually nice having had this discussion that we just went through before the slides because many of these themes are woven in the slides. I really hope that what I'm going to show you will really serve as more fuel for that discussion.

We've already gone through that, so I'll stop. I think the one issue that's already brought up, of course, is that diabetic neuropathy isn't a single syndromic entity. We have multiple

Page 146

different forms of neuropathy. This is a nice figure from an article that Amanda wrote on painful neuropathy in BMJ, which is really fantastic. I'm sure she hand-drew this.

We're going to be talking about many of these over the course of the day. I think the distal symmetric polyneuropathy is really in many ways the most challenging for reasons that I brought up in my last comment.

I think there are also issues in terms of core principles of what diagnostic criteria ought to look like, and I think it's worth going through these. Many of them were highlighted this morning, but ideally, the taxonomic criteria we come up for polyneuropathy and the other entities ought to be respectful of these attributes, so biologically plausible, exhausted in that the system should encompass but yet still be distinct, mutually exclusive. We've talked about reliability a lot in the discussion, and I'm going to show you some of the data that Vera was speaking of.

I think clinically useful is really

Page 147

important. This is abuts against the challenges in the neurological examination, and Roy referred to a meeting we had about CIPN earlier this year. If we struggle with this, I think it's right up in front of the challenges in creating a taxonomy, if you will, for CIPN where oncologists are not as comfortable with neurological examination skills as are our endocrinology colleagues. Then simplicity is an issue. I'm going to bring my own perspective on this in a moment.

Of course, the first issue that Amanda brought up, even before we talk about the taxonomy of neuropathy is the taxonomy of diabetes. I feel embarrassed showing this slide with a bunch of endocrinologists in the room, but we need to decide, is type 1 diabetes neuropathy different from type 2.

Below are the criteria for pre-diabetes as well as diabetes.

So we have these two competing questions or not two competing questions but issues we need to deal with. And what I thought I would do is work

Page 148

through the first, which is type 1 versus type 2.

Now, we say or at least neurologists will typically say, well, trials should only enroll patients with type 1 or type 2. This just shows recent neuropathic pain trials in diabetic neuropathy, and you can see more of our recent trials include patients with type 1 and type 2 diabetes. You may say, well, that's just neuropathic pain, but many of the disease-altering trials we're participating in now and have in recent years, and one that I'm in the process of planning includes type 1 and type 2 at the insistence not only of the company but one of their very well known external advisors. So I don't think it is all established out in the real world that trials should include only type 1 versus type 2.

What are the reasons that these might be separate entities? This is a really nice figure from Rodica's article that's been referenced a number of times this morning that points out that there are different inputs into the mechanistic

Page 149

pathways. These may converge on issues such as mitochondrial dysfunction or other final common pathways, but there are obviously different points of entry with insulin resistance and dyslipidemia as opposed to reduced insulin and C peptide and so forth.

I just made sure I had pictures from everyone's articles.

(Laughter.)

DR. SMITH: Another way of thinking of this is more mechanistic from a really great article that Eva wrote for Neuron, which highlights that these different front-end entry point mechanisms can field down to a final common pathway and what may look syndromically clinically similar.

I think other data that these are separate disorders, of course, comes from the response to therapy, and this is, of course, one of the first vials of insulin from Banting and Best at the University of Toronto. We've known since the DCCT that aggressive glycemic control is effective for mitigating type 1 diabetes-related neuropathy.

Page 150

This just summarizes the data you already know. If you just look at the intensive versus conventional, and these are the percent at closeout and at year 13 and 14 of EDIC of these various criteria. I don't need to walk you through the data about this.

This is a figure from EDIC up to year 8, which not only highlights the difference at entry, but this concept of metabolic memory. So very clearly, aggressive glycemic control is impactful in type 1 diabetes.

What about type 2 diabetes? This is data from the UKPDS cross-sectional data that shows a relationship with A1C and hazard ratio for various outcomes. The relationship between A1C and amputation or death, overall microvascular endpoints, cataracts, so forth, is impressive.

But what about treatment of hyperglycemia? The story is not the same. So this is data from the ACCORD study and shows the hazard ratios favoring intensive control versus standard control. And you can see in some diabetic endpoints, there

Page 151

is a significant difference, particularly in renal function. But if we look at the neuropathic endpoints in ACCORD, you'll see that for neuropathy defined by MNSI, loss of vibration, loss of ankle jerks, there was no significant risk reduction. There was a slight benefit in regards to loss of sensation to light touch, and even though this barely reached statistical significance, you can see the hazard ratio is not all that reduced.

This actually mirrors other studies, so I think in what must have been a Herculean effort, Brian did a very nice Cochrane review in this. And he's having PTSD from his Cochrane review, so give him a drink of water, Eva.

(Laughter.)

DR. SMITH: These show the forest plots for type 1 and type 2. They look deceptively close just because of how they're constructed, but if you look at the hazard ratios here, or the risk ratios, for type 1 versus type 2, dramatically different. So clearly, these disorders respond differently to moderation of one of the main inputs to diabetic

Page 152

neuropathy.

It may be that this is because of either different mechanisms or differential prevalence of risk factors in obesity and dyslipidemia. These are data from the Utah diabetic neuropathy study, so this is a population of a couple hundred diabetics where we looked at the risk ratio of having neuropathy if one had these various endpoints. You can see obesity and dyslipidemia or the aggregated metabolic syndrome conferred a twofold risk in this cross-sectional study. If one looks only at very well controlled diabetics, the risk ratios become even higher.

So I'm not necessarily saying that type 1 and type 2 diabetes are definitely different, although I suspect that they are, but it's very clear that these metabolic risk factors that are important are very different in these populations and therefore, something to be mindful of.

Then there's the whole issue of pre-diabetes, which I'm going to unabashedly punt to Rob later on, and I know he's going to solve all of

Page 153

this for you. But this is data just from Dan's cohort study showing that in patients who are phenotyped based on glycemic status, that there is an increasing prevalence of neuropathy as one moves through increasing degrees of glucose dysregulation and that the phenotype is really disproportionally a painful neuropathy; and again, highlights the importance of these other metabolic risk factors. And I'm going to touch on this issue a few more times but not really dig into it because I don't want to steal Rob's thunder.

This slide is actually timely because of Steve's construct here because it's likely that these different metabolic inputs into the neuropathy pathogenetic cascade, if you will, impact our endpoints differently.

This is data from the same cohort I described earlier, and just to walk you through it, this shows the relationship between different biomarkers, skin biopsy, sural sensory amplitude, and motor conduction velocity, and BMI and hemoglobin A1C.

Page 154

So you can see, for instance, that peroneal motor conduction velocity is not at all related in this cohort to BMI, but there is a relationship to A1C, whereas if we go up to a structural small fiber axonal metric, epidermal nerve fiber density, it's the opposite. There's no relationship with A1C, but there is with BMI. And interestingly, with sural sensory amplitude, it really correlates with both.

So this suggests that our endpoints may be related to different metabolic attributes of the disorder. This, I think, does touch on the diagnostic framework, and in particular, how we might rely on these different biomarkers within our criteria for diagnosis. And it clearly has impact on our choice of endpoints in clinical trials going forward.

To answer these two questions, I'm punting to Rob a little bit, although I have teed it up a bit, but we have really high expectations for your talk. But I would posit that at this point, type 1 and type 2 diabetes really are and for our

Page 155

taxonomic endeavor today need to be viewed as different disorders.

I suppose one might view this differently in regard to the taxonomy of painful diabetic neuropathy, which we could talk about. As I'll allude to, there's a separate taxonomic, or Roy mentioned, process going on for painful neuropathies that is addressing this issue.

Of course, the main taxonomic challenge we have -- now we've got the easy stuff, I think, out of the way -- are the core criteria for diabetic peripheral neuropathy. And one that again, I'm going to touch one now and again, particularly at the end, is, is painful diabetic neuropathy really a syndromically different entity? Is that separate in our taxonomy? Is it a subtype? What diagnostic criteria should we use? We've talked already about structured signs and symptoms and then the electrophysiologic aspects of this.

I really do think, all joking aside, we have multiple different axes that we need to consider. We've talked already about the metabolic axes that

Page 156

not only includes the role of obesity and other metabolic issues, but it touches on the criteria for diabetes, which I expect will evolve over time. Then we've got these other axes we need to think about.

I want to just summarize this study that I think most of you are familiar with it, that Vera brought up. I think it's really critical, so I'm just going to go through this. I think many of you were smart enough not to come to this, but I was. I looked younger then because I was.

(Laughter.)

DR. SMITH: The concept, which was, I think, really prescient and really brilliant on Peter's part, was to bring experts and to do sequential examination on patients that it turned out were randomly selected from the Rochester diabetic neuropathy cohort. After the first day, I went to Peter and I said, "You did a fantastic job of selecting these patients because it was really tough." And he said, "I didn't select them at all. It was just a subset of our cohort." And I think

Page 157

that tells you one thing.
So what we did was examine them in the Kahler Hotel the first day. They were disguised and had microphones, and we had headphones that plug in that would distort their voice. So while there were some people you could kind of identify the next day when we reexamined them in their street clothes without voice distortion, it was quite difficult, so this worked.
The first day, we saw each one of these individuals, and I merely had to say did they have signs and symptoms of neuropathy. We used whatever rules we wanted to have. I'll tell you what I did in a moment.
Then the next day, we came back and did the same thing. I remember having a lovely steak dinner with James at Michael's, which I'm told is no longer there, so I'm glad I got it back then. It was a lovely meal. We were very happy. We thought we had done a good job, but when the data were released, they were really dreadful.
So over there shows the number of times the

Page 158

12 experts got the right answer, and I don't even think it's the right answer. It's the number of times we agreed with Peter's answer, which as I recall, was really based on electrophysiologic criteria, I think some seven or something. But it doesn't matter, right?
You can see that one of us thought 20 of them --
DR. DYCK: NIS also.
DR. SMITH: It was NIS plus seven.
DR. DYCK: I think it was both as exam --
DR. SMITH: Okay. And it almost doesn't matter. That probably explains why some of us thought lots of them had neuropathy and some of us thought very few had neuropathy. But the fact is we were all over the board as experts, which is the point that Vera brought up and Dan brought up much more eloquently than I can.
If one looks at the kappa statistic, which Steve talked about, with intra-rater reliability, so the test/retest reproducibility, there was several of us that didn't even have a significant

Page 159

kappa statistic. So we didn't agree with each other, and a quarter of us were irreproducible day to day. So this was alarming.
I don't know who I am, but I think I'm one of these two because the way I approached this, I thought this was going to be easy. I just used the UENS because we use it all the time. I know the cutoff value, and I'll show you the ROC curve for the UENS. I'm not saying the UENS is right or wrong. I just used the same way of doing it, which meant I over-diagnosed relative to the NIS plus 7, but I was reproducible.
There were people there with their monofilaments and everything. I'll tell you the end of this story a little later on, but I think this highlights the need for what we're doing right now, because as experts, if we can't look at a cohort of 20-some patients and come to some agreement left to our own devices, then we need taxonomic intervention, as it were.
What are the criteria that are existing? So the first set to talk about are the old San Antonio

Page 160

criteria, which were published in 1988. These capture, I think, some of the challenges over time. First of all, the concept was that they should include a validated questionnaire, interview technique and examination with two classes, no signs or symptoms or signs and/or symptoms.
Without getting into it, you can see that these include electrodiagnostic autonomic functioning and QST data. You can just look at this from afar and realize that this is going to be extremely difficult to deploy clinically, and we're certainly not going to get people in primary care environments to use these criteria.
Another attempt was made by a consensus from the AAN, and John England was first author on it and published in 2005. I think there's some concepts in here that are important to highlight. So the first concept was that -- and this was based on a literature review, so they were somewhat hostage to what had been published. But that electrodiagnostic studies were considered an objective outcome, symptoms have poor accuracy,

Page 161

signs are better, and that ideally, patients should have combinations of symptoms, signs, and electrodiagnostic studies.

They created a rank order of certainty, essentially, that discordant signs and nerve conduction studies would be the lowest threshold for possible neuropathy. The highest would be multiple symptoms, multiple signs, and abnormal nerve conduction studies. So it makes conceptual sense. It really isn't a criterion in the taxonomic sense that we're dealing with today.

I think some of their conclusions are really driven by the Rochester diabetic neuropathy study, which, of course, is incredibly important, and was founded in a population-based survey in Olmsted County starting in '86 where they examined the patients in Olmsted County that had diabetes. Now, two-thirds of these patients had some evidence of neuropathy, but only 13 percent had symptoms of neuropathy, and only 10 percent had neuropathy based on the NSS.

There's some quotes, I think, that actually

Page 162

I pulled out are the foundation for the England paper. One is "because symptoms are not constant but tend to come and go, for purposes of following course, it's useful to have an overall measurement of severity excluding symptoms and that the frequency of abnormality was higher for attributes of nerve conduction than for individual clinical abnormalities."

This concept that nerve conductions are important and signs trump symptoms, and therefore, the gold standard was the NIS-LL plus 7, which is, as you know, a composite score.

The most recent criteria from which we've been working on that I actually think work pretty well that Solomon authored from our meeting that Vera was kind enough to host in 2009, the Toronto criteria. This paper and that meeting categorized neuropathies into typical, length-dependent, distal, symmetric, polyneuropathy, and atypical neuropathy.

I will say that some people have said that painful neuropathy is atypical in the literature,

Page 163

which I find a little surprising because that's certainly clinically the most common scenario I deal with. In my practice, that's certainly not atypical.

These are the criteria which makes --

DR. DYCK: Which is not surprising because patients with numb feet aren't going to go to doctors.

DR. SMITH: Right, they're --

DR. DYCK: Patients with painful feet will go to doctors. So if you're calling typical versus atypical percentage of a community cohort who have signs of neuropathy, typical neuropathy would be painless, numbness, whereas if you're going to review patients who are going to come to doctors, they're going to be painful.

DR. SMITH: I would say that's not typical, that it's a matter of prevalence.

DR. DYCK: Or atypical --

DR. SMITH: Yes. I'm more or less -- I don't like the term "atypical" in this context.

DR. DYCK: I don't either actually, but I

Page 164

think it makes sense.

DR. SMITH: No, no. That's, I think, the foundation for the way that term is being used.

Here are the criteria, and then again, you're all familiar with. These are basically England-like in that they start with possible and go into probable and then confirm. So possible are symptoms or signs. Probable symptoms and signs that include two or more -- sorry for the "or" -- of the following, so "Symptoms, decreased sensation, or abnormal deep tendon reflexes."

This, I think, probably makes Steve feel pretty good that we can operationalize this. And then confirmed requires the presence of a confirmatory test. So nerve conduction studies are a validated measure of small fiber function.

The first problem, just to echo Dan, is that I don't think -- and I think Peter's study clearly showed it -- even amongst ourselves, we probably aren't very good at our reproducibility for individual exam metrics, and clearly, putting a reflex hammer in an endocrinologist's office and

Page 165

expecting reproducibility -- and this is no way an indictment of endocrinologists -- is just not going to work particularly well. So we need to think through these issues. I think neurologists have a hard time with that.

What about painful neuropathy? So the Toronto criteria really adopted the ISP definition of neuropathic pain with distal, symmetrical, nocturnal exacerbations, these characteristics and the following nested criteria.

DR. PELTIER: Gordon, can I make one interjection?

DR. SMITH: Yes.

DR. PELTIER: One of the issues also that comes up is -- and I think Peter or Jim, I forget which of you, published -- was that nerve conduction studies are not actually terribly reliable either. So people are better as far as within themselves, but if you compare one electrophysiologist to another, we're absolutely horrid at that, also, so looking at reliable confirmatory tests is also an issue.

Page 166

DR. SMITH: I'm going to touch on nerve conduction studies in some length, not the reproducibility, but just to comment on that, I think reproducibility in nerve conduction studies, particularly for a clinical trial and by extension for diagnostic purposes, really requires a great deal of attention. One can do it in a clinical trial. It's just quite challenging.

The idea that we're going to reliably deploy nerve conduction studies in a community practice to diagnose neuropathy, I think we're going to run into even bigger problems than we are relying on a reflex hammer.

I'm trying to think of an MRI joke I can use to get Brian --

(Laughter.)

DR. SMITH: In any case, I think there are several assumptions that I've alluded to in our existing criteria. I think the first is that signs are more reliable than symptoms, and I think this is a feature of what Jim talked about in terms of the typical phenotypic spectrum of free-range

Page 167

diabetic neuropathy patients where many of them are minimally or asymptomatic and therefore, signs by default are going to be the main metric we use.

On the other hand, patients who have painful neuropathy, small fiber neuropathy, will be lost using an over-reliance on signs. It's in some ways, the flip of what Steve was talking about in terms of complex regional pain syndrome.

There is this concept that nerve conduction studies are a very early, usually preclinical and core feature, which we'll explore in a moment, and that we talked a little bit about this painful neuropathy. I think this touches on the issue of whether painful neuropathy deserves its own diagnostic category or is it a subtype of distal symmetric polyneuropathy.

DR. TESFAYE: I think the painful neuropathy in the Toronto consensus is actually typical, typical. Atypical is the acute painful neuropathy. Actually, the painful neuropathy that occurs in the distal symmetric chronic varieties is typical neuropathy.

Page 168

DR. SMITH: You're right. So I think the way the Toronto paper reads is there's DSP, there's painful, and then there are atypical neuropathies. But I think what's happened is the term "typical" and "atypical" has leaked out into the literature in different ways and is interpreted differently.

To go to Amanda's point on nerve conduction studies, what are the data about diagnostic utility of nerve conduction studies and skin biopsy? So nerve conduction studies are abnormal at about 70 percent of patients, all comers with neuropathy, looking across multiple studies, not just diabetic neuropathy. Although they're frequently normal, maybe 40 percent, maybe even more in patients who have primarily small fiber burning feet.

Unfortunately, we don't really have good specificity data on nerve conduction studies. I'm going to show you some in a moment.

For skin biopsy, we have pretty good sensitivity and specificity data that are 70 to 80 percent, but there is an issue regarding diabetes. And this is also true with nerve

Page 169

conduction studies where patients with diabetes who have no clinical features of neuropathy, signs or symptoms, have reduced intra-epidermal nerve fiber density.

Is that nascent neuropathy? Is that laboratory neuropathy, or does that mean there's something else going on? I think it's unclear. And regardless of that, where we are now, it raises issues in terms of using tests like skin biopsy as part of our core diagnostic criteria.

These are data looking -- I'm going to show you two different sets of data that more or less show the same thing, and then I'm going to do a little bit of Bayesian gymnastics with it.

These data come from several pooled cohorts from cross-sectional and natural history studies that we've done in Utah. This is probably like 500 patients with diabetes. It's skewed towards early neuropathy, and it shows the ROC curves for sural amplitude, peroneal motor conduction velocity, and skin biopsy with two gold standards. One is the combination of signs and symptoms, and the other is

Page 170

the signs, symptoms, and a confirmatory test that couldn't be the test being evaluated, so keep that in mind.

For instance, for a positive diagnosis of neuropathy using sural amplitude, it would require one of the others to be abnormal. But they look similar, and you can see the areas under the curve are okay but really not that great. These are the sensitivity and specificity data, which don't look too bad, over here 70 and 76 percent.

Apropos of what I think we've been talking about earlier, the positive predictive values are dreadful, but the negative predictive values are quite good. So from a framework perspective, these are usually used as inclusion criteria.

This is sort of a tomato/tomahto [ph] thing, but one probably ought to think of nerve conduction studies if one were to use them in enrollment criteria as an exclusion. If it's normal, the likelihood of you having neuropathy just dropped a great deal.

This sounds great so far if we deploy it

Page 171

that way, but I'll get to the problem in a moment. This shows data from another cohort of about 150 people, I think, in this. These patients are categorized -- our gold standard of neuropathy is really based on signs or symptoms in a clinical evaluation by a neurologist. It's more qualitative.

Not surprisingly, the UENS and a symptom scale, the NTSS6, perform extremely well in that environment because we're using a purely clinically-based diagnostic criteria. But if we look at sural amplitude, peroneal motor amplitude, or conduction velocity, skin biopsy, and CCM metrics, you can see they generally don't perform particularly well, although sural amplitude performs actually best. I don't have predictive values, but I think it would look pretty similar to what we saw with the other data.

I think the point I want to bring up, though, has to do with something that Steve raised, which is the issue of pretest probability. So if we're going to use nerve conduction studies to

Page 172

exclude people who don't have neuropathy, we need to really think about the impact of the pretest probability of neuropathy in the group we're screening and the impact that has on the negative and positive predictive values.

We modeled this using the sensitivity and specificity data, and to walk you through it, this shows the negative predictive value of sural sensory amplitude. Let's just say 6 has a cutoff with different pretest probabilities. So the pretest probability in our cohort was 18 percent had a neuropathy, and you can see the negative predictive value was about 90 percent.

Here's what happens if 50 percent were to have neuropathy, and I would posit in the patients we're screening for a clinical trial, the pretest probability that they're going to have neuropathy is going to be a lot higher. So the diagnostic performance of these in an enrollment criteria setting or diagnostic setting even is going to be quite different, which is why I don't feel so bad about these data because in clinic, it's probably a

Page 173

lower pretest probability.
This shows it in tabular form. So I think this is something that, David, you wrote something awhile ago on this way of thinking in carpal tunnel syndrome, if I recall correctly.
I think we need to be mindful of it. We can't just slavishly use our standard cutoffs in clinical trial enrollment criteria without at least thinking through this concept.
There was a remedial trip to Rochester, Minnesota. As I recall, a year later, we came back, and there was a really big snowstorm. The Mayo Clinic actually was amazing. They sent people out to bring these patients back again, and we did the same study one more time with one difference. We met the night before and had a discussion about how we were going to judge whether or not the people had neuropathy.
We weren't given a set of criteria, but the concept was that we were only going to capture unequivocal evidence of neuropathy. There was some specific discussion about how to factor in age in

Page 174

relation to ankle jerks and vibration assessment. That conversation, which wasn't very long, and I've got some lovely pictures of people like Peter showing us how to check ankle reflexes on people using one of the Mayo examination tables, we did much better. In fact, these statistics all improved dramatically, which is, I suppose, good news in that it took relatively little intervention to bring us along, but it still feels sort of MacGyver'ed to me that we scotched taped this thing together with agreeing on unequivocal.
Then, of course, the issue that Rob brings up I think is important because this may not capture patients who have earlier or milder neuropathy, so keep in mind that issue.
In terms of the core diagnostic criteria, painful DPN, there is another ACTTION paper in process that is delayed by a particularly slow co-author, I'm told, to remain nameless.
(Laughter.)
DR. SMITH: That will be coming up very soon after this meeting, I think.

Page 175

DR. FREEMAN: Just to let you know, the aspects of that paper are --
DR. SMITH: But the author will catch up.
I think as a general construct, the Toronto criteria work very well, and I think they have attributes that we'll be able to pull out in service of a taxonomic scheme at the end of this meeting.
I do have concern about using a structured specific instrument as part of these criteria for reasons that have been brought up, but I think the individual components make sense.
I have a lot of concern about how we deploy nerve conduction studies and skin biopsy. I didn't show skin biopsy data. It looks the same as nerve conduction data, the same issue as very poor positive predictive value, very good negative predictive value. Looks very similar.
So I think there are real concerns about how we do this, and I'm sure we're going to have a robust discussion about it. I'm not going to get into that now.

Page 176

The other issue that I haven't talked about is dealing with other causes of neuropathy. This is one of the other axes we need to think about. It's very common for patients who have diabetes and neuropathy to have other common risk determinants, so alcohol use, for instance, or other issues. So it is likely that we're going to need to include not only the safety clause that Steve advised us to use, we may want to have a little more specific safety clause in reference to that. I'm not really talking about that at all.
I think the other issue, of course, we have to deal with is the prevalence of idiopathic neuropathy, which is quite high, phenotypically looks like diabetic neuropathy. This starts to abut against Rob's definitive talk coming up later today, and it's going to answer that for us.
What about lifespan issues? I think this goes to subcategories of neuropathy. Jim already brought this up. Most patients who have neuropathy have a relatively painless neuropathy. Now, we have in our mind that this may occur later in the

Page 177

course with years of hyperglycemia and may have more motor conduction velocity abnormalities, whereas earlier, we see painful neuropathy due to small fiber involvement. Then there's asymptomatic neuropathy, so this concept of abnormal nerve conduction studies or abnormal skin biopsy. There's another I'll get to in a second.

Now, I'm going to challenge that a little bit as we go along, and I think we have a bit of anchoring bias in this scheme that I think we really need to take a close look at.

Then in terms of painful neuropathy and core clinical features, there are a variety of different symptoms our patients have, and I think part of the challenge in defining painful neuropathy is many patients who don't have painful neuropathy, yet have symptomatic neuropathy have milder versions of this that they don't self-describe as pain. You can look across these, and they'll all be familiar.

There are, of course, significant comorbid conditions which touch on Dimensions 3, 4, and 5, including depression and anxiety, sleep

Page 178

disturbance. I'll get to those in a moment because they're not only important in our full framework, but they probably have impact certainly on how we design clinical trials.

This is a screening tool slide similar to the one that Jennifer and Chris put together showing the frequency with which various positive neuropathic symptoms show up in commonly used neuropathic instruments. The gray boxes show when they're used in more than three instruments, and the lighter gray, two.

I bring this up in part just to emphasize the challenge in reading the literature because we're hostage to the instruments that had been used in earlier studies. I think this is an issue that supports Dan's contention that I think we need to take a fresh look at this, and I think it's probably true in symptoms. I think it would be very interesting to know in an authentic starting from scratch approach, what are the distribution of symptoms, the frequency of symptoms, do they differ between type 1 and type 2 and other forms of

Page 179

neuropathy.

The other concept that was implied in a couple of slides ago is that early neuropathy is painful and later neuropathy is more large fiber, loss of protective sensation, foot ulceration. Clearly, foot ulceration and amputation, which I'm not going to talk much about because it's such a distal endpoint, it's clearly related to longstanding disease.

I think the question is this shift, as I'll show in the next slide, from early small fiber, later large fiber, something we need to think about. One of the reasons I think we have this in our mind is that 10 or 20 percent of patients who have diabetes have evidence of neuropathy at diagnosis, and then there's a whole separate narrative around pre-diabetes.

I think what tends to happen is this idea that we lay on our clinical experience as an anchoring bias of thinking of this. So the idea is that type 1 diabetes, which I think has informed historically some of our concepts of neuropathy,

Page 180

natural history, and risk, obviously related to hyperglycemia, gets worse and more prevalent over time, and it involves mainly large myelinated axons, which also happens in type 2 diabetes. But there's this separate issue of metabolic syndrome and obesity, which we think may cause more small fiber injury, therefore, earlier pain. These kind of merge together to make type 2 diabetes look somewhat different than type 1 with earlier small fiber involvement in pain, later more large fiber involvement, and ultimately, risk of painless injury, foot amputation, and so forth.

This makes some sense, but it's anchored in our clinical experience, as Jim pointed out. Patients who don't have neuropathic pain generally don't come to see a neurologist and say I'm worried that I have asymptomatic neuropathy. So I think we need to really think about this in a fresh way. I'm not sure it's really true, but there are reasons to think that aspects of it might be.

I did want to talk a little bit about the physiology of these different fiber classes. Large

Page 181

myelinated axons -- this is Theodor Schwann -- obviously, have fast conduction velocity, but they are also relatively protected from the environment by their myelination. Yet when injured, it's difficult for them to regenerate for fairly obvious reasons whereas unmyelinated axons -- this is a picture of Robert Remak -- seem to be particular susceptible to injury, yet they're uniquely capable of regenerating.

Ahmet brought up the question this morning of the natural history of epidermal nerve fiber density in early diabetic neuropathy, and several groups have found that there's a decline in epidermal nerve fiber density in early neuropathy. Our work and others suggest that interventions can actually provoke improvement, stabilization, and this biomarker.

This also, I think, serves as part of our anchoring bias for the concept I showed in the earlier slide. It certainly has implications for the endpoint measures or the biomarkers we might use in clinical trials, but it has mixed

Page 182

implications for how we might deploy skin biopsy, for instance, which we're never going to do, but were we to in diagnostic framework. CCM is actually much more conceivable at least from a patient compliance and tolerance perspective that we might do that, yet the equipment is expensive and so forth.

I think there's data to suggest that this whole framework I've given you is perhaps not true. This is a recent study looking at sensory phenotypes and risk of neuropathy. If the framework I gave you was true, we would expect that there would be a disconnect between objective severity of neuropathy and the presence and severity of neuropathic pain.

It turns out that there are multiple studies suggesting that's not the case. So this shows in a very nice paper that just came out earlier this year, this is the modified Toronto scale looking at no neuropathic pain, mild, and severe. There are other studies that show this, that as we look at patients with diabetic neuropathy when they have

Page 183

more pain, they have more severe neuropathy.

Again, we have our preconceived notions, and in the past, I think we've tended to argue back and forth about this. But I think these data make me really want to understand for certain what the natural history of this is. Clearly, the implication is the patient who has painful neuropathy or neuropathy that's not painful but has dominant positive sensory symptoms, is that a different disorder from the silent majority that Jim talks about of painless diabetic neuropathy? Are those different? Are they subtypes?

I'm not going to get into that right now, but it's something that we need to hash out in our discussions. I'm going to skip over that in the interest of time.

Epidemiology -- I don't want to skip back over that because I think it's really neat. The concept here is that what may be determining pain is less axonal loss but axonal regeneration. This is, I think, work from Dan's group, that looked at GAP 43 staining and in skin biopsies and showed

Page 184

that essentially patients who have a higher percentage of epidermal axons in a regenerative phenotype have more neuropathic pain.

We found something quite similar in collaboration with Eva's group a number of years ago. So I think there are other reasons to think about or other ways of thinking about neuropathic pain.

I wanted a slide that color, and that was just to show Doug that we do a little bit of discovery science in what we do.

The epidemiology is something that I don't need to emphasize too much to you. This is a worldwide epidemic. Over 8 percent of Americans and Europeans, yada, yada, yada; you know all of that.

I did want to show this because diabetic neuropathy is a global health problem, and this shows the prevalence of diabetes in 13, projected in 35. It shows the growth by region, and this displays that visually.

The reason I show this is if you think it's

challenging to get primary care doctors in the UK or in the United States to use nerve conduction studies or use their CCM machine or do a skin biopsy, I think we need to be mindful in what we're doing that this is an international exercise, and that the criteria we're developing, at least base criteria, ought to be applicable in Africa or the western Pacific, or other places that may be more resource limited.

So I think it's fine to have biomarkers that we'll use in clinical trials and in parts of the world that have access to those tools, but we ought to be thinking about how one can go about diagnosing reproducibly neuropathy and following it from a clinical perspective using tools that are easily deployed in resource-limited environments.

I personally haven't been in discussions or heard people talk a lot about this, but I think it's important thinking of this as a global health issue. I think I would be remiss sitting in Washington, DC not to recognize that global health is right outside our front door. As James sees in

his patients from east Baltimore, we don't need to go to Africa to see these resource-limited environments. We have them in our cities and rural areas right now in this country.

What about common medical comorbidities, going to Dimension 3. Some of these are self-evident, and I'm not going to belabor them in terms of metabolic risk, which I want to remind you Rob is going to definitively solve later today in a highly anticipated talk.

DR. SINGLETON: Tomorrow.

DR. SMITH: Tomorrow. So we're going to be awake all night waiting for the answer to the questions that I raise.

I want to point out one issue -- or two issues. One is the role of the central nervous system in diabetic neuropathy, and a related issue, depression, anxiety, and sleep disorders.

Clearly, cerebrovascular disease and what appears to be an increased risk for CNS nerve degeneration probably impact the way in which patients experience neuropathy and the way in which

we might measure it. It's possible that these in part underlie some of the other behavioral or mental health issues.

I promised Brian I was going to display to him the role of MRI scan in diagnosis of neuropathy, and so this is from Solomon's group. But there is a literature now looking at what's happening in the brain in patients who have neuropathy, in particular painful neuropathy. Solomon can explain all of this to you, but this is looking at areas of differential cortical atrophy in patients who have peripheral neuropathy.

These are probably secondary effects, but we also have independent things going on in the central nervous system, both in terms of vascular problems and also in the neurogeneration that we're just beginning to scratch at. Thos I don't think are going to be in our core diagnostic criteria that Roy tells me we're going to have at the end of tomorrow, but it's something that I think deserves a lot more study as we try to understand covariance in terms of the neuropathy experience and how we go

about measuring it.

I'm going to skip this, and just show this is a recent summary from Dan's team about risk factors and the level of evidence. The reference is on this slide, and here are the references underlying it. They did a very nice job looking at the roles of various risk factors, and obviously, diabetes duration and hyperglycemia, age are large determinants. But there are many other of these that are risk determinants, and I think in talking to Brian over the break, one of our real challenges is, is obesity a risk determinant? Is it a separate pathway? What do we make of idiopathic neuropathy patients who have obesity? Is that really the same as type 2 diabetes and whatnot?

I won't go through all of these, but I do want to spend a little bit of time talking about genetics because I think this is a critically important area. There are clearly generic determinants of risk in diabetic neuropathy, and this is just a table of them.

My read of this literature -- and there are

Page 189

people in the room who know infinitely more about this than I do -- is that these are of modest impact in terms of risk for neuropathy. So looking at single gene variants and polymorphisms, they don't really individually confer a great deal of risk.

Now, there's not been a lot of work looking at the more complicated systems-based approach, but there are a few indications that this is at least useful from a mechanistic perspective. I think the biggest and best really comes from Eva's team where they looked at sural nerve biopsies, categorized them into progressors and non-progressors and did a really fantastic genetic and bioinformatic study that essentially came up with 530 differentially expressed genes in progressors versus non-progressors that really conformed to several different themes, lipid metabolism, immune response and inflammation, and axogenesis.

Others have done this with smaller numbers of patients. There's a micro RNA study that came up with the same sort of thing. This was looking

Page 190

again at smaller, I think about 12, nerve biopsies from an available database in progressors and non-progressors.

Then an even smaller study just recently published looking at, I think, 6 patients with and without neuropathy, suggesting that there were differences in gene expression and multiple steps in the pathway for neurotrophin MAP case signaling.

I think these sort of analyses are going to be much more informative than going on a hunt for monogenic influences of neuropathy risk, and I don't think we're at a point where this literature is able to drive our enrollment in clinical trials. It's certainly informing our understanding of mechanism, and clearly, more work is needed there.

Now, what about functional consequences of neuropathy? So obviously, these are enormous. There's enormous costs associated with neuropathy. Older data suggests about a quarter of direct healthcare costs attributable to diabetes are spent on neuropathy-related complications and outcomes. Painful neuropathy is second only to amputations in

Page 191

terms of impacting quality of life in neuropathy.

I wanted to comment on a couple of other issues. First, gait, and we don't spend a lot of time talking about this, but it turns out to be an enormous issue for our patients. So diabetic neuropathy have a three to five times greater risk of falling, and as I'll show you in a moment, there are multiple contributors to this, including sensory loss, loss of strength, joint and range of motion, and certainly, central nervous system determinants like I had talked about earlier. It turns out that abnormal gait is strongly associated with depression, and the opposite is true as well.

This just shows in a study of about 170 patients the difference in various measures between those who had neuropathy and those who did not. You can see there are changes in strength, range of motion. The ABC score is a score of balance confidence essentially, and it's a good metric for fall risk. You can see that there's a significant difference in the ABC score in those who have neuropathy and those who don't. This leads to a

Page 192

higher fracture rate and clearly is a main driver or one of the main drivers of reduced quality of life. It's something that we don't often think about and all too often isn't measured in clinical trials.

This is actually a nice example of this relationship between neuropathy severity and balance. This is the MNSI, which we're all familiar with, and the BERG Balance Scale. It just shows a scatter plot on a cohort of people with diabetes, and you can see that there is a clear relationship.

What's particularly interesting is this is sort of the threshold for overt neuropathy, and it really intersects nicely with the threshold of BERG Balance that predicts a moderate risk of fall. But you'll see that even with very low MNSI scores, the risk of fall increases, and those in this quadrant have a significant increase in fall risk despite mild neuropathy.

I think James published a long time ago that patients that have pre-diabetes and neuropathy,

Page 193

which we think of as being small fiber predominant and milder in terms of proprioceptive dysfunction, have very significant abnormalities in sense of postural position and so forth. I think this going back, this challenges our concept of the time evolution of diabetic neuropathy.

This is actually an interesting paper that looked at the relationship between functional status and quality of life, and it's basically a mediation analysis that shows that not only does diabetic neuropathy directly change in quality of life but measures such as the 5 times sit to stand mediate change in quality of life through measure of balance confidence with the ABC scores.

These are important determinants, and I can tell you that we're starting a trial in metabolic syndrome-associated neuropathy. We're using a timed up and go as opposed to this with an ABC score, which will be interesting to see how those perform in a clinical trial setting of a disease-altering agent.

I think the last issue before I start to

Page 194

wind up is that of anxiety and depression. There's a 50 percent relative increased risk of depression in patients who have neuropathy. It's actually work from Brian that is similar between those who have CSPN or idiopathic neuropathy and those how have diabetic neuropathy. Fifty percent of patients with painful diabetic neuropathy have depression or anxiety, and a quarter have both of these.

These really, and pain, as I pointed to earlier, are really drivers of these issues. They almost certainly are going to impact outcomes in clinical trials and something that one needs to be mindful of.

This is data from Bruce Perkins looking at long surviving type 1 patients. These are patients who've had type 1 for, I think, 50 years, very long survivors. It looks at two measures of depression, essentially. This is a measure. The pain score is a measure of distress, and this is the Geriatric Depression Score. The point here is that while painful neuropathy patients are more depressed, are

Page 195

more distressed than those who don't have neuropathy, non-painful neuropathy patients also have increased levels of distress and of depression. So it's not purely pain that's driving this. It's probably gait or perceived gait and balance issues, and other issues that are probably incompletely explored.

I think really the concept behind this is that there are probably if not different forms of diabetic neuropathy, there are different phenotypes, and there are probably micro phenotypes that really we ought to be thinking about in service really of personalized -- not only personalized medicine but personalized clinical trials.

We've started to do this in a very crude way in just thinking of type 1 versus type 2, duration of diabetes, whether or not patients have particularly severe neuropathy, and other measures here. I wanted to talk a little bit about neuropathic pain, though, and Solomon actually brought this to my attention. I was familiar with

Page 196

these articles, but he sent a few of them. He sent -- you sent four, and I actually had read a couple. I read the others, so I think there's a modification to your rule. If you've read two and you get four, you'll probably read them.

The idea here is that in the neuropathic pain literature, there is indication that one can use pain phenotyping to predict response or that pain phenotyping might predict response. So this is one trial of oxcarbazepine in neuropathic pain that shows that the response was much better in those who had an irritable nociceptor phenotype.

This is the early phenotype that I was alluding to earlier with neuropathic pain in the absence of small fiber dysfunction as opposed to non-irritable nociceptor where there is axonal loss and pain as well.

There are other studies suggesting this. One that I think is particularly nice is Solomon's COMBO-DN trial, which just to remind you, randomized patients to duloxetine or pregabalin. Then those who did not respond where randomized

Page 197

then to either an increase in dose, a high dose duloxetine, a high dose pregabalin, or combination therapy.

Then the take-home point was I think duloxetine did a little better and combination therapy did better than high dose monotherapy. But very soon after this was published, they went back and looked at a cluster analysis of pain phenotypes, which really seemed to inform the response to therapy. I won't get into the details and Solomon can tell you about it if you have questions, but I think this is an interesting idea that I think also supports Roy's notion that we ought to take an unbiased look at our data.

Here, this is taking a look retrospectively at data, but one could imagine that ultimately, we may do clinical trials in neuropathic pain in diabetes either specifically in subtypes or stratifying in these different subtypes of neuropathic pain categories. There may be a similar lesson in thinking about diabetic neuropathy more broadly.

Page 198

Right now, when we do disease-altering trials, if you have severe pain, that's great. If you don't have pain but you meet the neuropathy criteria we're using, great, whatever. It may be that we need to be more thoughtful or at least go back and look at the response to therapy in different disease categories, not just duration of disease or how early, but different phenotypes. Clearly, the neuropathic pain literature suggests this might be a fruitful endeavor.

I'm going to ignore the conclusions because I made them on the airplane, and they're meaningless. I have a couple of attribution slides.

This is the first two generations of Michigan diabetic neuropathy. I show it more as a statement of gratitude to Eva and Rob and James and Rodica and then the rest, and then of course, I think we all owe Chris --

(Photo shown.)

(Laughter.)

DR. SMITH: -- an enormous debt of gratitude for taking this on. I think this was a selfie when he was getting ready for the meeting, but it's turning out really well.

(Laughter.)

DR. SMITH: With that, I'll end because I'm the only thing between you and lunch.

(Applause.)

DR. FREEMAN: I think that's an appropriate segue into the obligatory photo, so put on your best faces, see if you can reproduce or how reliable Chris can be with regard to reproducibility of his image.

Rodica, can we use your camera?

Carlos, how steady is your hand?

Why doesn't everybody come up? I think probably this is the best place to do it. The light is reasonable.

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

Page 199

Page 200

A F T E R N O O N S E S S I O N

(1:03 p.m.)

Q & A and Panel Discussion

DR. FREEMAN: The figure ground separation is not clear at all, in fact, barely visible. Now is the time when the figure ground separation becomes a little clearer.

Can I get the first slide, or are you going to do it for me?

This is the reminder. The reminder is at the end of this meeting, we are going to need to come up with something like this. "Every patient entered into a research project, be it a drug trial or study of pathophysiology or biochemistry, must fulfill a set of diagnostic criteria."

We need the diagnostic criteria. We need Dimension 1, the core diagnostic criteria, and it's got to look like something this. The formatting is gone. We'll improve on that, but it needs to look something like that. This is the menu, and we're going to need to come up with something.

We do need to leave this meeting with that

Page 201

framework, and there are several possible approaches, which Gordon introduced. One might say he punted a little, but he almost got there.

(Laughter.)

DR. FREEMAN: In terms of the approaches, there are really several. I personally think we should actually do more than one of these and perhaps all of them, but I want you to begin to think in these terms.

There is the possible, probable, definite -- I prefer clinically confirmed just because nothing is ever definite, which is one approach -- one approach which the Toronto criteria are used, not in quite the way that I would like them to be used, but at least used. There's the preclinical, subclinical, mild, moderate, and severe, and there is the small fiber, large fiber, and mixed.

Why I think that we should consider doing more than one of these is just imagine you have somebody, for example, who is interested in looking at NAV 1.7 polymorphisms in patients with small

Page 202

fiber diabetic neuropathy or diabetic neuropathy with predominantly small fiber features. We want to give them the criteria that they can use.

If somebody wants to do a study on the likelihood of developing ulceration and amputation, we want to give them the criteria for severe diabetic peripheral neuropathy. So I think more than one of these approaches may be required.

Then the settings, we need to think in terms of the settings, and this has come up, but we haven't concretized this yet. Tertiary care centers where there will be QST and corneal confocal microscopy and nerve conduction studies and autonomic testing versus the field, Central Africa, where we would like them to have criteria for diabetic neuropathy and all of the range in between, a multicenter trial for disease modification in diabetic peripheral neuropathy where there may not be corneal confocal microscopy or autonomic testing.

Epidemiological studies, cohort studies, case control studies where perhaps the criteria may

Page 203

not, if we think of the continuum from signs to symptoms to special investigations, be quite as rigorous, may not be quite as specific.

Components of the menu. Symptoms, which symptoms? Signs, which signs? Special investigations, which special investigations? Then finally, and this is the heavy lifting, the menu that Gordon is going to include in his manuscript, which I remind you, is going to look like that.

So that's the setting. That's where we are. Let the panel begin.

Eva, you're in the corner there. Why don't you start?

DR. FELDMAN: Could I suggest then -- and I guess you're probably not going to like this, but I think we could divide up in three or four smaller groups and each take one of those. Our expertise is fairly homogenous, I mean fairly homogenous, and we could probably in an hour have migraine with aura 1.2.

We could actually produce, get real documents done if that is your goal, or is your

Page 204

goal now just for all of us to continue to talk about it?

(Laughter.)

DR. FREEMAN: I would like --

DR. FELDMAN: I mean really because we could -- this is too big of a group, I think. If you wanted to do all of that --

DR. FREEMAN: I think that's a very reasonable point. What I think we could do maybe is to make sure that we are on the same playing field initially, and as you put it in such a denigrating fashion --

(Laughter.)

DR. FREEMAN: -- I think we should talk about it.

DR. FELDMAN: I wasn't being denigrating. I was just --

DR. FREEMAN: No, I take --

DR. FELDMAN: ACTTION, isn't that our acronym?

(Laughter.)

(Crosstalk.)

Page 205

DR. FREEMAN: I think that's a great idea. Is everybody onboard with that, by the way?
DR. SMITH: We talked a little bit about this. I think to do that before hearing Rob's presentation puts us at some disadvantage.
DR. SINGLETON: I actually was going to say -- I think that's true, but I would actually say I'm going to advance the idea tomorrow that the phenotypic diagnostic criteria for metabolic syndrome neuropathy, pre-diabetic neuropathy, are basically identical to the ones that we'll choose for diabetes.
DR. PELTIER: Which type? I guess that's the first --
DR. SINGLETON: Type 2 diabetes. If we're going to have two, but I say that because I think spending time, as Eva's suggesting, in actually hammering these out will save time later, for me at the very least, because I suggest that we're going to -- it won't be that different, if at all different.
I really like the idea, Roy, that you have

Page 206

of those different forms of this. I think have one that's a form of diagnostic certainty because I think we need that. Having one that's a form of severity because that's really what we're talking about, those two aspects when we consider diabetic neuropathy versus metabolic syndrome neuropathy. They are undifferentiable in terms of their phenotypes. What's different is the attribution of the neuropathy.
DR. FREEMAN: I think that that's fine. So are we on the same page that we can actually do this without hearing Rob's talk, and we can make life easy for him?
DR. SINGLETON: Again, what I'm going to talk about tomorrow is not about the phenotype. Small fiber versus large fiber, I think there's room for that discussion a little bit. But mostly what I need to do, I think, is to get consensus from this group that there is such a thing as pre-diabetic neuropathy, that the attribution is sufficient that you guys think that that's something that we can talk about.

Page 207

DR. FREEMAN: You think that it will be -- if things go according to your plan, it will be on the continuum, and we might as well decide this --
DR. SINGLETON: That's right, right.
DR. FREEMAN: -- these different pies today. I'm totally fine with that. But I think we should talk a little bit about the component so that when we break up into these small groups, and we can decide how many small groups we can break up into, we're actually going to be, to some extent, on the same page. But I do love the suggestion.
I want to go back to this just a little because I broke this down really into three separate approaches, the level of certainty, as Rob said or said something like that --
DR. GIBBONS: Roy, they're going to get very upset in the back when they can't copy your speech.
DR. FREEMAN: The level of certainty, the severity continuum, and then the phenotype. Those are the three, but I've made them discrete. They're actually not -- they're not really separate

Page 208

because each one of those apply. Level of certainty with severity is quite important, too.
I think we need to have some kind of discussion on that and then also some kind of discussion on the components because those are going to be common. If signs, which signs? If symptoms, which symptoms? If signs, which signs? And if special investigations, which special investigations? What role do they play? How do we incorporate it?
I think it would be good to do this in the room rather than come up with something that may not quite mesh.
Having set that stage -- and, Eva, I'm glad I asked you first because I think that's a great suggestion, first of all, anything else to say?
DR. FELDMAN: Let me understand one point, and that is, what you're envisioning is that we actually come up with a set of diagnostic criteria for possible, probable, clinically confirmed separately for preclinical, mild, moderate, severe separately for small fiber and large fiber. And

Page 209

then we look at these in aggregate and see if we can agree upon one set of diagnostic criteria.
Is that the idea?
DR. FREEMAN: I think that would be the easiest way to do it.
DR. FELDMAN: I do, too. I do, too.
DR. FREEMAN: I think we can then mix and match if we wish, but I think that would be the easiest way to do it.
DR. FELDMAN: I actually really agree with you because I think we'll get a lot of very good input, and one group will think of something that another group has not.
DR. FREEMAN: Sounds good.
DR. POP-BUSUI: I have a question. So what is the evidence that we are going to use when we are going to make these decisions? Because that's actually very important to decide --
DR. FREEMAN: I think all of our --
DR. POP-BUSUI: -- is going to be again our expert or --
DR. FREEMAN: I think Gordon is going to be

Page 210

our resource on what the evidence is, and I think all of us know the studies. But one of the points that I didn't make, which was at the end of the study, we want to come up with something, as I say, something definite, and part of it is going to be evidence based. Some of it is going to be consensus. Some of it is going to be expert based. But it must be testable and refutable so that going forward, we can say, you know, we decided that sensory distortion should be one of the symptoms or allodynia should be one of the symptoms. That didn't work at all. We should drop that.
I think we want this to be a testable set of hypotheses, and that's absolutely critical to the process.
Any other questions?
DR. POP-BUSUI: But then we will have to have a way to test, right, because we need to derive a set of criteria based on evidence, let's say, obtaining a particular setting, whether it's a trial, whether it's an epidemiological observation, and see how reproducible that type of definition is

Page 211

in a completely different population. That's the way we have to do it. I think there is a lot of data there, but we have to agree how are we going to use the data.
DR. FREEMAN: I think we have a lot to do at this meeting. I think what I would prefer is in the discussion that we have at the end of the meeting is next steps, going forward, how are we going to test? What kind of studies do we need to do? How's the DNC going to do this, or whatever we're calling ourselves. How is CONCEPPT going to do this? What are the ways forward?
But I think at this point, we're going to accept that we have a good sense of the literature; that where we don't, we have opinions; and we're going to have to come up with something, and then we'll move forward on that.
DR. POP-BUSUI: I agree. One more small comment regarding the settings, and I completely agree that, yes, there are tertiary centers that have much more resources in general. But I think that we should not forget that diabetes care is

Page 212

extremely expensive even in countries like ours or western Europe. So we have to be also pragmatic here and take into account what does it cost just to treat hyperglycemia today and how complicated it is for providers to think about 15 classes of agents, for instance, that are available to treat hyperglycemia as well as other risk factors.
I think that we should think about it not only because diabetes is such a prevalent condition throughout the globe and there are countries that have not the same economic power, but even here in U.S., it's actually very expensive to treat diabetes. The access to care or diagnostic procedure, also, it's extremely not equal among nations.
DR. FREEMAN: David?
DR. HERRMANN: To add to that, I would agree with the approach that you're taking in terms of defining the phenotype according to those dimensions, but the other thing one might think about from a diagnostic approach is just to also come up DPN-1, which may be type 1 diabetes being

Page 213

the precursor to the phenotype; and then DPN-2, perhaps, adult onset diabetes in the context with that metabolic syndrome; and then DPN-3, adult onset diabetes with metabolic syndrome. So that you might have three or four types to put the phenotype in the particular context, and then that could be used or selected from for a particular trial.

DR. FREEMAN: I think that that's fine. But I think that that is subsumed under these groups.

Solomon, any --

DR. TESFAYE: I think that is perfectly reasonable.

DR. FREEMAN: Gordon?

DR. SMITH: I think what David said is really important. We're starting this NeuroNEXT trial in cryptogenic neuropathy in patients who have metabolic syndrome, and we self-made our criteria. But there was a lot of negotiating with NINDS and others about the boundaries.

For instance, we said patients initially just with neuropathies in the Toronto criteria who

Page 214

also had metabolic syndrome. Then someone said, "Well, what if they're non-obese?"

Then we said, well, okay. They need to be obese with metabolic syndrome. We've created criteria for the individual trial, but to your point earlier, the next trial may choose a different BMI cutoff for obesity.

Maybe they use waist circumference, and I think these things become really important. And maybe that isn't something that we need to decide right now, and that would come after Rob's discussion tomorrow. But I think defining particularly -- type 1, type 2 take care of themselves, but the pre-diabetes, obesity, metabolic syndrome discussion, I think, has some important granularity to it to achieve the objective that David talked about.

DR. FREEMAN: The way I would envision that is clarification notes where all of these secondary aspects come into that, and being, again, as prescriptive as possible.

Stephen?

Page 215

DR. BRUEHL: I just wanted to throw out something to think about here. One of the issues that we encountered with CRPS as a reaction to the definition of CRPS in the new criteria was clinicians would come back to us and say, well, what about the people that I've always diagnosed CRPS that have X, Y, and Z but are missing this factor? So they don't receive the diagnosis anymore.

That is an uncomfortable conversation to have because -- and my only response is, well, we've defined it differently, so they don't have it. That's not terribly helpful.

The example you just brought up was a good example of what can happen. You keep adding on more criteria, and eventually, you define it so narrowly that there are large sets of people that might not get it. What are we going to do about those that don't fall into that category now? Just something to think about.

DR. POP-BUSUI: This is actually a very important point, especially when it comes to

Page 216

clinical trials because if you make our criteria too granular, then we will never enroll our patients for trials. That's why it's so important to do it right.

DR. BRUEHL: I agree, and one option, kind of the in-between option, which we used, was to have the set of clinical criteria that are less specific so we capture more of those people, and then a specification that doesn't change the underlying criteria. It just changes the decision rule to narrow it down a little more for clinical trial purposes.

DR. SMITH: That was a question I have, is can you nest these, right? So what you just talked about is having a classification that may create, let's say, presence and severity with a measure of certitude built underneath that, if I'm understanding correctly.

DR. BRUEHL: I don't like the levels of certainty idea in diagnosis because to be clinically useful, it really needs to be dichotomous. You force it to be either a yes or a

Page 217

no. Traditionally, that's the way it's done.
Now, if you wanted to be a little different, you certainly could have some limited type of ranking of probabilities. It wouldn't be my preference because it makes things like trying to determine reliability if you were to try to test that, makes it harder to do because then what -- if you have somebody who's probable, do you count them in the definite or non category if you're trying to determine reliability of diagnosis?
DR. FREEMAN: Vera and Brian.
DR. BRIL: The comment again is the setting, right? If we want to impact the greatest number of patients with diabetes, we will use a simple screening method, something like we did, normal or abnormal. You have it, or you don't.
This is what we did years ago when we used the pinprick or the tuning fork to try to detect neuropathy present or not, with all the issues around, and very simple yes-no answers to get the diagnosis in the greatest number of people no matter how specific it is, but just to get the

Page 218

diagnosis. But then as you step up, you get into the other things. Because if people are not taking footwear off, they're not asking about symptoms, and they're not examining. Mostly, they're not diagnosing unless it's a painful patient that has brought themselves to attention.
That's why the simple screening study we did was important for the large majority, I would say, of diabetes patients, if people actually use those screening methods, but otherwise, all of this is more into endocrinology clinics, neurology clinics. And we all know what we would be asking the patients and what we would be examining because we all pretty much do the same thing.
DR. FREEMAN: I think if we take Dan's point, which I think many of us do, I'm not so sure. I do think that in some way, we need to combine the setting -- doing the study in Central Africa -- [inaudible - off mic] -- look at those three groups and I accept Steve's point about dichotomy being ideal.
DR. GIBBONS: To the microphone, you're not

Page 219

getting heard.
DR. FREEMAN: Okay. So I accept Steve's point about dichotomy being ideal, but I think each one of those three approaches should be shaded by the setting. If done in setting X, then this is what would be; however, if done in Central Africa, then.
Dan, then Brian.
DR. ZIEGLER: I think that that's a fundamental question. The question is whether we add clinical practice to the settings or not, because as it stands now, it's research. In the clinical practice setting, what Vera is addressing, is a fundamentally different scenario. But I agree that we should address that.
We should give some recommendation or whatever or statement about what is appropriate for screening and what is appropriate in the clinical practice setting because that is --
DR. FELDMAN: Could I say something? Isn't that we just did? That is what we just did with the ADA criteria.

Page 220

DR. ZIEGLER: Yes, that's what we did. The question is whether we want to repeat that in this --
DR. FELDMAN: No, I don't think so. I think the whole goal of this meeting -- I feel like we're mixing -- we're losing our focus or our goal.
DR. POP-BUSUI: I agree.
DR. FELDMAN: The whole goal of this meeting was to come up with a taxonomy, very specific definitions primarily for tertiary centers, multicenter trials, drug trials, epidemiological trials. So this is more of a research goal or focus.
We did a very nice job, I think, with the ADA criteria for the clientele, for the population you're discussing. I don't think we can easily do both in a day and a half here.
DR. POP-BUSUI: I also agree with that. I think that our scope right now, if we want to get out something of this two-day meeting, is to try at least to understand what are the best criteria for research studies, whether they are epidemiologic or

Page 221

they are clinical trials, and come up with a set of measures that can be applied even in 10,000-patient trials in a standardized and approachable way.

Once we identify these methods and criteria and we see that they indeed have a lot of validity, then we can think whether it's needed to rethink the clinical practice recommendations, but there is no point to try to overrule everything right now because, in fact, you don't have anything to offer those patients, whether you are going to propose very expensive evaluations or not. The standard of care of diabetes, it's not going change.

DR. RUSSELL: Couldn't we maybe take a vote? Can we take a vote and see if we all agree that we should just have clinically confirmed and that's what we should focus on as part of this meeting? So in other words, if this is going to be research criteria, we should decide on focusing on clinically confirmed.

DR. FREEMAN: Typically, clinically confirmed with a special investigation. That's the confirm. That's the so-called definite, so not

Page 222

just symptoms and signs. The standard approach is possible signs, probable signs plus symptoms, clinically confirmed with a special investigation, whereas I do think this is for research, but I think it's research epidemiology and not only research multicenter trial and research tertiary care center.

I don't know if epidemiology Central Africa, which I do think this must play a role in those kinds of studies, I don't think they're clinically confirmed. That would be my view, but let's hear what others think.

DR. ZIEGLER: Epidemiology can never be confirmed. I think the simple question is whether we restrict our research or not, and we can vote about this. My feeling is that the majority feels that it should be restricted to research.

DR. TESFAYE: The ADA criteria as they stand focused on clinical exam in clinical practice to diagnose neuropathy, but the problem we have in clinical practice at the moment is we're under-diagnosing the patients. So we're not doing

Page 223

a good job of -- we're diagnosing in about 10, 20 percent of patients' neuropathy using very crude measures. And that's not fit for purpose when you compare it with retinopathy now with digital camera. You can achieve precise -- in the old days, we used to fiddle with the ophthalmoscope, and we didn't know what we were doing, but now in the UK, everybody undergoes retinal photography annually, and you diagnose the condition in a much higher proportion.

The clinical practice that we are engaged in at the moment and is actually using monofilament, is useless. It's diagnosing the patients at risk of foot ulceration, but it's not diagnosing the condition early, which is what we want. So the clinical practice measures -- using Toronto, we managed to diagnose neuropathy in around 30 percent, which is twice that of monofilament, but we need more confirmed.

The confirmed neuropathy shouldn't just be for research purposes, but in well developed countries such as the US, UK, Europe, actually we

Page 224

do need to do better. We need to use confirmed neuropathy as a proper standard of diagnosing neuropathy annually in our diabetic patients.

DR. FREEMAN: Brian?

DR. CALLAGHAN: I think we have a good framework from Toronto and ADA on how we think of neuropathy. I think the settings kind of naturally fall out of clinical trials and tertiary centers, looking at confirmed neuropathy versus epidemiologic ones, being more in the possible and probable.

I think where we can take it to the next step after Toronto and the ADA is to start focusing on the components, which are what's the questionnaire that we want to standardize to use as our symptom definition? What exam tool do we want to use to be our signs definition? How can we standardize the skin biopsies and nerve conduction definitions such as that doing it at Utah is the same as doing it at Michigan, same as doing it in Germany, et cetera?

I think that's how -- I feel like we have a

Page 225

framework, and we can build on that by becoming more precise.

DR. FREEMAN: Let's talk a little bit about then the symptoms, and I think at this point in the whole process, my bias -- and I think this is where views may not be unanimous, and I really do anticipate this is where the controversy emerges.

My bias would be to be agnostic at this point in terms of instruments and not say that this specific symptom score or this exam score is our ideal unless this is absolutely unanimous and rather look at the components as individuals.

What symptoms are we interested in? What signs are we interested? And not even at this point talk about how do elicit these signs, and that is work that needs to be done. I think none of us would disagree with the point that Dan made. Then finally, what special investigations.

Stephen, you've got something to say.

DR. BRUEHL: With that issue that you're just talking about there, you have all these measures that have been already validated, and I

Page 226

guess the question I would raise, because I'm ignorant of exactly what's on these -- what I would ask if you've gone back and done these reviews as was presented earlier showing these measures cover these aspects of things and these differentiate better than others, instead of looking at the full measures, can you look at the item level? If you get seven measures that all are the best predictors and you look at the items and they've got 85 percent overlap, that tells you that's the symptoms and signs that you would want to address in here.

I'm just saying maybe go at it not so much from the scale perspective, but look at the item level at the overlap, and that might be helpful.

The other issue -- and I just want to raise this because it's going to come up with the investigations -- is I thought it was pretty profound when I saw the receiver operating characteristics curve that was presented showing that the confirmation test, the value of the confirmation test, had a negative predictive value that was virtually worthless.

Page 227

For research purposes, that's what you're really concerned with is are we weeding out the people that don't really have it. I would argue that if we're trying to optimize this for research, and that's the only justification for including these tests, why would you do that if they're not predictive? Just to be provocative because I don't work in this area –

(Crosstalk.)

DR. FREEMAN: Gordon, you shared this slide, so what do you think?

DR. SMITH: I agree. It was actually the negative predictive value is low, but if you model it --

DR. BRUEHL: It depends on the base rate.

DR. SMITH: -- so the negative predictive value is high. Positive predictive value is terrible, but if you model it for a highly prevalent population, it stinks. So I agree. I am actually ambivalent about using nerve conduction studies or skin biopsy to confirm neuropathy. It's not clear to me that it really adds value.

Page 228

I think they are definitely valuable tools. They're essential tools in monitoring disease progression. They're clinically useful when applied judiciously, but our foundational almost religious belief that these tools convey a higher certainty of neuropathy in an individual patient in a screening setting for a clinical trial I think is suspect at best.

DR. FREEMAN: That is the question. What about the pretest probability, which in those patients, there was a relatively high pretest probability?

DR. SMITH: Well, it was 18 percent in that group, so if it's that low, it's good. The problem is once the pretest probability goes up, then your risk of having a false result goes up as well, so then the negative predictive value starts to decline as the false positive goes up.

DR. CALLAGHAN: I think part of the problem is our constructs don't all overlap. In some ways, maybe we shouldn't be trying to lump tests and a clinical definition together but have our best

Page 229

clinical definition, our best large fiber quantitative definition, our best small fiber quantitative definition. Maybe part of the reason we're struggling and why we get some of these strange results is because we're meshing these things that don't overlap as well as we would all like.

DR. FREEMAN: Can I just ask Jen to say -- because Jen's looked at signs. And you've looked at symptoms as well, and symptoms, I think, is one of the critical pieces.

Can you talk to us a little -- and I'm sorry for putting you on the spot. Maybe you should have some time to think about it. Can you talk now, or do you want me to hear from somebody else first?

DR. GEWANDTER: Do you have a question?

DR. FREEMAN: The question is, if I were to say I want five symptoms that, to address Stephen's point, are present in the vast majority of tests. We can't answer Rodica's point yet whether there's overlap, which is the most likely to predict the presence of disease. We can test that later. But

Page 230

we can answer Stephen's point.

DR. GEWANDTER: Oh, can I have a minute?

DR. FREEMAN: Of course. So it was Dan, I think.

DR. ZIEGLER: I'd just like to comment to that, to Gordon's statement. We did a number of studies in recently diagnosed type 1, type 2 diabetes. That's the first -- that's the earliest time you can go. What those measures show, nerve conduction and also skin biopsy, is that these are sensitive. These are the gold standards for large fiber and small fiber, and these detect abnormality very early. They are very sensitive, and therefore, they will detect more abnormality in people who do not have neuropathy.

So that all these test sensitivity and specificity discussion is a little bit questionable because if it's the gold standard, it is the best thing. This is our impression, that those tests actually are the gold standards for small and large fiber deficits.

DR. SMITH: That was my impression, too,

Page 231

going into it, but the fact remains there's still false positives with the gold standard.

DR. FREEMAN: Amanda, then Rayaz, then anybody else other than Jen who has -- James. So Amanda.

DR. PELTIER: I think one of the things that you have to think about if you're designing your criteria for either the clinic or research is that what you want to think about actually are the syndromes that are going to be confused with neuropathy and how do you differentiate those. I think that's really where you want to think about it.

Because as Dan suggested, you can have a lot of preclinical patients who are going to have abnormal tests and very few symptoms and maybe only a handful of signs. The bigger issue is how do you rule out the person with plantar fasciitis? How do you rule out the person with a tarsal tunnel or some other mononeuropathy of the foot and making sure that they're not included in your trial and they're not confused with having polyneuropathy?

Page 232

DR. FREEMAN: Rayaz?

DR. MALIK: With regard to this sensitivity/specificity issue, we look at this data, and we don't actually think about what goes behind the test. What goes behind the test is the definition that you use to define a condition. So if you're using criteria which are weighted towards a particular -- I don't know -- maybe large fibers and you're looking at skin biopsies, of course, it's not going to do well.

That's the thing that we forget because we just generically say, oh, this has got a bad negative or positive predictive value, but it's the definition that you use. I think that is again going to be useful for what comes out of this as do we need to think about how we define diabetic neuropathy. Do we need to incorporate a more holistic approach as opposed to the previous approach that we've had?

DR. HARATI: In ALS, in definition of the different classes of ALS, we have definite, possible, probable, but there is also a category of

Page 233

laboratory-supported diagnosis. There is nothing wrong to include that, and we may choose for a particular research to use only definite or possible or we may want to choose all four categories.

DR. FREEMAN: I think of definite as autopsy, and clinically -- of course, that's the only definite.

DR. PELTERI: Not really, though, Roy, because if you think about it, if you do an autopsy and you do the sural nerve biopsy, and you just say a lot of loss of nerve and you didn't have all the other information, how would you know that that loss of nerve was really due to their diabetes?

DR. FREEMAN: But the point about it is I like the clinically confirmed because that's what it is. It's accurate. You don't know whether this patient definitely has a neuropathy. You've confirmed it clinically, and I think most criteria actually do have the autopsy if you look at Lewy body dementia, Parkinson's, so most of the central neurodegenerative processes use that approach.

Page 234

DR. SMITH: Can I comment, though, because I think Amanda hit the nail right on the head, and it goes to Dan's point. The problem with these tests, first is not everyone who has obvious neuropathy has an abnormal nerve conduction or an abnormal skin biopsy, and there are reasons for that.

There may be changes if we had been able to see those metrics from their pre-disease state, but the fact is we're enrolling for trials now where we look at these patients and say they obviously have neuropathy, yet they don't quite meet the criteria. So there are false negatives, and it's just the way the tests are constructed.

The real issue is what Amanda talked about, is trying to prevent enrollment of patients who have plantar fasciitis, and people with diabetes, they're allowed to have plantar fasciitis. Because of the frequency with which there are preclinical abnormalities of these tests, using them as a positive enrollment, a confirmatory criteria, runs the risk of enrolling patients who don't have the clinical phenotype, whereas relying on them also

Page 235

will exclude patients who clearly have the clinical phenotype.

I think the real major problem is the one that Amanda talked about, and it shows in the performance data where the positive predictive value is terrible, and that's because it's based on clinical criteria.

DR. FREEMAN: There was James and then Jennifer.

DR. RUSSELL: Roy, in part answer to the question that you actually posited to Jennifer, we already have this information. So in 2015, we looked at seven of the major scales that are used across the board, and what turns up from that study is that the positive predictive value, the negative predictive value, the sensitivity and the specificity turns out to be best for the modified Toronto Clinical Neuropathy Scale. The two top scales were that and the Total Neuropathy Scale. The thing that drives the overall sensitivity is actually the presence of the symptoms.

Now, if you look actually at the validity of

Page 236

the different domains, the thing that determines the validity is actually the sensory signs. If you're going to look at a scale and you want to make it more sensitive, you are going to have to include symptoms, but if you actually want perhaps to make that scale more valid and more reproducible, then you're really going to have to focus actually on the signs.

We already do have some of that information. Now, I would suggest that we can probably actually come up with clinically confirmed based on symptoms and signs. We're going to have to decide which of those signs and symptoms we're going to use, and then prospectively in coming years, we're going to have to test those objectively in trials conducted by this group.

DR. SMITH: An autopsy.

(Laughter.)

DR. SMITH: An autopsy maybe.

DR. GEWANDTER: So you wanted to know what were the most common symptoms and signs in the scales. So as far as symptoms go, by far most

Page 237

common is numbness and tingling. It is in all of them.
DR. FREEMAN: So that one slowly.
DR. GEWANDTER: Numbness and tingling is in all. I can't find the total, and I'm having trouble. But it's 17 of them. We only reviewed, I think, 18.
Then the next most common is pain, and that was in seven of them. Then the next most common was altered warm and cold perception was in six. Allodynia was in six, and specifically sharp pain was in six. Then difficulty feeling your feet or instances when walking was five.
So these scales mix functional report as well as symptoms, so after this, it gets a little murky, so I'll stop there.
As far as the signs go, the most common are vibration, reflex, pinprick, and then to a little bit lesser extent, muscle strength, and touch pressure.
DR. FREEMAN: All right. So should we divide into those groups? It looks like it's

Page 238

roughly -- what's up?
DR. FELDMAN: This is just a suggestion because it's a quarter till 2:00, and we have two talks. What do you think about having the two talks, taking a break, and then dividing into the groups? You've got another discussion session planned --
DR. FREEMAN: You know what? Here's what I thought --
DR. FELDMAN: -- just based on time, what would be most efficient?
DR. FREEMAN: What I thought is that we would do the discussion because that is so tightly connected to this most previous session. We can then do the next talks. We do have time, and if we only do Jim's talk, that will be okay, too, or if we do the session on the Diabetic Neuropathy Consortium tomorrow or later, that will be time. But I think we're all geared up for doing this, and I think we can do that.
I think roughly a half an hour should be enough. I'll walk around and see.

Page 239

It looks like the way we are seated is pretty random, so why don't we say -- and I think of the panel, pick your group that you're going to go with, but one, two, three, four, five, six, seven, up to is one group.
Maybe that group -- Chris, you were telling me where?
DR. GIBBONS: We're going to split up into three rooms. There's the eating room here on the right. There's a small room for about seven or eight people right behind the check-in desk over there; they'll direct you over. These will be the three spaces we'll move to.
DR. FREEMAN: That group who I called out plus one or two panelists, you'll go to the small room.
Jen, one, two, three, four, five, six, seven, up to Jim Dyck, go to the dining room with one or two panelists, and then the rest stay here. And remember that you are going to shape your views on what you want from the setting.
(Whereupon, at 1:47 p.m., a breakout session

Page 240

occurred.)
Breakout Discussion
DR. FREEMAN: Here is the story. To be quite honest, I was worried that we would finish early because nobody would say anything. I really had no idea this was going to go, let's say, so well.
(Laughter.)
DR. FREEMAN: What we're going to do this afternoon, just the big picture, everybody will come up, at least the representatives from each group will come up, give their spiel. There will be discussion about that. I have no idea how long that's going to take, but let's say it will be somewhere around 30 minutes, maybe more.
I want to give the perspective on this that this is not yet cast in stone. Gordon will have the onerous task of merging this, sending round questions for voting. We once did something, I think which was very effective, using the Delphi method where people voted, and we came down to definitive conclusions, which may be an approach

Page 241

for doing this. But let's try and get as close to final as we can this afternoon with this.

We will then have Jim Dyck give his talk, and depending on timing, perhaps Chris give his talk. And then we may have a working dinner, depending on the timing, where the Diabetic Neuropathy Consortium -- somebody said the DPNC.

Is that the new name?

DR. GIBBONS: We're still working on --

DR. FREEMAN: Still working on it?

That consortium -- what's that?

DR. FELDMAN: I was just going to ask Troels Jensen if maybe we can have the name.

DR. FREEMAN: If we can have his name? Okay.

DR. FELDMAN: Because the consortium is just David Bennett, myself, and Troels, so it's a small --

DR. FREEMAN: It's small. We're happy to include Troels, so then we'll -- yeah, okay.

Whatever it's called, they will -- we will meet over dinner, possibly.

Page 242

Let's go with group 3, which is -- Chris, going to do the presentation?

DR. GIBBONS: Sure. I might need some help scrolling since I put this on Word.

We were basically coming up -- our focus was, again, small fiber, large fiber, mix, and some of the discussion. We actually came up with a very simple solution. We decided there was no small fiber. There was no large fiber. It was all mixed, and that was pretty much it. We're done.

(Laughter.)

DR. GIBBONS: Actually, it gets in a little more detail. So what we tried to do was come through and define a little more clearly. We thought again, small fiber did exist, in gest, but it's going to be less likely.

One of the things we were looking for were symptoms, which had to be bilateral, symmetrical, length-dependent, positive symptoms. We thought for an isolated diabetic small fiber neuropathy, we had to have one of the following symptoms: burning pain; prickling, tingling, lightning, stabbing

Page 243

pains; hypersensitivity; or paradoxical temperature sensations, so hot being cold, et cetera. So those were the presenting symptoms, one of those.

Negative symptoms were not required, but they were supportive. Again, for my group, if I typed this incorrectly, please correct me, but lack of feeling temperature, pain was supportive but not diagnostic.

Signs, we thought they needed one of the following signs: either loss of pinprick being the predominant one. We really all felt that cold temperature, although it's really been used historically, was so far down on the bottom of utility as a clinical bedside test that we didn't want to recommend it. Warm temperature, also pretty far down from a clinical bedside test, so we thought pinprick was really the way to go.

Then allodynia or hyperalgesia were things we wanted to use in addition to pinprick as one of the following, and it was primarily pain and hyperalgesia or a loss of pinprick that would put you in the positive sign.

Page 244

Then the negative, if one of these were abnormal, this would move you to the mixed neuropathy by definition. So if you had abnormal reflexes, abnormal vibration, proprioception, or motor, that would automatically move you into the mixed category.

The other comment we had --

DR. PELTIER: We did have the age caveat.

DR. GIBBONS: Oh, right, I have the age caveat a little later. But the age caveat for reflexes, and, again, we have to --

MALE VOICE: And vibration.

DR. GIBBONS: -- and vibration. So there's some variability, but I think absent vibration, would still not fall into that. There would some definitional operation there.

Then light touch we thought was not particularly valuable. We did have comments about whether validated quantitative sensory testing should be used in place of examination. We thought not on a routine clinical approach, but something for discussion maybe afterwards in terms of where

Page 245

the QST fit into all of this.
From an investigational standpoint, not required but supportive, we thought confirming, so autonomic testing, so just thermoregulatory sweat testing or QSART showing a length-dependent loss would confirm or be supportive of the other diagnoses.
If you can move to the next slide or scroll up, if it's possible.
Or on the confirmatory testing skin biopsy with abnormal intraepidermal nerve fiber density, and in this case, it requires an and normal nerve conduction studies. Again, we're going to require -- we'll have to operationalize what those actually mean by age, et cetera.
Then we move to the large fiber --
DR. FREEMAN: I think it might be worthwhile just to stop now and discuss that.
DR. POP-BUSUI: I actually have a comment regarding the need of using positive and negative. We did have our discussion around those same terms as well, and I think it reflects maybe in some

Page 246

providers or even patients, negative feeling or mixed feeling or confusion.
Why do we need to use positive, negative?
DR. FREEMAN: Can you scroll back?
DR. GIBBONS: To the other page.
DR. POP-BUSUI: Why not just symptoms? Because I think they are relevant symptoms of neuropathy, but that I don't think that we can gain anything by using positive, negative.
DR. GIBBONS: Yes. I think from an operational standpoint as long as we understand what we mean, we can rephrase that. I don't think we need to indicate a connotation to the positive or negative, but it's the presence or absence may be a better way of thinking about it, which is fine.
Jim?
DR. DYCK: So we had lots of discussions about symptoms and the role of symptoms indicating the presence of neuropathy. We're mostly talking about severity.
Now, most people think of small fiber

Page 247

neuropathy almost by definition as being a symptomatic neuropathy. Theoretically, one could have a small fiber neuropathy where you don't have symptoms and you might have reduced pinprick and you might have reduced epidermal nerve fibers. Maybe it's not so important because they don't have symptoms, but your first thing required one of those symptoms. I don't know if that should be absolutely necessary.
DR. GIBBONS: Yes, we had a lot of debate about that, and I may have captured it incorrectly. I think one of the things I didn't have a chance to do is actually to phrase this in a way that made sense from a presentation standpoint. But we were thinking that the positive would really put us into the painful small fiber neuropathy. A symptom would move us into that category.
The absence of a symptom would not necessarily move us into a mixed category, but it would move us out of the painful small fiber neuropathy category. I didn't actually get to that point, and that's a great interlude.

Page 248

DR. FREEMAN: The one thing it should say, again, I'm thinking of this from the clinical trial standpoint, drug company X within that 1.7 blocker will want a --
DR. GIBBONS: Painful, right.
DR. FREEMAN: -- symptomatic small fiber neuropathy, and then drug company Y with a drug to treat, say, Rob's pre-diabetic neuropathy will not care about symptoms necessarily but would be quite happy to just have an asymptomatic small fiber neuropathy.
Maybe you want to subdivide it into symptomatic and --
(Crosstalk.)
DR. PELTIER: We also talked about practically that it's very rare to see an asymptomatic small fiber predominant neuropathy. It's possible but like --
DR. GIBBONS: I think we had disagreement on that. I think the referral to a physician for treatment of pain, you're not going to have it. But I did mention in my own clinics where I get

Page 249

general neuropathy referrals, I see that not uncommonly. So it depends on who's seeing what.
DR. ZIEGLER: Definitely. I could even say it's more frequent, more common than the painful entity. So it just depends on --
DR. SMITH: Is it the same thing? I think that's the question. Because I agree, if you look carefully, you find this all the time, particularly using abnormal pin sensation and abnormal skin biopsy, but is that the same condition as a symptomatic or painful small fiber predominant neuropathy? Or does it matter?
DR. ZIEGLER: But still I think you should have a heading for that, a name for that kind of neuropathy. So I would agree with Roy's suggestion to call this asymptomatic predominantly or symptomatic predominantly small fiber.
DR. GIBBONS: Yes, I think that's perfect and yes --
DR. DYCK: Or preclinical.
DR. FREEMAN: Can I ask a neurologist or anybody a question? Non-painful prickling and

Page 250

tingling, is that small fiber or large fiber?
DR. GIBBONS: We've got some mixed discussion.
(Laughter.)
DR. ZIEGLER: Yes, we don't know. We don't know.
DR. GIBBONS: We had a lot of debate about that.
DR. FREEMAN: But one of the questions is do we want to add this then as one of your one positive symptoms, and is one enough? Do you want two? I don't know the answer to this, and here we get into the possible, probable, definite story, perhaps.
DR. ZIEGLER: You could also define painless. You could also call it painless if it's numbness, paresthesias.
DR. FREEMAN: With the small fiber. Now, numbness I think most neurologists would say maybe it's [inaudible – off mic]. The question is really related to small fiber modalities. I don't know the answer to the question, but I wondered.

Page 251

Anybody have a definite view on that?
MALE VOICE: There may be answers, but I'd be worried about putting tingling as a small fiber symptom.
DR. FREEMAN: You'd be worried?
MALE VOICE: Yes.
MALE VOICE: I do see tingling in both large --
DR. GIBBONS: Yes, we were getting into the question of painful tingling and that operational definition --
DR. ZIEGLER: That would be dysesthesia. That would be dysesthesia if it's --
MALE VOICE: You might even say --
DR. ZIEGLER: No, not even that. That's unpleasant paresthesias would be dysesthesias.
DR. HERRMANN: What we did in the discussion one way we thought about it was say tingling or prickling wouldn't put you in a small or large fiber category. It's an acceptable symptom. You would make the determination of small versus large based on your signs.

Page 252

DR. SMITH: How do you know this isn't just early neuropathy? Because we know that if you follow these patients, most of them develop large fiber findings, and you're also making the judgment that they don't have large fiber findings at a single point in time, not knowing what the quantitative evaluation of their large fiber sensation would have been 6 or 12 months ago, and we know 6 or 12 months later, it's likely to change.
Does that matter, the --
FEMALE VOICE: It's the earlier comment that we said, okay, it's just all mixed. It really doesn't matter.
DR. GIBBONS: There was that impression.
DR. SINGLETON: You weren't joking? Are you really going to get to the point that it's all mixed, and you're just taking time?
(Crosstalk.)
DR. GIBBONS: No. So we're --
FEMALE VOICE: -- we did discuss that.
DR. GIBBONS: Yes, we are operationalizing

Page 253

this for a point in time theoretically for an entry to a trial. It's an isolated small fiber neuropathy at this point in time with the understanding that it will progress, and we expect that there will be at some point large fiber, theoretically.

DR. SINGLETON: I think we can think about the idea that small fiber or small fiber predominant neuropathy is also early diabetic neuropathy for many people.

DR. ZIEGLER: It's simply not true. It's not true.

DR. SINGLETON: I said for many people, not for everyone.

DR. ZIEGLER: Yes, it's --

DR. SINGLETON: It's the natural history to go from --

DR. ZIEGLER: I don't think so.

DR. SINGLETON: -- for many patients to go from small fiber to --

DR. ZIEGLER: No, no, no. I don't think there is enough evidence to support that notion.

Page 254

DR. HERRMANN: In the Rochester diabetic neuropathy study, my father did this really nice study 10 years ago that I think most of us have read where he looked at the heat pain thresholds and saw in normal and abnormal people with and without neuropathy that there was a shift to people toward -- in early diabetes toward the hyperalgesic. As time passed, it shifted to the hypoalgesic. So it went originally towards having increased pain thresholds, and then it went just to the other extreme.

I think that actually is an argument that it is early diabetic neuropathy giving you almost a painful small fiber neuropathy and then it goes the other direction.

DR. ZIEGLER: I think there's no support for that. You have always that selection bias, and you have to consider that. So if you want to study early diabetic neuropathy, you have to go to the early stage of the disease, and that is at the time of diagnosis or at least within the first year from diagnosis, and then to follow the patients

Page 255

prospectively. And only by doing this, you can say this comes first or not.

We've done some thousands recently diagnosed type 1 or type 2 patients, and we see very, very little allodynia or hyperalgesia in those patients. So this is clearly not documenting that this is an early feature, and very few patients actually among these have pain. That's a minority.

If you think of type 1, most of them have subclinical neuropathy, that is, nerve conduction deficits. And if you think of type 2, they have at best -- the most frequent category you see is possible neuropathy in those patients, but very rarely, you see the gain phenomena in those patients.

DR. HARATI: I agree. I think that's the neurologist's bias. Neurologists --

DR. ZIEGLER: Yes, definitely, there is a bias.

DR. HARATI: Diabetologists see the different group of patients, so I agree.

DR. ZIEGLER: It's the same -- we will

Page 256

discuss that tomorrow. It's the same with pre-diabetic neuropathy. You're coming from a very different angle. If you're a tertiary center, and a patient with idiopathic neuropathy comes to you and it is painful, and then you do your OGGT on them, of course, the OGGT will be frequently abnormal because this is an abnormal phenomena. This is the case in the general population that they have pre-diabetes. And in addition, they may be multi-morbid patients with polypharmacy and so on, so that the likelihood is very high that they would have pre-diabetes.

So you have to come from the other side. You have to go to the population level and then see how frequent pre-diabetic neuropathy is.

The same thing here, you have to start at the early stage of diabetes and have a representative population, and see whether those phenomena are found or not. We have a very, very meticulously phenotype population with several hundreds of people recently diagnosed, and I think that's the best way to see which phenomena of

Page 257

diabetic neuropathy will be painful or not, early or not. I don't know there is another appropriate way to look at that.

DR. FREEMAN: Just in the interest of time --

DR. ZIEGLER: Sorry.

DR. FREEMAN: -- it does exist whether it's highly prevalent, early, late, fixed, static, part of a window in time, if you catch it at one point and look at it the next day, or it will become large. Let's just accept that there is this entity.

I want to give Gordon enough to work with, so I'm not quite sure what you mean by "supportive, lack of feeling of temperature or pain."

We're trying to have the menu, the Chinese menu --

DR. FELDMAN: Roy, could you use the microphone? We can't hear you.

DR. FREEMAN: Sorry. It's funny. I always thought I spoke so loudly.

I want to give Gordon enough to work with,

Page 258

so I want to clarify a couple of things. Have we agreed that prickling and tingling is painful prickling and tingling, whatever we're going to call it?

DR. ZIEGLER: It's not. It's painless. It's painless. It's not painful.

DR. FREEMAN: In small fiber neuropathy, we're talking about?

DR. ZIEGLER: I think there is no agreement.

DR. GIBBONS: We're talking about a symptom that's enough to be reported as painful.

DR. FREEMAN: As painful?

DR. GIBBONS: Yes. That was our operational definition. And again, this is quick shorthand.

DR. FREEMAN: No, I understand that. Clarify "negative symptoms, supportive lack of." Is that part of the menu, or is that just --

DR. GIBBONS: Negative symptoms were supportive. They weren't going to --

DR. FREEMAN: Didn't matter one way --

DR. GIBBONS: -- modify the definition.

DR. FREEMAN: -- were not part of. Okay. I

Page 259

think that that's probably enough for Gordon to --

DR. GIBBONS: Again, I can clean this up to revise --

DR. SMITH: You're saying that there needs to be one positive symptom and one sign, positive sign? I'm not sure I understand --

DR. GIBBONS: One positive symptom, one positive sign, and in absence of the other things that could move it into a mixed.

DR. FREEMAN: And it was an "and." Could we scroll down? It was "and skin biopsy."

DR. GIBBONS: The investigations were confirming; they weren't required.

DR. FREEMAN: The biopsy?

DR. GIBBONS: Right, exactly. So you could use --

DR. FREEMAN: Before skin biopsy --

DR. GIBBONS: You could use again autonomic sudomotor function testing or skin biopsy and a negative nerve conduction study. Again, these were confirming.

DR. FREEMAN: And negative, Gordon, is going

Page 260

to have to work, what, negative means --

DR. ZIEGLER: Normal.

DR. FREEMAN: I understand that, but normal is --

DR. DYCK: How about QST?

DR. GIBBONS: We had a long debate about QST and how it might be a positive or negative. We didn't come to an answer I think was the shorthand. We determined that it might be a substitute for the examination, but we weren't sure that it was necessarily going to substitute for one of the other tests that were confirming.

It could substitute for the exam, but we weren't sure that that was necessarily going to be a reason enough to do QST instead of the exam.

DR. DYCK: In my institution, I have thermoregulatory sweat test, which I think is the best test for small fiber neuropathy. Now, I understand most of the world doesn't have that.

DR. GIBBONS: That's why we said QST or thermoregulatory --

(Crosstalk.)

Page 261

DR. GIBBONS: Sorry. It was on the other scroll, thermoregulatory sweat testing or QSART, yeah.
DR. BRUEHL: The things that you put like the negative being supportive, that is what goes in Dimension 2. So any things like that that are common enough that you would consider it characteristic but not is important that it's diagnostic, just falls down to Dimension 2?
DR. FREEMAN: The only question, I suppose, is one and one or -- maybe I should sit closer. The only question I think that we need to resolve is one enough of each of the one sign, one symptom, or more than that?
DR. GIBBONS: Yes, we had some debate, and at this point, we also thought it would be important to go back and see a little bit more in terms of the data from the literature to try and get at that. We didn't have that on hand.
DR. FREEMAN: I may be wrong on this, but I know I can look at my slides. But I think that Giseppi's study, he had QST or skin biopsy, or skin

Page 262

biopsy the definitive. Does somebody know?
MALE VOICE: It's QST and skin biopsy.
DR. FREEMAN: QST and skin biopsy. Worth looking at that, not that we need to follow that.
DR. HERRMANN: In Giseppi's study, basically, it was an "or." So a QST could have been one of the elements.
DR. FREEMAN: That's what I remember.
MALE VOICE: It performed fairly similar to -- skin biopsy was a bit better, but QST, it had some --
DR. GIBBONS: Performed similarly.
DR. FREEMAN: Let's move on.
DR. GIBBONS: Then --
DR. SINGLETON: I was going to say the theoretical concern with QST is that it doesn't necessarily measure the function of peripheral nerve.
DR. GIBBONS: Yes, so again, there was a lot of interest in defining it.
We moved to the large fiber --
DR. FREEMAN: Can I just ask one quick

Page 263

question? I'm sorry about this, but this is a really practical question, which is an ongoing issue.
There are a couple of drug companies that are interested in doing trials in small fiber neuropathy. Somehow they're quite happy about doing skin biopsy. They're not happy about doing nerve conduction studies as a definitive exclusion.
How strongly do we feel about that? Do we want to shade that? Are we hard nosed about a normal -- whatever normal means -- nerve conduction study?
DR. SINGLETON: I think it depends on do they want a pure small fiber neuropathy. We have a --
DR. GIBBONS: We address that --
DR. SINGLETON: -- category of small fiber predominant neuropathy, and we would be happy to allow abnormal nerves.
DR. FREEMAN: I think that's a very nice way of doing it. I like that a lot.
DR. POP-BUSUI: Plus I think that we should

Page 264

all agree that those criteria will be like a starting point, and then based on the type of questions that a particular study or trial needs to answer, we can decide whether all these measures are needed or just a portion of them.
DR. FREEMAN: Yes. Just of interest, of the Toronto meeting, Solomon's paper and Rayaz's paper actually say two different things for the definition of small fiber neuropathy. Rayaz's one is like you, predominant, and Solomon's is pure.
Let's move on. Sorry about that.
DR. GIBBONS: It's okay. So we moved on to large fiber as the next, and we actually had a lot of debate about if anyone had ever seen a pure large fiber diabetic neuropathy.
DR. ZIEGLER: Why not?
DR. GIBBONS: We just asked has anyone seen it.
DR. ZIEGLER: Sure.
DR. GIBBONS: You have?
DR. ZIEGLER: Yes.
DR. GIBBONS: Pure large fiber, no

Page 265

involvement of small fiber at all?
DR. ZIEGLER: Yes.
DR. SINGLETON: So nerve fiber density was normal in those patients?
DR. ZIEGLER: Yes, that's possible. Why not?
DR. GIBBONS: No. We're saying it's possible. We're asking has anyone actually in this room seen it.
DR. ZIEGLER: Certainly, I can go through the data based -- I'm sure I will find those patients.
DR. GIBBONS: So we're less interested in the database. We're just trying to figure out --
DR. ZIEGLER: I was not particularly interested in knowing that. I don't know --
DR. GIBBONS: Well, we were just wondering as we got to it. None of us can actually ever recall seeing one, ever. And so we're wondering from an operational definition how important that is. But we're trying to get there.
Jim?

Page 266

DR. DYCK: This whole thing about your pure small fiber and pure large fiber, I think are sort of -- don't really exist as such. I think you have small fiber predominant, large fiber predominant, but very rarely are you going to have pure either of those.
This obsession with pure small fiber neuropathy also seems artificial to me, too, because usually, there will be some small fiber involvement. In fact, my father's doing a study right now looking at correlations of things, and he finds that it correlates the most strongly with epidermal nerve fiber density is the sural snap. It's large fiber and small fiber correlated with each other.
DR. HERRMANN: We kind of create some of these definitions. I don't think we're really implying what the percentages are in each group. We just put the categories there. For the NAV 1.7 trial that Roy keeps talking about and based on other people's work, maybe they want that very small subset of pure small fiber. But for most

Page 267

diabetic neuropathy trials, you're going to maybe go with a small fiber predominant, which may include the few who have pure and the majority who have --
DR. SINGLETON: Jim, this is our charge, so that's what we --
DR. DYCK: But it seems a little artificial.
DR. GIBBONS: No, we agree, and that was our decision.
DR. FREEMAN: I wouldn't say artificial, but I think there's a low prevalence of that entity. Maybe it's irrelevant, but there are some who are focusing on that.
DR. DYCK: I hear you. "Artificial" is the wrong term, but it's a small minority.
DR. GIBBONS: At least operationally, what we tried to go through with this was that there were really no defined symptoms that were required for an isolated pure small fiber neuropathy. We thought signs, you again had to have normal pin, normal pain. There had to be abnormal joint position vibration.

Page 268

We talked about monofilament use, but it was difficult to actually get graded sensitivity, so we weren't sure the value of that. But by definition, it would have to have abnormal nerve conduction studies and a normal skin biopsy. But we also commented -- and that's what the yellow part is -- that frankly, we didn't think you were ever going to see this. And it also seemed like if you did see this, you really had to think this was not related to diabetes, and this was something else. You needed to be very careful about rethinking that potential diagnosis if it's a pure isolated large fiber neuropathy.
DR. POP-BUSUI: Then if it's so rare, who is going to be interested to study that disease?
DR. GIBBONS: That was what moved us to the next discussion point, which is the mixed neuropathies.
DR. DYCK: I understand it's part of the conversation, but Hugh Garland and company would argue that the diabetic amyotrophy was a pure large fiber neuropathy.

Page 269

DR. PELTIER: But we're simply talking about the --
DR. GIBBONS: Yes, distal axonal. We agree, but we're focused on distal axonal.
DR. FREEMAN: Chris, joint position, monofilaments, one of the above, all of the above, two of the three?
DR. GIBBONS: We thought that joint position vibration should be abnormal. Monofilaments, we weren't sure we actually needed. That was a debate.
DR. FREEMAN: Joint position and vibration?
DR. GIBBONS: Yes.
DR. FREEMAN: Okay.
DR. GIBBONS: For an isolated large fiber.
Then going on to the mixed neuropathies, which we thought were actually the vast majority of what we're interested in, and these were going to be a length-dependent neuropathy that was not an isolated small fiber neuropathy. We, again, didn't think we'd be looking at the large fiber component. So we were talking about one symptom, length-

Page 270

dependent.
If you want to go to the next slide. We had components that looked at these different things, but we were trying to, again, shift this into a discussion of small fiber predominant, large fiber predominant. And the way we went through this was for small fiber, again, it would meet the criteria for the small fiber neuropathy with the addition of some reduction in vibration at the toes.
We had some discussion about anything else, but anything else, which included abnormal proprioception, abnormal reflexes except with the appropriate age-related discussion, would move you actually into a large fiber predominant as opposed to small fiber.
DR. SINGLETON: Absent reflexes.
DR. GIBBONS: Absent reflexes, yes.
Then the large fiber predominant would be a big catchall there would be abnormal vibration at the ankles or above. Any proprioceptive loss at the toes would move you to large fiber. Absent ankle reflexes, again, would move you to large

Page 271

fiber. This would also be a length-dependent axonal neuropathy.
It was sort of a catchall. You, again, had the small fiber, the small fiber predominant, which included the vibratory reduction in the toes; anything else would move you into the large fiber predominant.
DR. SMITH: Do we really need criteria for small fiber predominant, large fiber predominant, small and large fiber equal, halfway between the other extremes? At some point, this gets to be a splitting exercise.
I understand why there's a need for a small fiber neuropathy set of criteria given the therapeutic milieu in which we live. I'm not sure I understand the need for any of the rest of this because it all seems to be part of the spectrum of what we would all agree is distal symmetric polyneuropathy.
DR. FREEMAN: Just to give my take on this, I agree that this is -- we actually are creating -- we're drawing a line in a spectrum,

Page 272

most likely because I think it is an evolving picture, and there's some patients that may come in or we may see for the first time who have mixed. And there are many patients who I think evolve, and this may be referral bias. I happen not to think so.
In the clinical trial world, just to give that example again, there are companies that do not want to do nerve conduction studies, so they are left saying that, well, this is a small fiber neuropathy because they fulfill all of those criteria, but the Gibbons' last criteria, the nerve conduction study, that's not done. What do we call that group? I think it's reasonable to call that small fiber predominant because they may have some large fiber element, and if you were to do a sural nerve biopsy, for example, even that pure small fiber neuropathy may have large fiber loss.
So I agree that all of this is artificial, but I think there needs to be some term to describe those patients who have an array of small fiber features but still will have either nerve

Page 273

conductions not done or mildly abnormal nerve conduction studies or mild vibration.
DR. SMITH: Then why not just use the small fiber and say small fiber predominant based on clinical criteria, or one might even say probable small fiber neuropathy, and then use the nerve conduction, normal nerve conductions is confirmed or put it into the rubric that we're going to be talking about.
But I get the whole small fiber thing. Where it starts to seem really irrelevant to me is in a pure large fiber or various gradations along that continuum. I totally understand the situation you're raising because we're dealing with it in trials now.
DR. BRUEHL: This is a good example of what happened with CRPS is there was an argument over whether it made a difference whether you had evidence of peripheral nerve injury or not. Historically, people paid attention to that. There's no evidence that it makes any difference.
What we opted to do was the criteria are for

Page 274

CRPS. So here the criteria would be for peripheral neuropathy. You'd have the criteria which are basically the same regardless of whether it's large or small fiber dominant, and then you'd have subtypes listed at the bottom that said small fiber predominant, specified this is XYZ conditions. If this pattern is shown, large fiber. This is shown.
I'll say pragmatically from the FDA's standpoint, we encountered this with CRPS, is if you do a trial where the entry criterion is CRPS, then the indication is CRPS. You can, though, restrict it to one of the subtypes listed in there, which in this case would be like a small fiber predominant. That's who the indicator would be for would be restricted to a subtype of peripheral neuropathy.
It doesn't leave anything out. There's no disadvantage to doing it this way.
DR. GIBBONS: Doug?
DR. ZOCHODNE: I just argue from a pathophysiological point of view that [inaudible - off mic].

Page 275

DR. GIBBONS: Can you use the mic, Doug?
DR. ZOCHODNE: Yes. The definitions will be useful for many reasons because we anticipate if these guidelines stand, we may be able to understand disorders, why there's large fibers and large neurons become targeted later. Maybe it's for completely different reasons than small neurons.
I think if these guidelines are helpful, we are going to want to know all the different types.
DR. FREEMAN: Dave?
DR. BENNETT: I basically agree with Gordon, that I'm comfortable with small fiber predominant and mixed. I think where I'm uncomfortable is where we get to large fiber predominant. Why should the presence of vibrations -- why should having vibrations trump other things that make that large fiber predominant? In reality, it's mixed. So I would --
DR. GIBBONS: Call it mixed.
DR. BENNETT: I think I'd rather have small fiber predominant or mixed, and that's it.

Page 276

DR. GIBBONS: It's very reasonable.
DR. FREEMAN: I think this is enough to work with.
Do you have more to --
DR. GIBBONS: That's all.
DR. FREEMAN: So this was the easy one.
(Laughter.)
DR. FREEMAN: I'm going to disrupt the sequence just because Jim Dyck has a plane to catch, and I think probably we should bring you on -- your plane is at 7:00?
DR. DYCK: 7:00.
DR. FREEMAN: We should bring --
DR. DYCK: I probably need to leave at 5:00.
DR. FREEMAN: Need to leave at 5:00.
DR. DYCK: It's an hour and a half. I have a half an hour talk, and you want discussion.
DR. FREEMAN: Well, yes. I think we should -- let's have your talk just to be on the safe side, and we'll come back to this in a while.
(Crosstalk.)
DR. DYCK: Sorry everyone.

Page 277

(Crosstalk.)
DR. FREEMAN: I should say -- thank you for reminding me. This is how you spend your vacation when you are at the Mayo Clinic.
(Laughter.)
DR. FREEMAN: Jim, we are really fortunate to have Jim. He took a vacation day to come here, so this is -- if you ever want -- if you feel that you don't want vacation any longer, the Mayo Clinic has a place for you.

Presentation – James Dyck

DR. DYCK: There are many very good things about working at the Mayo Clinic, but they guard their days very closely.
This is a completely different topic. We have really been focusing in on diabetic polyneuropathy and small fiber neuropathies and things like that. I'm going to talk about diabetic lumbosacral radiculoplexus neuropathy, and then about diabetic radiculoplexus neuropathy more generally.

Page 278

I'm going to focus in on what's been written about classifications of this or lack of classifications and then about some of the controversies. It seems to me that what we've really been talking about are controversies so far, so from that point of view, I will be right on them.
Radiculoplexus neuropathies are conditions involving roots, plexus, peripheral nerves, and can involve the cervical levels, the thoracic levels, lumbosacral levels, and they can involve people with diabetes mellitus and people without diabetes mellitus.
I'm going to begin with diabetic lumbosacral radiculoplexus neuropathy. This condition has been described under many different names, and I think it really gets at the very thinking about it. So neuritic paralysis by Bruns, paralytic neuropathy by Leyden. Hugh Garland talked about diabetic myopathy, diabetic myelopathy, and eventually, he said, "I don't know what it is," and he called it diabetic amyotrophy. That was the term that stuck

Page 279

for a long time, diabetic I don't know what it is.
It is known as diabetic femoral sciatic neuropathy, diabetic femoral neuropathy, diabetic mononeuropathy multiplex; proximal diabetic neuropathy, the Bruns-Garland syndrome. In my institution, they called it diabetic polyradiculopathy, painful lumbosacral plexopathy, diabetic CIEP, diabetic lumbosacral radiculoplexus neuropathy, multifocal diabetic neuropathy. So it's been known by lots of different names.
There were certain features that were accepted to be classical for this that was painful by weakness, complete recovery within a year, a pure motor syndrome, a pure proximal syndrome, accompanied weight loss, affecting only people with type 2 diabetes mellitus. In general, these features are correct but maybe not quite so strongly as stated there.
I'm just going to try to hit the key features that Roy gave us to hit. This is an overview of what I'm going to try to cover.
There are no agreed upon standard diagnostic

Page 280

criteria for diabetic lumbosacral plexopathy. Every study up to this point has developed their own diagnostic criteria, or they didn't even really talk about diagnostic criteria.
Hugh Garland didn't list any criteria. He talked about diabetes being short-lived, it being purely a motor syndrome, although pain was usual, that there were asymmetrical symptoms and signs, that the legs were affected first. Arms are rarely affected. Reduced reflexes. And he emphasized Babinski signs.
Now, I think subsequent studies have not found this, so this has gone by the wayside, but this is probably the reason why he called this a diabetic myelopathy, that he thought typically there were extensor plantar responses.
A subsequent study he did, he found many of the same features, progressive weakness and wasting of the pelvifemoral distribution muscles, most of the involvement above the knee.
Raff, Sangalang, and Asbury, New England Journal of Medicine, their inclusion criteria was a

Page 281

rapid, asymmetrical motor greater than sensory neuropathy in diabetic patients. They included people with cranial neuropathies, and recovery was the rule.

They showed infarcts in the nerve, multifocal fiber loss, occluded blood vessel. They saw some inflammation, but they felt that that inflammation was reactive. So here is a fossicle without nerve fibers. There's an occluded blood vessel, and they felt this was an ischemic event in the nerve. They showed inflammatory infiltrates, but they didn't think they were causative.

Chokroverty in contrast talked about 12 patients with a pelvifemoral weakness, wasting with insidious onset. So there is this debate whether it's a rapid and progressive or whether it's slow and insidious. They emphasize metabolic derangement and not microangiopathy. They felt it was different than Raff, Sangalang, and Asbury's diabetic mononeuritis multiplex.

Arthur Asbury coined the term "proximal diabetic neuropathy," said it was two poles of a

Page 282

continuum with asymmetric weakness, rapid evolution from an ischemic basis at one end, and symmetrical weakness, slow progression from metabolic factors at the other end.

At my institution, Bastron and Thomas wrote about diabetic polyradiculopathy. They said there could be involvement of the chest, abdomen, back, buttock, thigh, leg, or foot. EMG and neurologic examination would be in keeping with a polyradiculopathy.

They made a distinction from what we've been talking about so far today, which is diabetic sensory motor polyneuropathy. They felt the symptoms would begin focally and then become more widespread, and they emphasized lumbar and thoracic denervation and made the point that this is not just a pelvifemoral syndrome.

Subramony and Wilbourn included patients with diabetes, proximal lower limb weakness, a neurologist diagnosis of diabetic amyotrophy, and exclusion of other causes of the neuropathy.

Walter Bradley and colleagues wrote about

Page 283

painful lumbosacral plexopathy with elevated sedimentation rate. They had six cases, three with diabetes, three without diabetes. They showed cuffs of perivascular inflammatory cells, multifocal fiber loss, and felt that it was an inflammatory ischemic condition. And they made a distinction about cases who had the elevated sed rate versus those without the elevated sed rate. They shared perivascular inflammation and multifocal fiber loss.

Rick Barohn, Zarife Sahenk, Jerry Mendell wrote about the Bruns-Garland syndrome. The patients had to have diabetes; abrupt onset of hip, back, leg, thigh pain, unilateral or bilateral; lower limb weakness, proximal or proximal and distal unilateral or bilateral; EMG showing a neurogenic, not a myopathic abnormality; and imaging to exclude structural causes.

Gerard Said talked about proximal diabetic neuropathy, included patients with diabetes, proximal neuropathy of the lower limbs. Other causes excluded through imaging. He broke them

Page 284

into forms. In the severe forms, he felt vasculitic causes predominated, and the mild forms, he felt metabolic factors predominated. They showed some inflammatory lesions in the nerve.

Linda Pascoe, Tony Windebank, Phillip Low, Bill Litchy at our institution did a series. They insisted in bilateral lower limb weakness, progressive course, other causes excluded.

Gareth Llewellyn, P.K. Thomas, Rosalind King wrote about diabetes. Again, a motor neuropathy, pain, weakness, muscle wasting in the lower limbs. Usually subacute onset with asymmetrical pattern. Other causes of the neuropathy excluded by CSF studies and spine imaging.

In my study, we looked at diabetic lumbosacral radiculoplexus neuropathy. To be included, you have to have diabetes mellitus; a subacute developing unilateral or asymmetrical lower limb neuropathy; involvement of the buttock, thigh, leg or foot; but upper limb or thoracic could also be present. MRI or CT were used to exclude structural causes. Nerve conductions EMG

Page 285

were not confined to one peripheral nerve or one nerve segment. Typically, pain, weakness, and numbness were all present.

We found evidence of ischemic injury. We compared the nerves to nerves of diabetic polyneuropathy. We found multifocal fiber loss. We found injury neuroma. We found increased amounts of inflammation in the nerve and suggestion of microvasculitis. We saw inflammation involving vessel walls, fragmentation of the vessel walls.

We felt that this was a subacute painful neuropathy beginning unilaterally in the leg or thigh but progressing to be more widespread and bilateral. We felt it wasn't just a proximal neuropathy and it wasn't just a motor neuropathy, that usually sensory and autonomic fibers were involved. Ischemic injury best explains the clinical and pathological findings, and the cause of the ischemic injury is altered immunity and microvasculitis.

Kelkar and Gareth Perry wrote about diabetes mellitus and progressive painful asymmetrical

Page 286

proximal lower limb weakness and concluded that the pathology showed a PMN predominant vasculitis.

We didn't recognize that sometimes you'll get cases that don't have pain, so we did a study looking at a painless form of motor predominant lower limb neuropathy. These cases had diabetes. They did not have pain. They had weakness in one or both lower limbs, presence of sensory symptoms or signs, nerve conduction showing involvement from at least two different peripheral nerves from at least two different nerve roots. The findings could be demyelinating or axonal, and the patients could have upper limb or thoracic involvement.

That's an overview of many of the studies that have been done. As I pointed out, there is no consensus core criteria for diabetic lumbosacral radiculoplexus neuropathy. But going through those studies, there are some generally agreed upon features, and they seem to include diabetes mellitus, lower limb predominant usually asymmetrical peripheral neuropathy, motor predominance. Severe pain is usual, but not all

Page 287

cases have it. It can be unilateral, or it can be bilateral. There are reduced lower limb reflexes, and need to exclude other structural causes that can mimic this. So this is a diagnosis of exclusion. Other things can look a lot like this.

What is the differential diagnosis of diabetic lumbosacral radiculoplexus neuropathy? You can have lumbosacral radiculopathy, and it can look a lot like this. Lumbosacral radiculitis. I think the question comes up -- and I have a slide further on about this -- is radiculitis really a different disease than this? Lumbosacral spinal stenosis.

Then other things, peripheral nerve sarcoidosis, CIDP, neurolymphomatosis, necrotizing vasculitis, amyloidosis, infiltrating neoplasm into the lumbosacral plexus, radiation plexopathy, vasculopathies, retroperitoneal hemorrhage, and retroperitoneal abscess.

A lot of that can be diagnosed through imaging, but again, I think this ends up being largely a diagnosis of exclusion.

Page 288

What are some of the controversial issues when it comes to this diagnosis? One that I've been alluding to is, is this a pure motor syndrome? And it's interesting that we were just having this conversation about pure small fiber and pure large fiber because I think that comes up in this condition, too.

Garland, Chokroverty, Llewellyn, and others have emphasized that if it's not a pure motor syndrome, it's close to a pure motor syndrome. Through use of quantitative sensory and autonomic testing, I think we've fairly definitively shown it's not a pure motor syndrome, but it certainly is a motor predominant syndrome.

Is this just a proximal neuropathy? Again, Garland, Chokroverty, Said emphasized that this is a proximal neuropathy. But Bastron and Thomas and we have emphasized that it can also present in other locations, and it might just present with a foot drop without thigh involvement and really be the same disease. So from my perspective, although it's often commonly predominantly a proximal

Page 289

neuropathy, it doesn't necessarily have to be.
Then this issue of rapid progression versus insidious. Asbury wrote that it's a spectrum with insidious, slowly progressive, symmetric at one end of the spectrum, and a rapidly progressive asymmetrical ischemic form at the other end of the spectrum.
Pain, do all cases require pain? Probably more than 90 percent of these cases do have pain, and the pain is severe, lancinating, burning, contact allodynia. But as I've mentioned, we have a series of painless lumbosacral plexopathies with more insidious progression, more symmetrical, and more upper limb involvement.
When we compared our painless cohort to the painful one, they were more subacute to chronic, they were more bilateral, and they had more distal involvement. There was more upper limb involvement as well, but the pathology really was the same.
There was evidence of ischemic injury, so multifocal fiber loss was common. This is an injury neuroma; it's common. There was evidence of

Page 290

inflammatory infiltrates in the nerve and microvasculitis in the nerve, so big inflammatory infiltrates involving blood vessel walls. So from the pathological point of view, there really wasn't a difference in the painless form versus the painful form.
We concluded that the painless lower limb motor predominant neuropathy in diabetic patients really was a form of diabetic lumbosacral plexopathy. The findings confirmed that the clinical spectrum of DLRPN is you have more rapid ones on one end and more insidious ones on the other end, and the underlying mechanisms of both of them is ischemic injury and microvasculitis.
The pattern involvement, the focal versus multifocal, for our research studies, we required that EMG involvement of two peripheral nerve and two nerve root levels would be required, but again, this debate whether you're going to make everybody have an EMG and all of that, I think is apropos here as well. But we wanted to make sure it just wasn't a mononeuropathy, that it was involvement of

Page 291

more than one nerve and more than one nerve root level.
Then I've alluded to this already, in isolated radiculitis, pain and weakness in one nerve root distribution really may be a form of this condition, but it doesn't meet those electrophysiological criteria. So what do you do with those patients as well?
Similarly, should we have pathologic confirmation? I would argue probably you don't necessarily need to have pathological confirmation, but it might be nice to have nerve biopsies showing inflammatory infiltrates. But in fact, most of the cases I see, we don't do a nerve biopsy on.
Then another controversial issue is the lower limb syndrome versus the whole body syndrome. What I've been talking to you so far about is diabetic lumbosacral radiculoplexus neuropathy. But in fact, a more generalized diabetic radiculoplexus neuropathy exists.
Most of the published literature is really focused on the lower limb form, but you can have a

Page 292

lower limb form, an upper limb form, a thoracic limb form, cranial neuropathies occurring in the same patient. So maybe it's best to think of this as diabetic radiculoplexus neuropathy which is made up of the components of diabetic lumbosacral radiculoplexus neuropathy, diabetic cervical radiculoplexus neuropathy, and diabetic thoracic radiculopathy. So how one should write the criteria taking that into account also needs to be thought about.
Then does diabetic cervical radiculoplexus neuropathy exist separately from diabetic neuralgic amyotrophy? I would argue it did. We did a series of 85 patients with diabetic cervical radiculoplexus neuropathy. They presented mostly as a lower trunk brachial plexopathy. Your typical Parsonage-Turner syndrome is mostly an upper trunk brachial plexopathy, so the clinical pattern is different.
Half of these patients had other forms of radiculoplexus neuropathy occurring in the same patients. So half of them had contralateral other

Page 293

limb involvement and other segments involved. These conditions present very similarly to the diabetic lumbosacral plexopathy with pain, weakness, sensory loss. They usually begin unilaterally, and half of them become bilateral. They usually begin in the subacute fashion. They have pain, typically neuropathic pain. They have weakness. They have sensory symptoms. Twenty percent or so have recurrent episodes.

As I mentioned, other segments are often involved, often the contralateral limb, often thoracic, often lumbosacral plexus in these patients. So the fact that they're getting so many other segments involved I think means it's really part of the diabetic radiculoplexus neuropathy.

They also had ischemic injury and upper limb nerve biopsies as shown there, multifocal fiber loss. They also had inflammatory collections in the nerves as shown there.

We feel that diabetic cervical radiculoplexus neuropathy is a subacute monophasic painful neuropathy beginning unilaterally in the

Page 294

upper limb, sometimes becoming bilateral. It has many similar features to the lower limb syndrome. It's not a pure motor syndrome. Sensory and autonomic fibers are involved. The pathological basis is ischemic injury from microvasculitis occurring at roots, plexus, and nerves, and it's part of this clinical spectrum of diabetic radiculoplexus neuropathy.

What role does diabetes mellitus itself play in all of this? We classify them as forms of diabetic neuropathy. However, non-diabetic forms occur. So it seems that diabetes is a risk factor, but the precise role is unknown, and should we, in fact, classify them as diabetic neuropathies?

Proposed core diagnostic criteria for diabetic lumbosacral radiculoplexus neuropathy alone or more generally diabetic radiculoplexus neuropathy. I took a shot at this, and of course, we can change this after having all of our conversations. I said one lower limb motor predominant neuropathy primarily involving the back, buttock, thigh, leg, or foot either

Page 295

unilaterally or bilaterally.

Either they need to have the presence of diabetes mellitus; three, usually a rapidly developing neuropathy in a subacute fashion in an asymmetrical distribution with a monophasic course, but it may be insidious or recurrent. Of course, this gets at this whole issue that it's usually that, but it may not always be that. So it's sort of contradictory to say that, but in fact, that is the truth. I don't know how you get around that. It's usually one way, but it's not always that way.

Weakness and pain are almost always present. In fact, you might say weakness has to be present really to have this. Sensory loss is typical. Then again, are you going to insist that everybody have nerve conductions and EMG? Nerve conductions and EMG show neuropathic involvement in the distribution of two peripheral nerve from two lumbosacral roots. I'd say an upper lumbar plexopathy would count as two nerve root levels.

Then I think you always have to have exclusion because you don't want to include lumbar

Page 296

radiculopathies and all that. So I don't know how you handle this is third world countries and all that because other neurologic diseases are going to be excluded through imaging of the spine and the plexus to make sure you don't have a structural lesion causing that or you don't have an infiltrative tumor. I think CSF is also a good thing to make sure your cytology of that is negative.

Anyway, that is my attempt at lumbosacral plexopathy. Then for more generalized diabetic radiculoplexus neuropathy, diabetic radiculoplexus neuropathy is a motor predominant syndrome of weakness, pain, and sensory loss occurring in lower limbs, upper limbs, or thoracolumbar levels.

It can be present in isolation, or it can be present in a combination of those syndromes. There needs to be presence of diabetes. Usually, the neuropathy is rapidly progressing in a subacute fashion in an asymmetrical distribution with a monophasic course, but on occasion, may be insidious or recurrent.

Page 297

Again, nerve conduction studies, EMG show involvement of two different nerve roots and two different peripheral nerves, and other causes are excluded through imaging.

Next turning to features that may be present but not necessarily part of the diagnostic criteria, weight loss is a very common feature of this. In our series, we found weight loss of 10 or more pounds in 28 of 33 patients. So again, I don't think you require weight loss to be there, but it is certainly a very commonly recognized part of this disease.

Most of these patients have type 2 diabetes mellitus, but type 1 patients certainly can present with this. So last week in the Mayo Clinic, we had a severe type 1 with a raging lumbosacral plexopathy. Nonetheless, 32 of our 33 patients had type 2 diabetes mellitus.

Compared to the regular population, there is less insulin use, less retinopathy, and less cardiovascular disease, so they probably have less complications of diabetes, better metabolic control

Page 298

than your typical diabetics do.

Again, I've already brought this up, but what role does elevated blood sugar have? The non-diabetic lumbosacral radiculoplexus neuropathy occurs with very similar electrophysiological and pathological findings. Should these illnesses be classified as forms of diabetic neuropathy or inflammatory neuropathy or other?

To date, there haven't been epidemiological studies done. People assume that diabetes is a risk factor for developing these. Peng-Soon Ng, our fellow last year at Mayo Clinic, we have been doing an incidence study of lumbosacral radiculoplexus neuropathy in Olmsted County in Rochester, Minnesota to look at this question to see if diabetes mellitus is a risk factor for this.

We defined lumbosacral radiculoplexus neuropathy by the criteria presented above. We defined diabetes by the American Diabetes Association criteria. We reviewed 1800 medical records.

Fifty-nine patients, 33 men, 26 women had

Page 299

lumbosacral radiculoplexus neuropathy. 52 definite, 7 probable. The average age was 70 years. 39 of those patients had diabetes. 20 were non-diabetic. 10 of those were pre-diabetic. The mean hemoglobin A1C was 7.8 in the diabetics and 6.2 in the non-diabetics, including the pre-diabetics.

Overall, the incidence of lumbosacral radiculoplexus neuropathy was 4.13 per 100,000 per year. Incidence of diabetic lumbosacral radiculoplexus neuropathy was 2.57 per 100,000 per year. The incidence of non-diabetic lumbosacral radiculoplexus neuropathy was 1.6 per 100,000 per year.

The odds of having lumbosacral radiculoplexus neuropathy among diabetic patients was 6.35. The odds of having lumbosacral radiculoplexus neuropathy among pre-diabetics was 1.0.

Lumbosacral radiculoplexus neuropathy is a common inflammatory neuropathy, and I think this is something that the world just doesn't understand.

Page 300

This is three times more common than Guillain-Barre syndrome. People talk about Guillain-Barre syndrome all the time. You never hear about lumbosacral radiculoplexus neuropathy.

This is an important inflammatory neuropathy that is ignored by the world. We're talking about having a neuropathy crisis and all that. I think this is something that is largely ignored. It's an important -- this causes major morbidity.

Diabetes mellitus clearly is a risk factor for developing lumbosacral radiculoplexus neuropathy, and because of that, I think it's probably okay to classify this as a diabetic neuropathy.

Lifespan considerations, there is no data about life expectancy, so I'm going to look at all these patients I told you about, and maybe we'll have some data on that, but I don't have any data about that. It clearly is a disease of middle and old age.

How about comorbidities? Well, of course, diabetes is a comorbidity. As I mentioned, there's

Page 301

less complications than in the general population. But there's little other data existing about other problems in this.

Gordon mentioned that in diabetic polyneuropathy, depression is very common. I didn't list that here on a separate slide, but depression is incredibly common in these patients. They almost get all depressed, the severe ones, and it makes sense. They're doing very well. Their life is going along great, and suddenly, they get this horrendous disease where they get this terrible pain, weakness, and it knocks them off. They often can't work, and they almost all get depressed with this disease.

I'm sure that Chris is going to talk about this in his treatment-induced diabetes neuropathy, but this is also is a treatment-induced diabetic neuropathy. I think it's somewhat ironic that attempts to be more healthy and often will precipitate attacks of the diabetic lumbosacral plexopathy.

Triggers for this include overzealous

Page 302

correction of the hyperglycemia, overzealous exercise routine, overzealous weight loss program, and post-surgical reaction.

So a typical patient will find out they're a mild type 2 diabetic. They will be fat, overweight, and they'll get on an exercise routine. They'll go on a diet. They'll be feeling really good about themselves. They'll go on treatment for their diabetes. They'll start losing a lot of weight. Everything will great, and then they won't be able to control that, and they'll develop pain, and they'll continue to lose weight, and it's very frequently induced by good intentions.

Nathan Staff and I in Mayo Clinic reported 21 cases of biopsy confirmed, post-surgical inflammatory neuropathy, a third of whom, 33 percent, could be classified as diabetic radiculoplexus neuropathy. All the biopsies showed inflammatory infiltrates.

This is microvasculitis from one of the diabetic lumbosacral plexopathies from these post-surgical inflammatory neuropathies. So these

Page 303

patients will get a surgery. They'll wake up with a post-op neuropathy that will continue to progress after the operations.

Functional consequences. The usual belief is that diabetic lumbosacral radiculoplexus neuropathies are monophasic illness and most patients will have complete recovery in a year. This is not the case. In our prospective cohort of 33 patients, most were improved, but most did not recover over time. So initially, half of them or 16 were in wheelchairs, 14 were using walkers or canes, and only 3 were walking normally independently. At two years, 3 were still in wheelchairs, 16 used aids, and 12 walked independently. So they get better, but they are often left with long-term morbidity.

Falls are common. Most patients with diabetic lumbosacral plexopathy will fall, and they often fracture bones with this. So hip fractures are not uncommon in diabetic lumbosacral plexopathy.

Some patients have ongoing long-term pain

Page 304

from this, too. Long-term morbidity from weakness, pain and ongoing needs for walking aids is a very common problem with these patients.

In conclusion, there are no established criteria for diagnosis of diabetic lumbosacral radiculoplexus neuropathy. I think there are lots of controversial areas in this. Is this a pure motor syndrome? What's the role of pain? What do you do with rapid versus insidious, symmetric versus asymmetric, need for nerve biopsy, need for EMG, and whether we just should have criteria for the lower limb.

I've given you some proposed criteria for both diabetic lumbosacral radiculoplexus neuropathy as well as diabetic radiculoplexus neuropathy. I think they can be fairly easily definable and usable.

Diabetes mellitus clearly is a risk factor for developing diabetic lumbosacral plexopathy. These syndromes are precipitated by over-correction of blood sugars, exercise, or weight loss similar to treatment-induced diabetic neuropathy, and long-

Page 305

term morbidity from pain and weakness is common.
Thank you all for including me.
(Applause.)
Q & A
DR. FREEMAN: That was really great. I'm going to move things along. So let's have questions, and then I want to get back to the core criteria so that we can actually come up with something operational.
Just to give the perspective for where we want to be at the end of the presentation, Jim did a trial on a diabetic lumbar radiculoplexopathy with methylprednisolone. Vera wants to replicate or show that it actually does work at some point in time. She needs to have the cookbook, no usually, no maybe, no sometimes, 1, 2, 3, 4. So that's where we want to be at the end of the session so that we can be in the situation that we can do another clinical trial using that cookbook.
Vera, off you go.
DR. BRIL: Thanks. It was an excellent presentation. My question is a little bit off. So

Page 306

these are, what, 60 to 70 years old, these patients, and you do an MR of them. Almost everybody has spinal degenerative disease at multiple levels.
I understand if it's in the upper limb or thorax, and I know when you've done the biopsy, but now you're not doing biopsies. How are you so clearly distinguishing between degenerative spinal disease? Because they don't have clean MRs, most of them.
DR. DYCK: No, they don't. Most people don't have clear MRs.
I think what you do is you do your MRI. You look at their findings. You look at their EMG. A little bit of degenerative change in the spine is not going to cause it. If they have an upper lumbar plexopathy and there's a big disc pushing on the L3 nerve root at that level, then you think, well, maybe that is due to that, and then you have them see a surgeon.
I've had patients who I'm convinced have diabetic lumbosacral plexopathy who I've then sent

Page 307

to surgeons and had operations that helped them. And I've had the opposite happen much more where a patient will present with pain and weakness in the lower limbs, have an MRI on the outside before they ever see me. Go to a surgeon, have an operation; that doesn't help them, and they progress, and then they come to see me.
DR. BRIL: I think there's a contradiction in there when you say they clinically have a plexopathy and then say, oh, but they have L3 --
DR. DYCK: Yes.
DR. BRIL: -- so I think you can do it by --
DR. DYCK: That's the issue. I agree with you.
DR. BRIL: -- exam and/or by EMG to show that it's outside one nerve root.
DR. DYCK: Yes. So this is the whole issue of the EMG criteria for involvement of more than one nerve root. The real problem of that comes with the upper lumbar plexopathy, and that's why I used the L3 as an example.
L3, if you do an EMG and you find

Page 308

involvement of the adductor longus and L2-3 muscle of rectus femoris in L3-4 muscle, vastus medialis L3-4 muscle, you could say, well, there are two different nerve root involvement, there are two different nerves, the obturator nerve and the femoral nerve. But that still could potentially be an L3 radiculopathy. But the problem is that you will get pure upper lumbar plexopathies that are part of this, so I don't think you can exclude them.
So these attempts to try to differentiate them are imperfect. I don't know a way around that.
DR. FREEMAN: Yad, then Nathan [sic}, then Doug.
DR. HARATI: Is there a place for spinal fluid studies positive or negative, sorting it out?
DR. DYCK: I went through a lot of stuff very quickly. Again, I think this whole issue that we brought up in the past of the criteria for the practicing physician in the community and the criteria for research studies probably are going to

Page 309

want to be somewhat different. But for me, the work-up I do -- either I do it or it's been done, an MRI of the lumbosacral spine, an MRI of the lumbosacral plexus. The spine to make sure you don't have some compressive spinal stenosis disc pushing on something. The plexus to make sure there's no infiltrating tumor. I do a CSF.

The average CSF protein is elevated in these patients, but the bigger reason you're doing it is you want to make sure they don't have lymphoma, they don't have some tumor infiltrating the nerve. So I do a CSF for the cytology predominantly.

I do blood work-up looking for other causes. I do the EMG to meet that criterion to make sure it's not some other disease, and then I may or may not do a nerve biopsy. I'm doing a nerve biopsy mostly when I think it might not be this, if it's gone on too long to judge disease activity, that, and potentially treat them.

DR. FREEMAN: So this is a disorder -- and I just want to again keep us focused -- that is rare enough that I think our goal over here is not to

Page 310

give clinical criteria for the practicing neurologist or diabetologist, but to come up with criteria if somebody wishes to do a clinical trial, immunomodulation, one kind of another, that they have a cookbook, the recipe.

Nathan [sic]?

DR. KOLB: Along those lines, if you want to include people, it looks like the hemoglobin A1C for the non-diabetic group, the mean was 6.2, so do you think a lot of those patients are pre-diabetic and --

DR. DYCK: A lot of those patients are pre-diabetic. So there are 20 patients; 10 of them were pre-diabetic. I actually gave you that data, but I agree, I went through this quickly. So yeah, they were.

DR. KOLB: So do you think that we should reconsider in the pre-diabetic people that definition?

DR. DYCK: Well, again, we used controls. What I showed you there was from the Rochester -- the odds ratio of the pre-diabetic was

Page 311

1.0 compared to the population. So it was an increase in the pre-diabetic.

DR. FREEMAN: Sorry, Jim.

DR. DYCK: Doug.

DR. ZOCHODNE: I don't want you to miss your plane.

DR. DYCK: My plane's at 7:00. It's okay.

DR. ZOCHODNE: My proposal would be to accept your carefully one criteria as is. I think they look pretty good. I wouldn't have any difficulty with them.

I may be a little out of line here, but a sidebar, which is you got this kind of cohort of these people in Rochester, what are we doing to look at the etiology of this condition in terms of autoantibodies? I think you're perfectly set up with Vanda Lennon or substitute. We just had Jan Willem Tervaert join us at U of A who discovered ANCA, so let's push this along to the next step. I think it would be a major breakthrough if we could identify what the etiology of this --

DR. DYCK: In fact, we did look for some

Page 312

several years ago and didn't find any.

DR. ZOCHODNE: I think we should keep at it because the technology is charging ahead, too.

DR. FREEMAN: David, and then Solomon.

DR. HERRMANN: Two questions. You mentioned most of the time there's some proximal involvement, but you did define some patients who had foot drop. In a foot drop, wouldn't you exclude patients who just have a mononeuropathy --

DR. DYCK: I would.

DR. HERRMANN: You would?

DR. DYCK: I would.

DR. HERRMANN: Even though it probably can occur, you want to make sure that --

DR. DYCK: Whoa, whoa, whoa.

DR. HERRMANN: -- plexus or root is involved?

DR. DYCK: I have argued that -- I wouldn't exclude mononeuritis multiplex, but they do have to have two nerves involved and two roots involved.

DR. HERRMANN: Have the roots involved.

DR. DYCK: Yes. Well, two roots involved.

Page 313

So if you had some focal proximal process and a focal distal process, then you get that. An isolated foot drop just in and of itself probably isn't going to meet those criteria, but really what's more common is they'll present with a foot drop, and then with time, it evolves into having more than that.

DR. HERRMANN: One other question, just a really short one to Doug's point. Are there exclusionary blood tests? I don't know who had mentioned the ESR. Are there exclusionary blood tests for this diagnosis?

DR. DYCK: Exclusionary --

DR. HERRMANN: Yeah, in other words --

DR. DYCK: No, no, I'm thinking about that. You do blood tests to look for other causes, so you may find things that then may lead you -- for instance, you might do a monoclonal study. You'll find a monoclonal approach, and you'll do a nerve biopsy, and you find amyloid in there.

The blood tests by themselves, are the exclusionary, probably not. If you had all kinds

Page 314

of inflammatory rheumatological things and you ended up finding that this person really had rheumatoid arthritis, maybe this is mononeuritis multiplex in rheumatoid arthritis and not due to the diabetic syndrome.

I don't know if there are exclusionary blood test in and of themselves, but I think you're doing those blood tests to look for other conditions.

DR. FREEMAN: Solomon, then Gordon. Then we're going to go back to the slide, and we're going to put both Stephen and Jim on the spot, and we're going to fix those criteria.

DR. TESFAYE: The question for me is, is there a pattern of recovery? Is there a natural history? I always say to the patients -- and I have seen about a dozen of these patients over many years -- that the pain will get better. I reassure. They're profoundly depressed. They're completely devastated when they see you. The pain will get better. Weakness will improve. Reflexes appear to be the last ones that recover.

Do we have a naturalist?

Page 315

DR. DYCK: Well, so I have a lot of experience seeing these people over time, but then again, that's -- so I'm going to look at this cohort that I just showed you, the preliminary stuff, to try to get some of that information.

I think it is clear -- so back to my original prospective study in '99, I did follow-up with them, and it was really interesting to me that where many of them had been in a wheelchair originally, now almost all of them walked, but many of them still had foot drop. And I think in some ways this makes sense.

Proximal nerve segments rennervate, and they can walk. The thigh muscles come back in almost all of them, but they're often left with that foot drop. I think that makes sense. Proximal segments rennervate better and more completely than distal, so patients are often left with a foot drop where they are not usually left unable to walk, which is good.

Most of the pain gets better, but some of these people do develop chronic pain state. So I

Page 316

think it is not correct to tell patients that their pain necessarily will get better. Almost all of them, the pain gets better, but some of them are left with chronic pain situations.

Quadricep reflexes usually come back. Ankle reflexes often don't come back, not that it really matters if you regain your reflexes or not. But often what these patients look like years down the road is a severe length-dependent diabetic polyneuropathy because it's all distal and they might have foot drop, and then the proximal stuff is all rennervated.

DR. FREEMAN: Let's have Gordon, who I think was next, then Yad. That will be the last question, and if we could start moving back, maybe about eight slides back, and I'll let you know when to stop.

DR. SMITH: This is all making me a taxonomic catastrophizer.

(Laughter.)

DR. SMITH: Thinking about David's question, a patient who was diabetic, who has a subacute

Page 317

onset of a foot drop, who has denervation in multiple nerve roots, does that fit the criteria? Because I can start to see where if one aligns the typical features, let's say a progressive onset, let's say absence of pain, let's say distal predominant, one could end up with a lot of confusion with other disorders.

DR. DYCK: Well, again, I think one important thing in this -- and if it's not clear the way it's written, it should be -- is that this is a diagnosis of exclusion. So other conditions that this could be need to be excluded, and if they are those, then they're those.

I think we absolutely need to write it in such a way because -- and I say that when I get up and give talks about this, this is a diagnosis of exclusion.

Most of these patients will have proximal involvement, but they don't all have proximal involvement. And I think we would be wrong to exclude those patients who don't have proximal involvement.

Page 318

DR. FREEMAN: Yad, and then can we get the presentation back on, please? This one.

DR. HARATI: I just wanted to add, doesn't the improvement coincide on those who have lost weight with the resumption of the weight, normal weight?

DR. DYCK: Usually. So improvement, I often will tell patients that when their pain goes away, that's a good sign. When the weight loss stops, that's a good sign because that usually is an indicator that the disease activity isn't so much. But that's not a hard and fast rule.

DR. FREEMAN: Sorry. Amanda, you have something? No.

DR. PELTIER: I was going to comment on the criteria --

DR. FREEMAN: Remember, we want this to look like the migraine with aura, so 1, 2, 3, 4. The principle, these are core criteria, so we're focusing on specificity. If there are variants that fit the picture but are not quite typical, that's okay. Those will be the variants, and those

Page 319

will be discussed. We can't deal with -- I get the feeling that this is diabetic radiculoplexus neuropathy, what smells like it, therefore, it is. This is so somebody who's not an aficionado can say these are the patients I want to include in the trial.

DR. CALLAGHAN: It's hard to operationalize number 3, right?

DR. FREEMAN: Sorry. I can't hear that.

DR. CALLAGHAN: It's hard to operationalize number 3 because it's --

DR. DYCK: I agree with you, but I don't know what you'd do with it. It gets to be like his point about there's some preceding damage or injury in patients with complex regional pain syndrome.

It's been recognized for 50 years that most of these patients are subacute rapidly evolving, but some of them are insidious. You could leave it out completely, but I think you're missing the flavor of the disease if you completely drop it, and I don't know how to get around that.

DR. PELTIER: I would actually make the

Page 320

argument --

DR. FREEMAN: Amanda and then we'll have Stephen. Amanda?

DR. PELTIER: I just was going to make the argument actually, I would get rid of the insidious and the recurrent because I think those are a different population.

DR. BRUEHL: Stephen, fix this for us.

DR. BRUEHL: All I'm going to do is I'm going to give you the same feedback that I gave [inaudible - off mic]. The things that I see that you would want to consider changing, one is whether you want even the lumbar versus cervical because to me, if it doesn't really change the basic description, the basic clinical features, it would make more sense to have just the one.

DR. DYCK: Not two criteria but one criteria?

DR. BRUEHL: Yes, just one set of criteria.

DR. DYCK: I wrote them both, and we can open up. The lumbosacral is probably the most common thing, the thing that has the most agreement

Page 321

to, and that's part of the reason why I wrote it that way, because I think that's the one that everybody agrees with, and then the other one, you know.

DR. BRUEHL: That makes perfect sense. That's fine.

Number 1, motor predominant neuropathy, how do you operationalize that? What does that mean?

DR. DYCK: It is you're weak.

DR. BRUEHL: So it would be associated with weakness, right?

DR. FREEMAN: Yes, and he means, I think, motor greater than sensory or autonomic. I think that's what he means.

DR. DYCK: That is.

DR. BRUEHL: You just need to have it worded in a way where somebody who isn't an expert --

DR. FREEMAN: -- all of that because we do more if feels like this is the entity, it smells like it's in the entity. So help us operationalize it.

DR. BRUEHL: I would just say on number 1,

Page 322

since the back, buttock, thigh, leg, and foot could all be considered lower limb, for complexity reasons just say lower limb or back --

DR. GIBBONS: Motor greater than sensory --

DR. BRUEHL: Yes, neuropathy, yes.

DR. BRIL: Or could you just say weakness?

DR. BRUEHL: Yes, weakness associated with --

DR. BRIL: Pain and --

DR. DYCK: That's number 4, but you might be able to --

DR. BRUEHL: Yes, so you might just combine those. So the definition would be weakness and pain with weakness predominant in a lower limb or back. You don't need to get into unilateral or bilateral if it could be either one. You don't need the specific body areas.

I think 4 and 1 could be combined pretty easily there to capture the essence of it. Number 2's perfect.

DR. FREEMAN: Can I just ask, Jim, can you live with weakness and pain, that pain is part of

Page 323

the core diagnostic criteria?

DR. DYCK: Well, I think that --

DR. FREEMAN: Or do we need to say variants, painful and painless?

DR. DYCK: Well, I think you have to at some point take into account that there is a painless variant. I don't know how you want to do it. It just needs to be taken into account somehow.

DR. BRUEHL: I would just say then neuropathy associated with lower limb weakness as number 1.

DR. DYCK: Yes, but the problem is then you've got ALS.

(Crosstalk.)

DR. DYCK: Pain is a very stereotypical component of this in 95 percent of the cases, but it's 95 percent of the cases.

(Crosstalk.)

DR. FREEMAN: And that's what we want to live with --

DR. BRUEHL: Then you lose the 5 percent and figure out later what to do with that.

Page 324

DR. DYCK: This is what Amanda is saying, but they exist.

DR. BRIL: Can you put a note at the bottom saying up to 5 percent are painless?

DR. DYCK: I wouldn't have a problem with that.

DR. FREEMAN: We have a section for variants, and that would be under variants. So I think that's great.

DR. BRUEHL: Other than that, the number3, that is not very clear to me.

DR. DYCK: No. Again, it's this exact same issue. Most of these patients will present in a subacute fashion quite asymmetrically.

DR. TESFAYE: Subacute for weeks and months?

DR. DYCK: Exactly, so subacute weeks.

DR. TESFAYE: It's got to be weeks --

DR. FREEMAN: Can you give us usually end rapidly? What do we mean? We need a time frame?

DR. DYCK: Yes, I think they hit their nadir within about 6 months on average.

DR. TESFAYE: Yes, weeks, months.

Page 325

FEMALE VOICE: So it's more than 10 days?
DR. DYCK: Yes, exactly. Right, exactly. This whole issue, subacute is one of these nebulous terms that's very --
DR. FREEMAN: So we want to --
DR. DYCK: -- but if you say chronic, you get this idea of a very long drawn-out thing, and it's not that.
DR. BRUEHL: You can say, though, rapidly developing neuropathy over 2 weeks to 6 months, something like that.
DR. DYCK: Weeks to months, I think you could, yes.
DR. FREEMAN: Even ideally, we want to know that.
DR. DYCK: The problem with the numbers, I see lots of patients who walk into my office who are two years into this disease. They say, "Oh, I'm so atypical." I do a nerve biopsy, and this is one of the reasons I do a nerve biopsy because it's still active, and I see microvasculitis.
It is not uncommon for that to go on for a

Page 326

couple years. Now, not uncommon in my experience. That may be uncommon in the community, but that's not so atypical.
DR. BRUEHL: Symptom onset, though, within 6months?
DR. DYCK: Symptom onset usually is quite rapid, but then it progresses over time.
DR. BRUEHL: I think that would be a point to make here is that's kind of the pattern that you would expect to see is rapid progression of symptoms from normal functioning over a period less than X time, something like that.
DR. DYCK: It progresses over weeks. I think on average it hits its worse about 6 months, but that's average.
DR. FREEMAN: We just think 80 percent. We aren't interested in the 90 percent cases. The rest will be variants, so that David Bennett can do the clinical trial at Oxford. He needs to include those representative patients.
Can we deal with the usually rapidly progressing in a subacute fashion and put numbers

Page 327

on that? I'm assuming we can.
DR. DYCK: No. I think that's typical.
DR. BRUEHL: I agree with you. The insidious or recurrence, it can be both. It's pointless to even mention it.
DR. DYCK: No. I --
DR. BRUEHL: But then to mention it here, you do put it under Dimension 2.
DR. DYCK: But this is the issue, and it's always this issue about this contradictory sort of things, and they both can occur. But if you leave it out completely, you lose the flavor of the disease, and that's why I think you need to have it in there.
Yes, Ahmet?
DR. HOKE: Are the insidious ones actually the same disease as the ones who --
DR. DYCK: Well, I have a paper arguing that they are. You can argue with me.
No. So my problem was I had these motor predominant ones that often had a lot of upper limb involvement. There has been this debate -- and

Page 328

Vera is a big part of this debate -- of whether this is or there is not diabetic CIDP. I argued that if there would be a diabetic CIDP, these people with a more insidious, more symmetric, more upper limb predominant neuropathy, a polygeneralized polyradiculoneuropathy, that should be diabetic CIDP.
I did nerve biopsies from 20-some of these patients without pain, and most CIDP doesn't have much pain. So I thought if there's diabetic CIDP, this should be diabetic CIDP. We found multifocal fiber loss, perineural thickening, neovascularization, microvasculitis. We did not find segmental demyelination. We did not find onion bulbs. We found no significant differences in the pathology.
So from a pathological point of view, I say they're the same. Clearly, from a clinical point of view, they're not the same. It depends on, you know.
DR. FREEMAN: How should we deal with this, do you think? Do you think we should have two sets

Page 329

of core diagnostic criteria, painful and painless, or do you think we should include in your core diagnostic criteria one set of diagnostic criteria and, say, maybe painful or painless?

DR. DYCK: I don't have a problem saying painful, rapidly progressive with an asterisk saying there are rare cases that don't have pain and are more insidious.

DR. FREEMAN: Is that okay?

DR. DYCK: I don't have a problem with that. That's kind of what I tried to do here, just putting it into that because that is the flavor, and that's why I did it this way. I was quite aware that number 3 seems completely contradictory, but that is the truth is the problem.

DR. PELTIER: Back to your pathophysiology, Jim, are the insidious/painless cases respond to Solu Medrol and IVIg in the same way? Because if they don't, then one could argue are they really truly the same disorder.

DR. DYCK: That was a retrospective series. They did seem to go monophasic illness. They did

Page 330

seem to get better. But again, it's a retrospective chart review, so it's imperfect data.

DR. SMITH: I'm trying to operationalize 3. Chronic things always begin -- this is like Yogi Berra -- at some point, and if they're progressive, they get worse from that point to when I see them. As you pointed out, we often -- in fact, the norm is that we see these patients a year or two years in.

If the criteria says that there's an onset with a progression over weeks to months, I'm seeing them two years later, how do you word it so that we're not capturing an insidious linear progression from onset to where I am two years later? How do we prevent that or differentiate that from the typical subacute, or does it matter that we do so? Kind of operationalizing the third criteria.

DR. DYCK: If we do future studies in this, I would encourage anybody involved -- I'd be very interested in being involved in that, too -- to get early cases.

In our study, we required them to come in

Page 331

within six months of the onset of the most recent lower limb, and I don't think that was early enough because I think they all on average already were hitting their disease nadir. I think that was the big problem with our study. The problem is, is that you've got to find a different way of identifying these patients because essentially, that's when I was seeing these patients.

DR. FREEMAN: If we go back to the onset because that's probably what's critical to the diagnostic criteria, not necessarily when you see them six months later, but the onset, we're going to come up with something operational, I think. It sounds like we are.

DR. BRUEHL: Just out of curiosity, so if somebody came in two years after it really started and the criteria says rapid onset of symptoms within three months, do you think the average patient, would that stick out in their mind so they could go, yes, it definitely did?

DR. DYCK: Yes, no. They tell you that story. So the typical story is I will see them two

Page 332

years in, and they'll say, two years ago, I developed terrible pain in my anterior thigh and a foot drop. Three months later, I got terrible pain in the thigh. One year ago, I got terrible weakness in my other thigh, and it started atrophying. Three months ago, I got foot drop in my other leg. They tell you this story of this patchy asymmetrical involvement.

DR. BRUEHL: That seems reasonable to me.

DR. FREEMAN: Nathan, and then Yad.

DR. KOLB: I was thinking that if we think this is an important distinction, much like we do migraine with and without aura, we could just point a time point on it and have them 1.2.2. If we think that's an important distinction at the separate time.

DR. FREEMAN: We'll leave that to be sorted out as this evolves.

Yad?

DR. HARATI: For the inclusion of these patients, I'm sure that since you're at the tertiary referral centers, you have seem some

Page 333

patients who actually were operated on their back.
DR. DYCK: Many.
DR. HARATI: Many of them. How do you deal with that?
DR. DYCK: Well, so typically, I wouldn't use that as an exclusion criteria. If they had a back operation, usually what happens is they come in with more focal involvement. They have their operation, and then they get worse in the post-operative period, and then they develop a more widespread plexopathy, but that's really quite common.
DR. FREEMAN: Last couple of things, for a clinical trial, do you think we need to have the neurophysiology showing --
DR. DYCK: Absolutely.
DR. FREEMAN: So that's part of the diagnostic criteria.
DR. DYCK: Yes, right.
DR. FREEMAN: For a clinical trial, I asked do we need to have the neurophysiology showing that there is more than one nerve root distribution, and

Page 334

the answer was absolutely. And then for a clinical trial, do you think we need to do a lumbar puncture.
DR. DYCK: I would.
DR. FREEMAN: Does David need to do that?
DR. DYCK: I absolutely see people who have neurolymphomatosis, who have sarcoidosis, that are mimickers of this illness.
DR. FREEMAN: David needs to do that.
DR. DYCK: You don't think you need to do it, David?
DR. HERRMANN: He's smiling.
DR. BENNETT: Actually, I normally do exactly what he suggests. We do nerve conduction studies, imaging, and a lumbar puncture, and I rarely do a biopsy.
DR. DYCK: So I brought the biopsy up. I don't think you need to do a biopsy, but I just thought we should have that conversation.
DR. FREEMAN: Gordon?
DR. SMITH: Asymmetry?
DR. FREEMAN: Yes, because I was also

Page 335

wondering about that. Asymmetry, you say bilaterally. Do you say bilaterally but asymmetrically or not?
DR. SMITH: Recognizing that some are symmetric.
DR. DYCK: But then that's the issue. It's usually asymmetric. It's not always asymmetric.
DR. FREEMAN: Usually 60 or usually 90?
DR. DYCK: Usually 80-plus.
DR. GIBBONS: So that would move to the criteria to the diagnostic 2, right?
DR. BRUEHL: If it's just descriptive, yes.
DR. HARATI: Jim, would you require an imaging with and without contrast because of the inflammatory process, the spinal AVM, et cetera?
DR. DYCK: Yes, well, no. An AV dura fistula is another thing that this could be. I guess I have vascular on there. It's certainly better. If you're just looking for a structural thing, maybe that's not needed, but I think you're going to see tumors and things like that way better with contrast. It's definitely better.

Page 336

The other thing is do you require one imaging or two imaging? In other words, spine imaging or spine and plexus imaging? Because again, you can get both.
DR. FREEMAN: I agree. Look, I think one last thing, cervical, do you think we can say lumbosacral, cervical, thoracic, all of these criteria apply? Thoracic is a little tougher. So it will, as Nathan said, 1, 2, and 3, or do you think we need to combine all of these together?
DR. DYCK: I would separate.
DR. FREEMAN: You'd do it separate.
DR. DYCK: I think lumbosacral stand alone, and then you have a diabetic radiculoplexus neuropathy made up of these other ones.
Jim?
DR. CALLAGHAN: It seems that each of the main criteria has a caveat: diabetes but maybe not diabetes, pain but maybe not pain.
DR. DYCK: Yes.
DR. CALLAGHAN: Is this one of those where maybe we should have like here are the core five or

Page 337

six, seven features, and if you have greater than four or five of them -- I don't know what the cutoff would be -- that that would increase your level of certainty, knowing that it's not perfect?

DR. DYCK: Well, no. The whole diabetes issue is another one. We are at a diabetes consortium meeting. I think when it comes to the lumbosacral one, there is no question the diabetes -- I've just shown you good evidence that diabetes is a major risk factor for developing that.

For the brachial plexus one, I think it's much more controversial. In our series, though, as I say, 50 percent of the ones that have a brachial plexus have other segments involved, and I think that really argues it is a little different than your typical Parsonage-Turner. So I think in that sense, it's reasonable to classify them that way.

I don't know if it's really the best, though, just to say 4 of these 7 or whatever because, for instance, weakness. I think we're talking about a weakness syndrome here, so I think

Page 338

everybody has to have weakness. There are probably mandatory things.

Pain is really typical in this, but there is this cohort that doesn't have pain. But really, you're expecting most of them to have pain.

DR. CALLAGHAN: Like POEMS syndrome, POEMS syndrome has some criteria that are mandatory and then --

DR. DYCK: Yes.

DR. CALLAGHAN: -- so you could think about weakness being mandatory.

DR. FREEMAN: Rayaz?

DR. MALIK: Should there be some kind of system to say pain more than an NRS of 4 or weakness more than an MRC grade to give it a bit more solidity? Because otherwise, at the moment I'm left, how much weakness, how much pain.

DR. DYCK: It is a variable severity disease. The EMG criteria in a sense, although it's not measuring weakness per se, to say you have to have denervation, neurogenic changes in two different peripheral nerves from two different

Page 339

lumbosacral roots is getting at that. You have to have a fairly severe syndrome to show that.

DR. SMITH: This feels to me a bit like the way you would test is the vignette approach, right? You're going to throw out a set of criteria that we have a sense for what they look like, and they're going to deal with these atypical features. Then we can easily create typical, atypical, and then non-entity vignettes to see how they perform.

DR. FREEMAN: I think that's a good one to put on the list of research studies. I think that would be great; both.

DR. HERRMANN: I'm thinking ahead to the trial that you're going to be conducting in this. Would the trigger be relevant in terms of eligibility? So you have the subgroup who goes on extreme exercise, extreme weight loss, et cetera. Would you want those individuals that have that very defined trigger in the same trial as the ones that we see just occurring?

DR. DYCK: I don't know. I have no reason -- other than that, they seem to be really

Page 340

very much the same syndrome. In fact, some of these post-surgical inflammatory neuropathies, I have a case who had a diabetic lumbosacral plexopathy happening on its own. Two years later, he had a CABG. After his CABG, he developed a little bit of numbness; woke up with a little bit of numbness over the back of his wrist. Then progressively over the course of the next three weeks, he had a plegic upper limb that was completely allodynic and wouldn't let anybody touch it.

I did a superficial radial nerve biopsy. He had vasculitis in that. So he had had a spontaneous lumbosacral plexopathy, and then he developed this induced cervical radiculoplexus neuropathy.

I'm not sure that they are different, but it's true with all these things that you have to learn more.

DR. FREEMAN: Any other questions?

(No response.)

DR. FREEMAN: Jim, this was fantastic. You

Page 341

really made our jobs very, very easy.
Anything else?
(No response.)
DR. FREEMAN: No, good.
What I think we should do now is move back to the previous presentations, have Eva come up and do her group's talk, and then finally, James' talk.
But, Jim, thank you very much.
(Applause.)
DR. FELDMAN: I'm going to have Gordon give it for us.
(Crosstalk.)
Breakout Discussion (continued)
DR. SMITH: This was in some ways the Toronto criteria redux, and I'll get to, we basically came up with a very similar framework with just a couple of differences. The process we went through was first to think about symptoms and then signs. We created a list of the symptoms and signs that we thought were relevant. And just as a way of organizing these, thought of positive and sometimes painful symptoms and negative symptoms,

Page 342

although we don't differentiate these in the diagnostic criteria and then signs. Then we organized how these were going to be used into possible, probable, or confirmed groups. Then had a discussion about how to use confirmatory testing for the confirmed.
This is the definition that we arrived at for positive, and you can see here the symptoms. So positive and negative aren't really differentiated in the criteria per se. They're just for organizing.
Pain, sharp sensation, shocks, burning, aching, contact sensitivity, pins, needles, paresthesias, dysesthesias, tingling, numbness, or other descriptors of loss of sensation. Solomon talked about the weird feelings people get walking on stumps, feeling of swelling, and the absence of swelling, and one might better define these.
Then the signs being vibration abnormalities with the 128th hertz tuning fork. We had a discussion about whether to be definitive about what those criteria would look like timed, on, off,

Page 343

and these sorts of things. We came down at least at this point for just abnormal vibration.
Same with pinprick, light tough, temperature, ankle reflexes. For light touch, it would be normal or absent and not in a graded fashion. We actually suggested using cooling, which is separate from or different from the first group but thought not to use heat sensation. And then something I failed to mention is that this needs to be in an appropriate anatomic pattern, so a lower extremity, distal, symmetric, a length-dependent pattern for these.
For possible, it would be either one or more symptoms or one or more signs, essentially. Actually, it should be just a symptom or a sign, I think, as we get to the next one.
We did have a discussion about whether or not this even was worthwhile. Why have a possible category? I raised as someone who's a recovering plantar fasciitis victim, I would be a possible neuropathy patient if I weren't particularly eloquent in my description. I blame Noah for my

Page 344

plantar fasciitis, by the way. I had aching pain in my feet.
So that's okay in an epidemiologic study. So if one is in Central Africa doing a prevalence study of diabetic neuropathy and using just a survey, then that would be the sort of study where one might use this approach.
Probable neuropathy was either one symptom or one sign. So for instance, electric shocks in the feet with abnormal vibration or more than one symptom or more than one sign. So if electric shocks and numbness or abnormal pinprick and abnormal reflexes, so one symptom, one sign, or more than one symptom or more than one sign. So that would be probable.
Then definite was essentially probable with a confirmatory test. This is where we had some discussion. I tried my best to lobby for a purely clinically-driven definite neuropathy, to no avail, which I can understand why. We then had a discussion about which tests would be appropriate. And similar to the first group, we talked about the

Page 345

utility of quantitative sensory testing and decided that quantitative sensory testing really is nothing more than a different way of assessing the same sign modalities that we're already assessing with the clinical examination.

I see nodding over here so that's good. It's always good when Amanda -- I think you agree.

DR. PELTIER: Except I'm going to pick on you for simplicity's sake. What is really the operational difference between a paresthesia and a dysesthesia? I don't even know if I would be able to quantify that. So I would say use one word or the other.

DR. SMITH: I actually think I would not use either word.

DR. PELTIER: That's fine with me.

DR. HERRMANN: I may have this wrong, but isn't paresthesia spontaneous symptom whereas dysesthesia is invoked with a --

DR. SMITH: Right, so I think I would describe these differently.

(Crosstalk.)

Page 346

DR. TESFAYE: It's painful paresthesia.

DR. SMITH: So paresthesia is unpleasant --

(Crosstalk.)

DR. SMITH: It's an unpleasant paresthesia. But I think we should capture these in words that -- we're struggling with this here, that people who are non-endocrinologists and non-neurologists would understand.

DR. PELTIER: This is my point is that if you're a family practice doctor or you're out in the community -- if you say two or more symptoms, well, that could be two symptoms, but are they really that significantly different?

DR. POP-BUSUI: This is for research.

DR. PELTIER: Right, but again --

DR. SMITH: But you can describe these in an easily understood way, right?

DR. FREEMAN: But you do want to say pain. That could be electrical shock, burning, aching because those are all pain variants, I'm assuming.

DR. SMITH: Right. Well, then there's the other question is we really aren't necessarily

Page 347

saying there has to be pain.

DR. BRIL: No, but these were put in that line because some people say the tingling is very painful, so a dysesthesia, right? But tingling was repeated because it need not be painful. So it was done kind of quickly. So there was a distinction there, pain of all these types or tingling and going on to the other symptoms.

DR. SMITH: I think we have a separate taxonomy for painful diabetic neuropathy. So what I would posit is we really don't need to say whether or not it's painful in this. We need to describe the different sensory phenomena, and clearly, you don't want to have a tingling -- maybe you don't need tingling and pins and needles. I don't know. We need to throw something out to capture that.

I don't have a moderator. Doug?

DR. ZOCHODNE: Doesn't Peter Dyck have a paper that says in Minnesota that you have to use a descriptor "prickling"?

(Laughter.)

Page 348

DR. ZOCHODNE: There is a paper on this for [inaudible – off mic].

DR. SMITH: Tongue out of cheek, that's probably an issue as one thinks to validate individual symptoms as part of a diagnostic criteria cross-culturally. I don't know what you say in the UK.

DR. FREEMAN: Just looking at this, we want two or more symptoms, and can those two both be dysesthesias and paresthesias or dysesthesias -- remember, we can work on this, but I just want to be sure that pins and needles and paresthesias are --

(Crosstalk.)

DR. BRIL: How often do you get one without the --

DR. SMITH: It's an affective component of it, right? So your paresthesia might be my dysesthesia because I'm a wimp.

DR. TESFAYE: Pins and needles paresthesia.

DR. SMITH: Yes, so pins and needles --

DR. POP-BUSUI: Pins and needles is the lay

Page 349

term for paresthesia.
DR. TESFAYE: I think if you say paresthesias, you don't need tingling in addition.
DR. SMITH: Pick one or the other, yes.
DR. TESFAYE: Pick one, yes.
DR. BRUEHL: In fairness to Jim, I sat in on this. I did not critique like I did his. I was kind of withholding judgment, but I agree with some of the comments that have been made. And one way to do it would be to have your main criterion be paresthesias and then parenthetically say such as and just give a few examples like that where it doesn't have to be exhaustive.
(Crosstalk.)
DR. PELTIER: I would include itching.
DR. FREEMAN: It seems like we can deal with pain examples.
(Crosstalk.)
DR. PELTIER: A lot of patients have like inexplicable in their feet and their lower extremities and do not realize that it's a neuropathic symptom.

Page 350

DR. HARATI: Other symptoms may get better, but the itching doesn't because they're different small fibers.
DR. FELDMAN: Gordon, if you go back to the very first slide we did on probable neuropathy, I think that what we -- possible. I'm sorry. "Continue to discuss pain in more refined definition," and then I just copied and pasted for the next.
If you remember, we had this discussion or began to have this discussion as we were talking about possible, probable, and confirmed. And I do think we've really started discussing in more detail confirmed neuropathy, and I think it's important whatever we decide needs to hold for both possible and probable.
DR. BRUEHL: For example, one way this could be worded up here would be pain -- you can have, let's say, four items, and you say must -- three of four of these -- if you wanted to go this route, and you could say pain that is frequently described as sharp, electric, whatever. You could have a

Page 351

separate one that's paresthesias. You could specifically list tingling if you thought it was key enough, or itching, to have a separate item on there. Then the numbness or dead feeling, however that one would be worded.
The way we've structured it here, it's just like any one of those would qualify, and none is really primary. My understanding was that's intentional, correct?
DR. SMITH: I don't think, though, we want pain as a core feature here. I think the idea is that we're going describe the sensory phenomena. There's a separate set of criteria that will deal with whether or not this qualifies as painful neuropathy. But here, we can almost be pain agnostic. Whether or not the pins and needles are merely paresthetic, dysesthetic is less of an issue here. It's just that they're paresthesias, that it's an abnormal positive sensory phenomenon that in Olmsted County would be prickling. I think prickling is kind of good. I like that.
DR. GIBBONS: Just one question then. Our

Page 352

group was really negative on the temperature cool sensation on the feet.
DR. FELDMAN: Well, David, do you want to speak up for that?
DR. BENNETT: I think it works very well, a cool thermal roller. Is there a reason why you were negative?
DR. PELTIER: Because there's a lot of patients who have very cold feet that they're not -- I find it to be less sensitive or less helpful, and if it's usually positive, the pinprick is almost always positive, also. So if you're going to do one, just do the pin.
DR. SMITH: We don't have to do only one.
(Crosstalk.)
DR. BENNETT: I'm not sure I agree. I didn't have the same experience. It may be suitably, not clinically.
DR. SMITH: I think thermal -- I think cool sensation can be helpful. It's not always.
DR. GIBBONS: I guess the question if you're operationalizing, it is one.

Page 353

DR. PELTIER: Right.
DR. GIBBONS: And you're saying that cool is abnormal in someone with cold feet, is that leading you astray?
(Crosstalk.)
DR. HERRMANN: I think the problem is testing it reproducibly --
(Crosstalk.)
DR. SINGLETON: The problem is a specific place.
DR. HERRMANN: -- because the pain, if the pain isn't from the temperature of the limb, which pin sensation isn't, and you can't control those things at the bedside, so I would say if you want to introduce it, it should be in the form of a quantitative sensory test as opposed to a bedside evaluation.
(Crosstalk.)
DR. SINGLETON: -- telling you about the Mayo setup of brass disks that are used for this purpose.
DR. FELDMAN: Then they're specifically kept

Page 354

at --
DR. SINGLETON: Right, in a refrigerator.
DR. BENNETT: That's what I'm talking about, thermal rollers that are kept at a temperature. They can work very well.
(Crosstalk.)
DR. GIBBONS: I think you can test it if you use the right approach.
DR. SMITH: I think you can, too. If you want to go down this route, then we should start talking about a tuning fork. I think that this is a dangerous thing to do because --
(Laughter.)
(Crosstalk.)
DR. SMITH: Yes, I think you can use the same argument for a reflex hammer. There has to be Tromner hammer, otherwise, it's not -- yes.
DR. BRUEHL: Gordon, can you jump ahead one slide just for a second? On the probable, one the ways you could get it is more than one symptom, right, or more than one sign.
So when we are starting to talk about

Page 355

needing more than one in a category, it starts to make a difference how the items are broken out. Things that are redundant, listed more than once, such as sharp and electrical over-weights pain descriptors, because you could get the diagnosis just with two of those -- and I'm not sure what the answer is, but I think some thought needs to be put into how to lay these out.
So the paresthesia is one, is numbness separate? How many of them is on the list that you can choose from?
DR. FELDMAN: I think that was why I guided everyone to our very first slide. I think at least our group realized that this was the big weakness in what we had laid out and that this is what needed work. But we wanted kind of what Rodica implied earlier is that we wanted to have more data in order to do this in, I think, the optimal way.
DR. FREEMAN: It seems to me that the symptoms are pretty easy. You can just say painful symptoms, everything in parentheses; non-painful positive symptoms, another whole bunch of stuff in

Page 356

parentheses; negative symptoms, numbness, a lot of stuff in parentheses, including dead in a way. I think that's relatively easy.
I'm troubled --
DR. SMITH: Roy, can I interject, though?
DR. FREEMAN: Yes.
DR. SMITH: Doesn't that mean that you just need a positive and a negative symptom?
DR. PELTIER: That's what I would argue. For probable, you would have positive and a negative, not just --
DR. SMITH: We opted not to do that, but what you just described is essentially you have to have one of these, so either --
(Crosstalk.)
DR. FREEMAN: I like your one, but it could be one which is either pain or non-pain or numbness. So one of the two positives and I think one negative. I think the negatives probably, and I think that's fine.
DR. SMITH: Two positives, but then you run into overlapping.

Page 357

DR. FREEMAN: I think what I'm actually doing is removing the overlapping because I'm saying pain, which encompasses everything. Those are all pain.
DR. SMITH: Yes, pain or non-painful positive symptoms, so a positive symptom whether it's painful or not or a negative symptom.
DR. FREEMAN: If you think you can delineate the negative symptoms in a --
DR. RUSSELL: Gordon, can I just clarify --
DR. SMITH: So that would mean by extension that a positive and a negative would make you probable.
DR. RUSSELL: Gordon, can I just clarify something because we had a terrible problem with whether you should have symptoms or not symptoms, and we said you may or may not have them. Are you saying you have to have symptoms, or could you just have signs?
DR. SMITH: No.
AUDIENCE: You can just have signs.
(Crosstalk.)

Page 358

DR. RUSSELL: That's fine. I just wanted to clarify how you were doing it. Okay. Perfect.
DR. SMITH: For possible, you could have just a positive or a negative symptom or a sign. For probable, you would need to have a positive and negative symptom or multiple two signs, or either a positive or a negative and one sign. Then for confirmed --
DR. POP-BUSUI: Why do you really need to separate positive and negative? We don't need that.
DR. BRUEHL: We do if pain and positive -- if you're trying to have pain as something that might allow somebody to qualify --
DR. POP-BUSUI: But that's different. That's painful.
DR. SMITH: No, but I think the point is that these are overlapping, so that's the challenge.
DR. BRUEHL: The positive sensory could encompass pain if you wanted to, but you could list it as separate if you want to have somebody be able

Page 359

to make it either way. I don't know what the answer is, but that was the rationale.
DR. FELDMAN: I don't think, Gordon, we said if you have to have more than -- like a cluster of symptoms that they had to all be -- they had to be both a positive symptom and a negative symptom. We can define it that way, but that's not what we said.
DR. SMITH: That's not what we said. We've kind of talked our way into that. We can talk our way out.
DR. ZIEGLER: Why should numbness be a negative symptom? I could easily say it's another positive symptom, so I would skip that dichotomy.
DR. FREEMAN: That's a semantic issue.
(Crosstalk.)
DR. ZIEGLER: I can say that anything the patient reports to you is positive and anything you find on your neurological exam is negative. That would be a straightforward view as well.
(Crosstalk.)
DR. SMITH: The problem with that is then

Page 360

you --
DR. RUSSELL: So this is based on Jim Dyck's original definition. So you disagree with that --
DR. SMITH: -- painful symptoms is also having non-painful symptoms, right?
(Crosstalk.)
DR. SMITH: This is devolving in a tomato/tomahto sort of thing. So I'm self-moderating --
MALE VOICE: Just forget the positive and negative symptoms. Symptoms and signs and categories.
(Crosstalk.)
DR. SMITH: Well, but then you run back into the problem here. If you get rid of the positive and negative, then you have the issue of redundant or overlapping symptoms in patients --
(Crosstalk.)
DR. CALLAGHAN: Aren't there three symptom categories; pain, paresthesias, numbness?
(Crosstalk.)
DR. SMITH: But pain and paresthesias are

Page 361

basically --
DR. GIBBONS: Put them in parentheses with the burning pain, shooting pain --
DR. SMITH: But once you're at pain, you're going to have a paresthesia.
(Crosstalk.)
DR. SMITH: Usually you're going to have -- not necessarily --
(Crosstalk.)
DR. GIBBONS: Could do pain or paresthesias or one of those two as one category or numbness as the other.
DR. SMITH: Then how do you do the two categories or two-symptom domains?
DR. GIBBONS: Symptoms would be this or that or this, and that would be one as these two, and then one --
DR. SMITH: Right, so that's where we are now with --
DR. GIBBONS: But they're just -- the semantics bother people, positive or negative, so just put one and two.

Page 362

DR. BRIL: We didn't say you had to have one from each domain.
DR. SMITH: No, we didn't, but we --
DR. BRIL: We just said symptoms.
DR. SMITH: This goes to Steve's point about the overlaps, the fact that these are going to aggregate together.
DR. BRIL: You've got pain and then paresthesia and numbness. They are three separate things. If you've got pain, it can be painful tingling if you want, but the patient will tell you that. Others will say I have tingling and no pain. It doesn't hurt.
I don't quite understand this dichotomizing --
DR. SMITH: The challenge there, Vera, is when we come to here, that patient has painful tingling --
DR. ZIEGLER: It's pain. It's just pain. That's pain then.
DR. SMITH: Right. But the tingling is the pain, and so you're saying that they get the two

Page 363

criteria to --
DR. BRIL: No.
DR. ZIEGLER: No, no, it would be pain.
DR. SMITH: So we're saying the same thing.
(Crosstalk.)
DR. PELTIER: Would it be possible to say a spontaneous sensation that's not -- so then you could be anything.
FEMALE VOICE: Then say non-painful paresthesia.
(Crosstalk.)
DR. SMITH: You would require the person to have -- either way the patient is going to -- it's saying the same thing I've been saying. So if it's non-painful tingling, that by definition means they don't have pain, thus to be probable, they have to have one of these, right?
So we're saying the same thing minus positive and negative so --
DR. FREEMAN: Lose the non-positive, negative.
DR. SMITH: So kind of neutral.

Page 364

(Crosstalk.)
DR. HERRMANN: There are a couple of other symptom categories I think we may be missing. So truly negative symptoms is the awareness of a lack of sensation or a loss of sensation, and we sort of covered that. The patient who tells you when they put their foot under hot water, they can't feel that. I don't know where that --
DR. SMITH: I think that would go under the numbness --
DR. HERRMANN: Define that under the numbness. Then also balance, there are --
(Crosstalk.)
DR. HERRMANN: -- under the definition issues around --
DR. SMITH: We brought that up, and I think the concern we had is that balance problems are extremely common.
DR. FREEMAN: I've got concerns with the signs. I think you've got --
DR. SMITH: Sorry. Did you have a symptom issue, Doug, or a --

Page 365

DR. ZOCHODNE: [Inaudible – mic] -- Journal of the Neurological Sciences 2001, Positive Sensory Symptoms [inaudible – off mic].
(Crosstalk.)
DR. FELDMAN: We published this. That's why I think that we said -- I really do think this discussion needs to be tabled until we can look at what we've all done because there is good data on this.
DR. FREEMAN: It is unnecessary for me to remind you, I'm sure, that that was a negative trial. (Laughter.)
DR. SMITH: I would say any trial that's accurate is a positive trial.
DR. TESFAYE: I think this is okay for a start, and we can refine one or two things later. But effectively, what we came up going through this exercise previously is that you have positive symptoms and persistent burning or dull pain, achy pain; paroxysmal occasionally, electric shock type, shooting, stabbing, knife-like, these sort of sharp pains; dysesthesias; painful paresthesias and

Page 366

tingling; and then the evoked pain, which is contact hypersensitivity as a positive.
The negative symptoms are numbness, dead feeling or hypoesthesia and hypoalgesia. Some patients do say, as was indicated, I can't feel my feet when I put -- I can't feel that. That is also a symptom.
I think these encapsulate what we're trying to do, and we can refine it later. I think everything that's here is captured.
DR. SMITH: I think we're actually all saying more or less the same thing in different ways.
DR. FREEMAN: Five tests, five examination tests, five signs would be in line with -- having concern about specificity. Would the guy with plantar fasciitis have all of those?
DR. SMITH: It depends on how old they are.
DR. FREEMAN: That's where I think we need to have some granularity. It's hard to operationalize that temperature --
DR. SMITH: I don't understand how you

Page 367

operationalize this.
DR. FREEMAN: -- deficits and a light touch.
(Crosstalk.)
DR. SMITH: Roy is worried about temperature, operationalizing temperature.
DR. FREEMAN: I worry about how to operationalize temperature, and I worry about five tests and the likelihood of one being a false positive.
DR. SMITH: There are concerns over deep tendon reflexes, and we had discussions over that and whether or not to include them and how to assess vibration.
DR. ZIEGLER: I personally think it's fine because there are scores which include both, the temperature, and for example, the Neuropathy Disability Score and others. I think it's a useful test, cooling, taking the rod. I would keep those five. Those are the typical bedside tests you can do.
DR. GIBBONS: But would you then say one or two signs is the question. How many signs do you

Page 368

need?
DR. ZIEGLER: Both sides, of course.
DR. GIBBONS: Signs, how many signs?
DR. ZIEGLER: Oh, signs. I think with those definitions, especially with the possible one, we are very unspecific because it's very easy in a healthy person to find one symptom or one sign by chance. There are people dealing with normative data that should go through the databases and see how frequent that is. I would guess you will find this quite often. So I think the specificity will be lousy.
DR. FREEMAN: I think we probably want to get more specific, and that's really the point I'm making, that maybe we need more than one sign.
DR. SMITH: We do have that now, so we wanted to be able to capture asymptomatic. So for probable, either one can have -- so you mean if there is one symptom --
DR. FREEMAN: Two signs.
DR. SMITH: -- so there always need to be two signs.

Page 369

DR. FREEMAN: That would be my sense.
DR. POP-BUSUI: But we can actually test to see how this type of definition performs in a newly diagnosed patient population where you can argue that the likelihood of having the disease, it's very low because all these tests -- what I'm trying to say is we can test to see how accurate these tests perform based on the data that is already available, because this test has been done in various patient populations.
DR. ZIEGLER: I think what you have to do is to look at an appropriate healthy population and see how it performs there, and from there, you can embark upon the diabetic population.
I call tell you the opposite; we published that. We found using the bedside test, we found very often in newly diagnosed type 2 patients, very often a possible neuropathy with signs or symptoms. So it's not that it's infrequent.
DR. POP-BUSUI: I didn't say that.
DR. ZIEGLER: Those are patients under excellent control, so their A1C is 6.5, and they

Page 370

are within the first year from diagnosis. It's all published.
DR. SMITH: So the suggestion is for probable one symptom and two signs. So is that it, one or more symptoms and two signs? Or if you have two symptoms, is one sign acceptable? Is that what you're suggesting?
DR. HERRMANN: Based on HIV, in the HIV literature, Dave Simpson and others have looked at the one sign versus two signs with a confirmatory test, and the one sign leads to a lot of loss of specificity. I would encourage sticking with the one sign for the possible.
I think for the probable, understanding that you need a confirmed retest for your definite, I would insist, to Roy's point, on having at least two signs for the probable.
DR. BRIL: Is that with a symptom? Because if you don't have a symptom, then you have to have more than one sign. Here for probable, you have to have at least one symptom and one sign.
DR. HERRMANN: I would say for probable two

Page 371

signs whether you have symptoms or not. Symptomatic neuropathy would be a symptom and two signs, and asymptomatic would be two signs.
DR. SMITH: So someone who has bilateral severe burning of their feet, pins and needles, smells like neuropathy, and the only thing we find is abnormal pin sensation, that would not be probable?
DR. HERRMANN: Based on what they've done in HIV, they've called that [indiscernible].
DR. GIBBONS: I would agree that if you had plantar fasciitis with achy burning pain in your feet and you had abnormal temperature, that would not be probable because you'd still possibly fit that criteria. You'd still be possible.
DR. SINGLETON: I think you might have trouble because there's a difference in sensitivity of the different signs, and I think in general, small fiber signs are more sensitive. I know Dan's going to disagree with me about this, too.
But I think especially if you have two signs and you have only a large fiber predominant

Page 372

neuropathy, you have decreased vibration and then nothing else.
DR. BRUEHL: Are you arguing to subclassify the signs?
DR. SINGLETON: I'd rather be inclusive than specific in this case.
DR. SMITH: You're going to base your confirmed --
DR. SINGLETON: On a confirmatory test.
DR. SMITH: There, I have problems because those confirmatory tests are abnormal in so many people who don't have signs and symptoms that --
DR. SINGLETON: Were you willing to have reduced ankle reflexes in an age-appropriate group?
DR. SMITH: We said absent.
DR. SINGLETON: Absent only.
DR. SMITH: Absent only.
DR. SINGLETON: That would help with the large fiber construct of two signs required if you were willing to go reduced and not absent.
DR. SMITH: Is this a bargaining -- well, if we're going to do --

Page 373

(Laughter.)
DR. SINGLETON: We're making real progress if we're down to this kind of haggling.
DR. SMITH: Yes, yes.
DR. GIBBONS: Can I maybe just suggest --
DR. SMITH: No, you may not suggest.
DR. GIBBONS: Yes, I will do so anyway. Can I suggest that maybe we already have these databases and our own item responses, and table it and just say do a quick check against our database to see how that falls out. We already know --
DR. PELTIER: That's what I said.
DR. ZIEGLER: For now you can keep it loose like the Toronto consensus. There, you don't mention any number of signs or symptoms.
DR. SMITH: They say sensory --
(Crosstalk.)
DR. SMITH: -- and that's the way it is and I guess that is a question. Is this different enough to warrant changing --
DR. FREEMAN: We can't be loose here. This is --

Page 374

DR. ZIEGLER: But it's not loose. The difference is that possible is the same, and probable will be the same if it stays like this.
DR. FREEMAN: We're moving through degrees of specificity, so from nonspecific, the possible, to the probable, more specific.
I take Rob's point about the small fiber neuropathy. It's a challenge where perhaps temperature is not as reliable a test, but I think we've got to move through these phases of possible to probable with greater specificity.
DR. SMITH: I think what we're going to do is align the first talk on small fiber neuropathy into this framework, so I don't think there's going to be any problem with that.
DR. FREEMAN: I agree, I agree.
DR. SMITH: I think the point is taken. Two signs as a requirement.
DR. FREEMAN: I think we're good. I can't wait to see --
DR. SMITH: Back to Vera's point because I'm confused, you're writing all this down, right?

Page 375

We're allowing probable neuropathy with just two signs, which means symptoms are not really germane to the designation of probable neuropathy. You'll have symptomatic probable neuropathy and asymptomatic probable neuropathy is the way we would construct it.
DR. BRIL: Yes, because you know --
DR. FREEMAN: Does that reflect everybody's reality?
(Chorus of yeses.)
DR. PELTIER: There are lot of diabetics running out there who are not going to tell you anything. They'll have more than [inaudible - off mic].
DR. TESFAYE: In terms of operation for the temperature, if somebody has been in the snow and freezing feet and coming on the table, we need to specify that it's done in the proper way and that we need to correct for that. That's important.
DR. SMITH: I think that's true with all of these. That's why I'm not sure how far you wanted to get into this, Roy. What's the proper way of

Page 376

evaluating vibration and what are the age normative values, and which brand of pins should you use or --
DR. FREEMAN: I would say I think this is going to be a topic for future meetings. I would say this is not methodology heavy. It's methodology light, but it's not methodology neglected.
DR. SMITH: We'll say appropriately performed by highly trained crackerjack teams, sensory physiology.
DR. HERRMANN: Position sense is missing from that list, the original.
DR. SMITH: Yes, position sense, what do you people think?
FEMALE VOICE: That should be included.
MALE VOICE: I think it's as useful as light touch.
FEMALE VOICE: Actually, I think it's more useful than light touch.
DR. TESFAYE: With position sense, they've found it is very much in advanced disease that you

Page 377

find it's not sensitive, and therefore, I don't think it should be included.
DR. SMITH: What's the downside of including it, I suppose? If it's abnormal, it's other going to come along. I think that was the --
(Crosstalk.)
DR. BRIL: Also, difficulty walking is a symptom.
DR. SMITH: It's a negative symptom, or it's positive if they tell you --
(Crosstalk.)
DR. ZIEGLER: There are several people sitting in this room who participated in the Toronto definition, and obviously, this is different. So the question is whether we should have a vote as to whether we define this symptoms and signs or just by signs plus/minus symptoms because it's a deviation of what has been published.
(Crosstalk.)
DR. ZIEGLER: I don't think it's slight.
DR. BRUEHL: Within each version of this

Page 378

because this is going to evolve a lot because we have another group that's defined it slightly differently. I think we can circulate via email.
DR. BENNETT: Can I just check? The two signs, it's got to be different domains. Because small fiber neuropathy, you're going to have to have bilateral changes in temperature and bilateral abnormality in pinprick.
DR. SMITH: Right. So we're going to have to --
DR. BENNETT: That's a pretty tight definition.
DR. SMITH: I think we need to map that onto this. So David's point is for small fiber neuropathy, does that imply that we have to have both abnormal pinprick and abnormal temperature? So it may be that --
DR. BENNETT: Bilaterally, that's asking a lot.
DR. SMITH: That's captured up here bilateral and symmetric, but it may be that we're going to have to modify this a little bit for small

Page 379

fiber neuropathy.
DR. ZIEGLER: One is enough. One is enough for small fiber bilaterally because otherwise, that's really tough, very tough.
DR. SMITH: Yes, I tend to agree.
(Crosstalk.)
DR. BRUEHL: This needs to say bilateral signs, by the way because that's only referring to the symptoms. We need to say the same language for both.
DR. SMITH: We end on accord. We agree.
DR. FREEMAN: Are you going to do definite or clinically confirmed or whatever you called it?
DR. SMITH: Highly probable, what makes Roy comfortable; although we're changing this.
DR. BRIL: I think the not needing signs was because of the small fibers, right, small fiber neuropathy. We might have the burning pain and yet not have any deficits, but then you have the confirmatory test.
DR. SINGLETON: Are you guys willing to accept hyperalgesia to light touch or to pin like

Page 380

allodynia? Is that there someplace amongst the signs?
DR. POP-BUSUI: It's context sensitivity. We put it into the symptoms.
(Crosstalk.)
DR. SINGLETON: It's very testable as a sign, right?
DR. GIBBONS: Where does the painless severe neuropathy fit in?
DR. SMITH: We're not doing severe, and the other people are doing --
DR. GIBBONS: Not so much severe but --
DR. SMITH: Painless would be --
DR. GIBBONS: -- a confirmed neuropathy, in other words, painless.
DR. SMITH: Two different signs, two different signs.
DR. GIBBONS: But it says --
DR. SMITH: We changed it.
DR. GIBBONS: Two and/or, got it. Okay.
DR. SMITH: Stay with us.
DR. ZIEGLER: They also may have painless

Page 381

symptoms, so paresthesias plus two signs is a painless neuropathy.

DR. SMITH: But does the painless tree fall in a forest when you're there or not?

(Laughter.)

DR. SMITH: I think it's time to move on. We already talked about that. Good.

DR. FREEMAN: Can people survive another half hour? James, and then we will break.

FEMALE VOICE: Let's get done.

(Crosstalk.)

DR. RUSSELL: The shorter we make this, the sooner we get to dinner, just as we put it up here.

We kind of made ours pretty simple. The biggest sticking points were really symptoms, and the problem was whether or not you really had to have symptoms or not in defining whether something was going to be clinically mild, clinically moderate, or clinically severe. We'll go down here in a moment to what severe is.

The problem with this was that we kept getting to the conclusion that while symptoms would

Page 382

be present most of the time, they may not always be present. The next problem was really which symptoms were going to define mild or moderate or severe, and we had a real problem with this in that it's very clear that pain may be very severe if it's clinically mild, but it also may be present, for example, in patients with moderate severity neuropathy.

We tried to make this as simple as we could, and the preclinical one then was that there would be no symptoms due to neuropathy. The reason why I say due to neuropathy is because we had the question, well, if people have some type of sensory symptom but we don't think it's a neuropathic sensory symptom, what does that mean? So we said they have to be symptoms consistent with what we would think would be neuropathy, and then signs as well consistent with neuropathy, so no signs.

Then for preclinical then since these are both negative, you would have to have an abnormality. We went through what would be the possible tests one would use in order to determine

Page 383

the presence of abnormality, and these were ones that we came up with that at least have pretty good validation, certainly for somatic symmetrical polyneuropathy.

With QST, we didn't go into the specific measures here, but the ones that have been most validated will be vibration and cold perception. We took the 95th percentile cutoff level, and again, you could debate about whether that's as good as using the 99th.

Then these parts here are more debatable. So clinically mild, we said that you may or may not have symptoms of neuropathy, although we do agree that most people will have symptoms, and they've been very well defined by Gordon. But you would have reduced sensory signs consistent with neuropathy but loss of sensory signs. So this would separate this from the other groups.

The sensory signs and what may they be, and we didn't get into a great deal of discussion about this, so I added this in. The one part that we did talk quite a bit about was ankle reflexes and

Page 384

reflexes in general and how you really define this and what determines whether it's due to the neuropathy, so I left it out of here.

Certainly, in the talk Gordon gave a little earlier, one of the things that actually increased the reproducibility of the testing the second time the neuropathy expert study was done in Rochester was simply saying we're not going to use absent ankle reflexes as defining the presence of neuropathy. So in other words, if you're over the age of 60 or 65 and the ankle reflexes are absent but you can't find other features, then you wouldn't necessarily call it neuropathy. But that is debatable.

Cold perception, we've already discussed. Vibration, I've just simply said this is touch, and that's because if you are a sensory physiologist, you will have a lot of debate about which exact receptors and fibers are affected by things like the monofilament or other forms of touch. And pin perception, we've discussed.

Then the next thing is if it's clinically

Page 385

confirmed, you would have items 1 and 2, and then you would also have an abnormality of one of these measures, so quantitative sensory testing, nerve conductions, intraepidermal nerve fiber density, or corneal confocal microscopy.

DR. GIBBONS: James, I just want to interrupt for a question. So looking specifically at the preclinical and moving to the clinically mild, for the preclinical, you have no symptoms, no signs, and your only abnormality is corneal confocal microscopy.

DR. RUSSELL: Or one of these other measures.

DR. GIBBONS: Right, but say that was the only abnormality, it's a test in a different unrelated tissue bed. We're talking about distal symmetric. How do you put that together? I'm just wondering if that's bringing us maybe into the wrong realm.

DR. RUSSELL: Well, the consensus by democratic vote was that in preclinical, you would not have signs and you would not have symptoms. So

Page 386

you have to define it in some other way.

The question is -- and this is a separate discussion -- which of these measures would you really take as your most sensitive measure? We don't really have time to go into that. That's a whole other debate.

Would you consider the intraepidermal nerve fiber density to be the right measure, or would you consider the nerve conductions to be the right measure, et cetera? We sidestepped that one. That's another whole area of discussion.

DR. BRIL: It's debatable, but there's a growing amount of work that shows that those parameters are related to intraepidermal nerve fiber density related to clinical severity and many other things. It's being used as a surrogate endpoint. So it's early on, but it is being used. And you can stratify patients based on corneal nerve fiber length, which we just did in that study we published in Neurology this year.

I think that is one possible option, but I do know there's a lot of work that needs to be done

Page 387

on that particular one.

DR. PELTIER: I guess I would question, is there normative data? For somebody who's 75, what's a normal corneal density that you would --

DR. BRIL: There is normative data for CNFL and for fiber density and all of that, yes.

DR. PELTIER: If there is, then you could argue to leave it in.

DR. BRIL: Absolutely, there is normative data.

Rayaz, you should speak a little bit about this.

DR. MALIK: Chris, it's getting tiring now that we have the data, and I don't know, the neurology community wants to ignore the data. So we've got two published papers that show very clearly you use standardized criteria for diabetic neuropathy, the Toronto criteria, in two different populations, and you put IENFD up against CCM, and it performs as well, if not slightly better.

Whoever it is who reviews the papers tends to ignore that and says, well, let's go back to

Page 388

physiology, and it's a different nerve, whatever.

DR. BRIL: There's a publication -- and you've got to forgive me the women's name, but she's done all the normatives, male, female, different decades all through the life. Mitra Tavakoli. Sorry. She did that --

DR. MALIK: From all of the consortium.

DR. BRIL: -- from all of the consortium. There's a whole consortium looking at this. There's a lot of normative data out there, and what it does is less invasive than a skin punch biopsy, far less invasive.

DR. HARATI: How specific is it?

DR. MALIK: It's specific.

(Crosstalk.)

DR. HARATI: -- corneal sensory, cocaine abusers.

DR. BRIL: No. It's as specific as anything up there. That means it's a sign of neuropathy.

Again, Rayaz, you did CMT, or what did you do?

DR. MALIK: T1A.

Page 389

DR. BRIL: CMT and showed loss. But then loss of intraepidermal nerve fibers is not specific, either.

DR. RUSSELL: I'd just like to interject here and say this is a complete separate discussion, and we've been here nearly four hours on the first two.

(Laughter.)

DR. RUSSELL: This is about another week of discussion as to how you define --

DR. BRIL: You deserve an hour.

DR. RUSSELL: -- and which one you're going to use. I love all your tests, by the way. They're all great.

(Laughter.)

DR. RUSSELL: Clinically mild, I went through this, and we said clinically confirmed, you would have to have these two and then you would have to have an abnormality in one of these.

Then clinically moderate -- can we move it up a little bit? Clinically moderate and severe, clinically moderate, the symptoms I've just

Page 390

discussed. Here you would have a loss of sensory signs consistent with neuropathy, so there would be complete loss, which would then separate this from mild.

Then clinically confirmed, you would have this, and then we said that we wanted to really upgrade this as well so that you'd have to have two abnormalities of one of these measures here. Again, I'd like to just defer what those would be maybe for another session.

DR. SMITH: Can I ask a question?

DR. RUSSELL: Yes.

DR. SMITH: If there's a patient who has no symptoms, absent vibration of the toes, that's it, and then has an absent sural and abnormal vibration on QST, that categorizes them as a clinically --

DR. RUSSELL: There are two separate things here. There's clinically moderate, which is defined based on that, and clinically confirmed would be a separate category.

DR. SMITH: So absent vibration at the toes is moderately severe neuropathy?

Page 391

DR. RUSSELL: So based on what we have here, we have -- so, Gordon, what we have to do is we have to separate this and this, okay?

DR. SMITH: That's my point is that --

DR. RUSSELL: We could have more -- we could say here that it has to be loss of more than one sensory sign. That may be more consistent with what you presented.

DR. SMITH: And then this doesn't deal with patients who have, say, reduced pin sensation and extraordinarily severe neuropathic pain. Because I worry that for minimally symptomatic or asymptomatic neuropathy, the majority of patients are going to be severe, and this is really ordinal. It's not at all interval, and then patients who have neuropathic pain, I don't see where they fit on here.

DR. RUSSELL: The trouble in neuropathic pain is that it can be very severe in mild and it can actually be present as well even up to severe. So we had a lot of debate about how do you take symptoms and determine severity, and decided, in

Page 392

fact, that this was quite difficult. So just to address the symptoms part.

In the severe part we said -- and I've actually called this non-positive because Rodica didn't like negative, so I said non-positive symptoms usually predominate. It's getting into political correctness now. Again, you might think about positively taking that out.

Gordon, just addressing your other question here, so the parameter that determines severe is that you actually get weakness in addition to loss of sensory signs of neuropathy. So for moderate, which is really the one where you have to hang it between the mild and the severe, you need to decide how many sensory signs of neuropathy can you actually lose.

Would moderate be one? Would it be three? Which specific signs would they be? We said up here for the preclinical, sensory signs would include these items here. But this is debatable.

What do people feel? So for moderate, would people feel comfortable if you lost two signs or

Page 393

three signs?
DR. PELTIER: I would argue you should have an either/or. You can have loss of two or more signs for moderate, and on your abnormalities, I think they should be like less than the 5th percentile or something much more significant because if you just had an IENFD of, say, 5 epidermal fibers and I had a sural of 4, does that count as two abnormalities?
I think they have to be graded more severely in the sense that you should be less than the 5th percentile for age and gender on two of them.
DR. RUSSELL: One thing here is you do run into problems. So if you take greater than the 97.5 or greater than 99th percentile, you run into the problem, well -- you could do that for all of them. You could say that you need to have abnormalities at a higher percentile level, or you could simply increase the number of abnormalities.
DR. BRIL: James, if you do that and I'm looking ahead at severe, that means you're going to have to do QST nerve conductions and --

Page 394

DR. RUSSELL: No, no.
DR. BRIL: -- or you mean three abnormal parameters?
DR. RUSSELL: You'd have to do a combination here that would give you three, so you wouldn't have to do necessarily everything.
DR. BRIL: Three out of those four listed?
DR. RUSSELL: Yes.
DR. BRIL: That's a lot. You're asking them for IENFD or CCF. You have to do --
DR. POP-BUSUI: And QST and NCF.
DR. BRIL: Yes, those two.
DR. RUSSELL: The other way of doing this is to take this up to the 99th percentile.
(Crosstalk.)
DR. PELTIER: Then the other problem is your CCF is going to highly correlate with your IENFD, so you also have to look at which of those tests correlate. So if they do correlate like you're saying, then the problem is if you have one abnormal, you're most likely going to have the other abnormal. So how does it make it that much

Page 395

more severe?
(Crosstalk.)
DR. RUSSELL: We had a debate about it.
DR. POP-BUSUI: [Inaudible - off mic] -- abnormality instead of just saying abnormality because abnormality is very vague.
DR. RUSSELL: The other --
DR. POP-BUSUI: For moderate and severe, you should set some criteria that what is moderate.
DR. RUSSELL: The 95th would be abnormal, but you would make it more abnormal by saying you're going to go to the 99th or greater. That would be one option.
MALE VOICE: We could do 95, 97.5, and 99.
DR. TESFAYE: What determines severity, it's not that you find abnormality using different modalities of testing but actually having a high score in one. It could be Toronto. What determines severity is that the score is very high in that modality and not detecting neuropathy in different modalities. That doesn't make it severe.
DR. ZIEGLER: What you could do here is to

Page 396

define clinically moderate for confirmation, one of these being abnormal at the 99th percentile, and for severe, you can take two at 99.
(Crosstalk.)
DR. RUSSELL: We still have Amanda's issue here and that is --
DR. ZIEGLER: Then you don't need that many tests. You need only two tests.
DR. RUSSELL: Amanda's issue was if there's a certain measure you take on this, would you regard that as being equal to another measure on, let's say, the intraepidermal nerve fiber density?
DR. ZIEGLER: I don't --
DR. RUSSELL: Isn't that your question? You said not all things are equal in an individual case.
DR. PELTIER: I'm just saying that wouldn't you want to have different measures, so if one is more of a small fiber, one is more of a large fiber, wouldn't you want severe abnormalities in both to make it severe as opposed to just one or the other? The question I had is, if you had

Page 397

significant abnormalities on your CCF, then would you also have significant abnormalities on your IENFD? And that doesn't necessarily make you that much more severe is my point.

DR. ZIEGLER: I think you should not over-estimate the correlation of CCM with nerve -- you yourself in a landmark study, published that the correlation of NCV with CCM is something like 0.25, not more.

DR. PELTIER: No. I'm not talking about --

DR. ZIEGLER: And also, if you --

DR. PELTIER: -- nerve conductions, it's with the IENFD.

DR. ZIEGLER: Yes, we published in recently diagnosed patients that the correlation is not significant. So the correlation is 0.1 in that particular population. It may be higher, it will be higher if you take the spectrum of severity and tell me the correlation coefficient if you have a population with different severities of neuropathy. But it will probably not be higher than 0.3 or 0.4 or 0.6.

Page 398

DR. RUSSELL: Just a second here, one thing I do want to point out to you, remember that these patients have to have weakness, okay? So irrespective of what happens here, they have to have weakness.

DR. PELTIER: Well, that's my other point is that how can you have weakness and have no symptoms? You're going to be symptomatic.

DR. RUSSELL: We had a considerable debate about this, and the final conclusion was that you can occasionally have patients who can have quite severe neuropathy but don't specifically report symptoms. I don't think it's common, but that was a discussion.

DR. HERRMANN: Two points. The first thing, just at a very high level -- and we knew this was going to be the hardest category, right, of the three -- is that when you talk about clinically mild, clinically moderate, or clinically severe, I think we should distinguish on the one hand, what we're considering here is just impairment. Because what we're not considering here is the patient's

Page 399

perspective.

There are two ways of looking at it. There is mild, moderate, or severe from the patient's perspective because the way we're breaking it out, there may be a very severe impairment that doesn't translate into what the patient tells us is severe. But when you look at the impairment and the word "loss," I think about something like the UENS when you talk loss, is it loss of pin at the toe, if you have loss of pin all the way up the leg.

I think just if you're looking at the 95th, 99th percentile for IENF density, I think you also could look at length-dependent fashion loss that will help you bring out the --

DR. RUSSELL: Eva, can I just address this one very quickly?

We actually originally started off and said, okay, we could define clinical severity by a clinical scale in which we have percentiles. It turns out although we have great clinical scales, we don't have something like a Rasch-built model where we can easily and translatably say to

Page 400

everyone, this is what would be the 99th percentile based on corrections for age, gender, et cetera, et cetera, et cetera. We have it to some extent but not perfectly.

The second issue that I want to address with you is when we had this discussion about what constitutes mild or moderate and whether this is to the patient or the physician, it's a very, very slippery slope, this. Mild pain for me may be severe for somebody else, et cetera. So this is part of the problem with defining it that way.

Eva, sorry about that.

DR. FELDMAN: I just wanted to ask you about your discussion concerning weakness in your group because I certainly have patients, many, who have presented to me with frank ulcers who have no weakness at all, and I consider them to have clinically severe neuropathy.

I would say that's more common. I certainly see patients with weakness, but could you reiterate for the group what the discussion was concerning weakness? Because I question whether we

Page 401

should -- you could have plus or minus weakness, but to have to have weakness to be clinically severe is something I think may not necessarily be accurate.

DR. RUSSELL: That is actually a very valid point. What we actually did was we took this really from previous criteria, particularly the Dyck criteria, which actually in 2(b) requires weakness.

Now, part of the problem with this is you can actually skip the whole mild, moderate, and severe, which is what has been done previously because they had this same problem. What really constitutes severe? Instead of that, you grade it 1, 2, 2(a), 2(b), et cetera. But we decided as a group, we were going to bite the bullets here, and were going to do mild, moderate, and severe.

So yes, that's a very good point. One could say that you had to have weakness and/or ulcers, perhaps, making it severe. You could come up with that as a criteria.

DR. FELDMAN: I like that. Something like

Page 402

that I think would be more appropriate than saying you have to have frank weakness to be clinically severe.

DR. SMITH: I've got a lot of problems with this, and part of it's late in the day and my brain is fried, but what you're creating here is not mild, moderate, severe. It's less, more, and more yet. Eva brought up probably the best example. It's an outcome, so outcomes aren't always patient reported, but they're functionally significant or they're meaningful, right?

We don't even know the clinical meaning of nerve conductions, IENFD, and CCM at this point. I don't know what the clinical meaning of an individual sign is or the severity of the sign. We think it's true, and it has some face validity that the more abnormal signs we have, the more functional significance that this is going to have from a patient, including ulceration, gait abnormalities, neuropathic pain, and so forth.

We're haggling over details of these criteria without an anchoring heuristic. Eva gave

Page 403

one extreme of that, and I know you were charged with doing this and it's provocative I would suggest we ought to go back and think about just the overall concept of severity.

What are we trying to measure? Is it really just more abnormalities on the scales that we have, or is something that's meaningful for patients --

DR. RUSSELL: Again, I do have to stress, right, to be clinically severe, you have to have this, and this is simply to confirm. We're not saying that this is necessarily the major criteria for determining severity.

I think Eva has a very good point. Remember here that you have complete loss of sensory signs of neuropathy, so already everything is pretty bad from that. We can certainly add the clinical part, which is fair that you would have ulcers and/or weakness, but remember, that has to be there, and this is simply confirmatory.

DR. FREEMAN: I'm troubled by ulcers. Certainly, it's a functional outcome, but it's a very nonspecific functional outcome. It could be

Page 404

vascular. It could be due to atrophy. For me, while I recognize it is a vital functional outcome, as is amputation, it's not necessarily a measure of neuropathy. It occurs in patients who have severe neuropathy, but it also occurs in patients who have severe vasculopathy. I'm a little troubled by that.

DR. PELTIER: I'm thinking of this and maybe I don't know if I'm the only thinking of this. I'm thinking of this in terms of a clinical trial. If you're going to enroll people in, say, a neuroprotective agent, you do not want somebody that you're going to designate as clinically severe in that trial because the idea is that they have lost so many nerve fibers that there's not much left to save. So moving the needle in that patient population is going to be very hard.

I guess to me, that's where I'm coming from is thinking of maybe not so much from a patient perspective, but as far as our perspective in the sense of, okay, where do we think we can move the needle. If you're giving somebody a treatment

Page 405

agent, do you want to exclude people in a certain category? I guess that's where I'm thinking of this criteria at.

DR. FREEMAN: I take the point about the severity, but I also want to say I agree with Amanda. The other point, though, is if some epidemiologist wants to do a study to look at who is likely to get an ulcer, this is the group that you might think that they might want to begin to look at as part of their cohort or compare them to clinically moderate and to see who is more predisposed to ulceration/amputation.

I think we've got to come to this project with that perspective as well.

DR. RUSSELL: Doug.

DR. ZOCHODNE: I'm not sure how you're going to fit this in, but to be patient-centric, I think we're going to have to consider disability; disabled; unable to work; disabled part of the time, all of the time; able to walk, not able to walk. It may not fit with these categories very well.

Page 406

DR. FELDMAN: Have you done that in the pain field? Do you have a lot of quality-of-life measures? You do, don't you? So that is something we need to address at some point.

DR. BRUEHL: Yes, but those are not included in Dimension 1 even in the chronic pain --

DR. FELDMAN: That would be something we're going to do at a later date.

DR. BRUEHL: Functional consequence.

DR. FELDMAN: That's a later date?

DR. BRUEHL: Yes.

DR. FREEMAN: I think we all agree that the instruments measuring quality of life in neuropathy have their imperfections. In dimension, I think it's 4 or 5, we do look at activities of daily living. We look at functional, so all of those will be part of this, but not part of the core diagnostic criteria.

DR. RUSSELL: Just going back to this --

DR. BRUEHL: I did want to ask a question because I'm not even clear on this. In the clinical severity grading like this, is this really

Page 407

Dimension 1, or is this Dimension 2? Because you either get the diagnosis or you don't. The subcategorizations of severity seem to me like a secondary descriptive issue, which you could use in clinical trials, but I don't know that it changes what will go into the Dimension 1 criteria.

DR. FREEMAN: For me, it's a challenging question as to where this fits in the dimensions. I'm not sure that it really matters. I think as far as this is concerned, it's almost the Dimension 1. Dimension 2 is artificial, but what I do think is that we need to have operationalizable criteria for the early, for the clinical trial, and for the late, for the epidemiologists looking for predisposing factors for ulceration.

DR. RUSSELL: Part of the debate really that we had as well was should we just simply define mild since those are the people we would want to get into clinical trials, and then maybe there would be another group that would be moderate to severe. At the end, we decided we would try to actually follow the order that Roy had presented us

Page 408

with, that we would have mild, moderate, and severe.

So this is our attempt to come up with those three categories, although practically speaking, it may be that severe is not going to be used that frequently anyway.

DR. FELDMAN: James, can I ask a clarification on the at least three abnormal? Are we saying, though, we have to do three of those four tests in order to be clinically severe?

DR. RUSSELL: It's thought to be an abnormality --

DR. FELDMAN: I know we were discussing it --

DR. RUSSELL: It's thought to be an abnormality. So I guess --

DR. FELDMAN: Or is it --

DR. RUSSELL: -- if the vibration perception threshold and the cold perception threshold, that would be two abnormalities. And then one could define in the nerve conduction studies which measures you thought were the most important. So

Page 409

would they be the sural sensory amplitude? Would they be the peroneal conduction velocity? For the intraepidermal nerve fiber density, you could say would you count distal and proximal as being the measure. Would you perhaps use subdermal fiber densities as well as epidermal?

These are the questions one might ask. As I say, there's --

DR. FELDMAN: I'm wondering if we're --

DR. RUSSELL: -- a lot of discussion about exactly how you're going to define that.

DR. FELDMAN: I guess I would just throw this out, and I know we've discussed this already. But thinking about, for example, what Teresa Jones said this morning and what's permeated our discussion somewhat during the day is we are hopeful to use these trials in clinical research, epidemiological research, and even drug interventions. And to say that one must do three of these in any of those research scenarios seems somewhat cumbersome and maybe repetitive. Maybe at some point, this could be opened up for more

Page 410

discussion because I think that is actually probably unnecessary.

DR. RUSSELL: As a start here, could I just suggest that maybe what we do is for the mild, we say there's one abnormality greater than the 95th. The moderate, we say is two abnormalities greater than the 95th. The third, we say there's two abnormalities greater than the 99th percentile.

DR. SMITH: But do we know that having an abnormal skin biopsy and abnormal nerve conduction studies or for that matter, abnormalities of all four conveys greater severity? So for instance --

DR. RUSSELL: Gordon, you're missing my point.

DR. SMITH: -- we frequently see patients with preclinical neuropathy who have abnormal skin biopsies, abnormal nerve conduction studies, and abnormal CCM. I question whether or not this is really a matter of severity. It's just more. It's a certitude issue.

DR. FELDMAN: I agree with you, Gordon.

DR. RUSSELL: Let me stress again you have

Page 411

to have this. This has to be present, and this is just to confirm. This by itself is not determining severity. This is actually determining severity.

DR. BRIL: Can I clarify what you said? Did you mean vibration and quantitative thermal thresholds would be two abnormalities out of that list?

DR. RUSSELL: I'm saying you could consider that.

DR. BRIL: So it wouldn't be that you'd have to do all four. You could do two and get four --

MALE VOICE: Nobody's going to do --

DR. BRIL: I know what you're saying.

DR. SMITH: It doesn't mean it's not severe. I think we're arguing over something that isn't on the same axis. It's a certainty issue. It's not a severity issue, and it goes to -- foot ulceration, Amanda's point is really good. Those, I understand. I'm just not sure I understand --

DR. FELDMAN: I don't.

DR. RUSSELL: So one of the options here is to just take out the clinically confirmed part

Page 412

altogether and simply go with these measurements here.

DR. FREEMAN: Gordon, I just want to say that I'm not sure that the two of you are disagreeing. Because Gordon is talking about increasing the probability that the patient has a neuropathy by having a test, and I think you're saying the same thing, that you're increasing the probability by using the clinically confirmed. That really is what the clinically confirmed means.

The question, I think, is to what extent does having three or two or one of those abnormalities increase the probability. That's how I would delineate this discussion.

I'm very interested in people's views, whether thermal threshold, having both intraepidermal nerve fiber density decreases, and thermal sensory threshold increases are one in the same, whether they are totally concordant, whether having two is the same as having one, whether it really increases the probability. I don't know the answer to that, and that's something that there are

Page 413

data that exist. So that's the one thing.
The other is if we are going to take it out of the confirmation increasing the probability realm, then it's Amanda's thesis going from the 95th to the 99th percentile because there, I think, you're looking at severity. We can also then discuss whether severity actually increases the probability. So that's how I'm seeing this discussion, but I don't know if we're going to resolve it tonight.
DR. FELDMAN: I think that's a nice summary, actually.
DR. GIBBONS: Can I advocate that maybe we table this for now? I think everybody is, in fact, getting -- we're starting to rehash our arguments, and I think everyone's getting a little fatigued with the discussion. Maybe we should take an hour break. We can meet at dinner, further hash things out, but take a break for now or just to reset.
(Crosstalk.)
DR. FELDMAN: Chris, could we talk about the consortium this evening then, have a working dinner

Page 414

because I have to leave.
DR. FREEMAN: That's fine, to set out the tables. I asked them to do that. I don't know how well they can do that.
How many people want to attend the consortium working dinner? How many do not want to -- rather say who doesn't want to discuss neuropathy?
(Laughter.)
Adjournment
DR. FREEMAN: I think probably we should eat.
DR. BRUEHL: Can I make one note? We were talking earlier about the distribution of documents earlier. If anyone of you are interested in a detailing of what I presented in my talk today, including the examples, out on the table out there, they have copies of the Journal of Pain issue. I think it's the last or the next-to-last article in there. You can just grab one.
(Whereupon, at 6:01 p.m., the meeting was adjourned.)

C

D

E

F

G

J

K

L

N

P

U

W