PNS Episode 2

**Camila:** [00:00:00] Welcome to the Peripheral Nerve Podcast, the official podcast of the Peripheral Nerve Society. I'm Camila Pupe, professor of Neurology at Universidade Federal Fluminense, Rio de Janeiro, Brazil.

**Wilson:** And I'm Wilson Marques Junior. Full Professor of Neurology at Universidade de Sao Paulo, Ribeirao Preto Medical School, Brazil. This is the second episode of our special leprosy awareness series, where we explore the science, history and challenges of the often-neglected disease.

**Camila:** Well, today we'll be discussing one of the most complex and fascinating aspects of leprosy, classification and immunology, a topic that connects science, diagnosis, and clinical care.

**Wilson:** To help us navigate this, we are joined by two leading experts in the field. Professor Marco Andrey, dermatologist, leprologist and researcher at USP - Ribeirao Preto, Brazil and President of the Brazilian Society of Hansenology and by [00:01:00] Professor Ben Naafs, a globally respected tropical dermatologist with contributions on the reactions, spectrum, and immune response are fundamental for our modern understanding of leprosy.

**Camila:** Welcome, professor Marco Andrey, and Professor Ben Naafs to be here today. We are very happy to have you here.

**Marco:** Thank you so much, professor Camila and Professor Wilson to invite me to participate with this important podcast.

**Ben:** Thank you for having me here, because it gives me the possibility to tell you about the disease, what shaped my life. Thank you very, very much.

**Wilson:** Leprosy is often described as a disease spectrum — clinically, bacteriologically, and immunologically. Why is this concept still so central to our understanding, and how has this shaped your work?

Professor Naafs?

**Ben:** I will try to [00:02:00] explain. Already far before the burst of Christ, the Chinese and Indians were aware that there was a macular and a papular / nodular type of leprosy, and this was known also in Europe.

Danielssen and Boek in 1847 talked about *elephantiasis graecorum tuberosa* and *elephantiasis anesthetosa* and a mixta. But they realized that elephantiasis was not the right word. And then they went to nodular the next year to nodular and anesthetic. And after the detection of M. Leprae, Hanson and Looft made it in 1895. And they talked about tuberosa and macular anesthetic were nicer.

In 1903, they make it very clear the Lepra tuberosa, the Lepra cutanea, and Lepra nervosa. Leprosy is [00:03:00] highly infectious, but the attack rate is low, due to the genetics. Eighty per cent of people will never develop leprosy, not even when severely immunosuppressed. In order to predict complications in the ones who developed leprosy, they classify them according to the cell-mediated immunity.

And how do they come to that? Let's go back to Matsuda. He worked with Lepromin (a M. Leprae extract not unlike BCG). He started in 1916 and published his first paper in 1919. His original idea was to find a test that would distinguish leprosy patients from non-leprosy persons. But during his study, he found that the test results differed depending on the type of leprosy, strongly positive in TT and negative [00:04:00] in LL.

Thereafter, it became generally recognized that the essence of the tuberculoid-lepromatous classification is the resistance of the patient to the infection. This is accepted as the primary aim in classification must able to define grades of resistance.

The Ridley-Jopling classification like many others took this as starting point; this one side of the spectrum a stable polar tuberculoid (TT) leprosy, characterized by a single well-described lesion with loss of sensation and/or nerves with diminished function. No bacilli detectable, and a high CMI against M. leprae antigenic determinants, and, on the other side, stable polar lepromatous Leprosy (LL), characterized by nodules and/or plaques, with many bacilli. Moreover, there may be even only a generalized infiltrated skin (the Lepra bonita) [00:05:00].

Between the stable TT and LL leprosy is the unstable borderline group, which comprises the majority of the patients: borderline tuberculoid (BT) with predominantly tuberculoid features and borderline lepromatous leprosy (BL) with predominantly lepromatous features. Between those two groups, there is a small very unstable group of midborderline (BB) patients with typical punched out or dome-shaped lesions. When untreated the patients become more lepromatous; called “down grading”. When treated they up-grade, becoming more tuberculoid. This up- and down-grading may go together with a nerve damaging [00:06:00] reaction (T1R). Occasionally, it is not possible to classify leprosy. The lesions in those cases are clinical and histological “indeterminate”.

Concerning the histopathology of the leprosy spectrum, these are determined by the cellular reaction of the host; the granulomata will divide the spectrum in half, with epithelioid cells from TT to BB and macrophages in BL and LL. Prominent giant cells are often associated with activity. Langhans giant cells are present in upgrading BT. Lymphocytes are in variable numbers present. Erosion of the epidermis may be visible in TT, due to cross reactivity between M.leprae and epidermal cells. There are hardly bacilli [00:07:00] visible.

In BL and LL there are more foamy or fatty vacuoles in the macrophages. In BL there may be even more lymphocytes then in BT. But they are scanty in LL, because there is no resistance. These patients are completely anergic. In BB and BL, there is a free zone, that can be visible, the Zone of Una. There are many bacilli at the BL-LL-side.

Then, my biggest worry. The WHO classified leprosy into just two groups for practical visions. And they did it, according to the number of the lesions. They said: paucibacillary patients have five or less lesions, and the multibacillary leprosy has more than five lesions. Although this is a very practical approach, several reports have shown that [00:08:00] just by counting, up to 30% of the patients may be wrongly classified as paucibacillary and therefore undertreated.

**Camila:** Well, professor, it's fascinating how you could explain us all these history aspects and, how it is classified today. And now, I would like welcoming Professor Marco Andrey here. And I would like to hear a little bit from his perspective about this question.

**Marco:** Well, I agree. The disease is spectral and the Ridley-Joplin classification is satisfying essentially scientifically. It organized the disease in two poles of resistance and susceptibility, as mentioned before by Professor Ben. But in practice, over 70% of the patients fall in the borderline forms.

These [00:09:00] patients often present subtle symptoms, especially neurological ones, and they’re not being diagnosed. This is my worry. Many professionals only look for a classic skin lesions with anesthesia — which is a major misconception, in my opinion. HYPOESTHESIA for example alone can be a pathognomonic clue, but it's often ignored. Nowadays, our biggest problem is not underreporting, but underdiagnosis.

I think this kind of classification mentioned only ~~in, it's nice to do this, to~~ consider ~~this, for to do~~ the scientifical justifying of the natural evolution of the leprosy disease. But, we [00:10:00] cannot consider only skin signs.

For example, if you consider their operational classification by WHO. So, we have to think a bit more about nerves~~, so,~~ this is our big challenge.

**Camila:** Because of this, we are doing this podcast to raise suspicion and the diagnosis of the leprosy worldwide, Well, Dr. Naafs, in your 2016 review in clinical dermatology, you highlighted the gap between immunological advances and field application.

Why has it been so difficult to bridge this gap?

**Ben:** The article you mentioned, we were appalled by the amount of money, which went to our opinion into tests. It did not help in early diagnosis and only showed contact with M Leprae. That is, I think, the major reason. [00:11:00] And this money was taken away from teaching clinical knowledge that is still the way to diagnose leprosy and reactions and nerve damage.

Although, at present, fundamental research leads to new diagnostic methods and markers such as genetics like DNA, different mRNAs, proteomics, immunology, electrophysiologic, and color Doppler for the nerves.

**Wilson:** Professor Naafs, you also co-authored a study showing T-cell cross-reactivity between *M. leprae* and *M. tuberculosis* based on the ESAT-6 homologue. Could this explain diagnostic difficulties in co-endemic areas?

**Ben:** Since most of the diagnosis is clinical, the answer is no. Cell-mediated immunity tests are not handy to use and may test again, only exposure and not disease.

**Camila:** ~~Great.~~

[00:12:00] One of your papers explores whether granulomatous reactivation is a reaction or a relapse. Do we now have better tools to differentiate them?

**Ben:** That is difficult to answer, but it was already possible. In most patients can be done clinically. When you have a patient who becomes active, you treat him or her with steroids, and when you cannot go down with your treatment, then it is a relapse.

**Camila:** ~~Aham~~

And at the multibacillary site, you have the anti PGL one titer, which could be of help. If you see that goes up, then you know that there is a relapse. ~~But, at present, that I may be new methods, but I'm not really aware of it.~~

**Wilson:** Professor Marco Andrey, you have worked with WHO classification and digital tools. What do you see as the main limitations of [00:13:00] current operational classifications?

**Marco Andrey:** Well, the WHO classification is all very simplistic. It's made for the fields in the countries where you don't have good health system, for example, it's based only on the number of the skin lesions and ignores completely about nerves.

Even though, nerve involvement is a cardinal sign, but it's neglected. Because of this, most cases are being misclassified. We need to rethink this model. This model, in our work with digital tools, we know that most algorithms also are trained on ~~classic~~ classic cases. Skin lesions, based exclusively in the skin lesions, which represent today less than third percent of the cases in the [00:14:00] field.

There is disease, a serious limitation. We developed it, for example, artificial intelligence tools using the leprosy suspicion questionary here in Brazil. In which we have 14 questions about skin and also about nerve symptoms. ~~The~~ Artificial intelligence identified nerve pain, tingling, numbness, and number of areas on the skin as a high risk, over 15 times more predictive than skin lesions alone.

This approach can double the case detection rate in active searches. ~~Because of this, I criticize the WHO classification.~~

**Camila:** So, this is a very innovative tool to suspect the diagnosis and probably to make more diagnosis and treat ~~suitable the~~ patients [00:15:00] and prevent newer cases. So, let's return to immune mechanism.

Professor Andrey, ~~do~~ your work has looked at microRNAs and inflammatory mediators. Do you see any promising immunological markers for reactions or nerve damage?

**Marco:** Well, in this paper about microRNAs we have worked with university of Para, in the north of Brazil, our colleagues from there, we are working together, but unfortunately, we don't have exactly a good marker for reactions or nerve damage, exactly. But we found in this study some interesting pathway involving like Schwann cells, demyelination, and, also, epithelial–mesenchymal transition. Genes like SOX, ZEB, HOX, and RHOA may be involved. But, one of important genes is [00:16:00] Aquaporin-1 (AQP1), for example, appears related to leprosy pain and may be a future therapeutic target. But we still lack a practical predictive biomarker for reactions, unfortunately.

**Wilson:** Professor Andrey, in one of your recent publications, you uncovered hidden leprosy transmission in inner São Paulo. What did you find? And how does it tell us about surveillance?

**Marco:** Well, Jardinópolis, is nearby our city around here in Ribeirao Preto - Sao Paulo, leprosy was, supposedly eliminated, but after we start training, mainly focusing in the community health agents and using the leprosy suspicion questionnaire. It's a simple [00:17:00] tool. We screened more than 3000 people and in that time we diagnosed 64 new cases. All of them, multibacillary. It's important to say about these 64 new cases, 60 were inside of the group, the questionnaire Positive Group.

So, most had a nerve involvement as mentioned. And also, if you consider the neuro questions marked in this questionary, so, we treated all of them and follow these patients with MDT and ~~we~~ we could see that the MDT improved their neurological status completely. It's contrary of the WHO data suggesting that it doesn't have neuro damage with [00:18:00] MDT. We have a paper since 2010-2012, saying that we cannot ~~find~~ looking for the improvement of the neurological signs and symptoms after the MDT, because that work was made considered only epidemiological data about physical grading.

So, when you follow these patients properly, clinically and neurologically, we can see the improvement of the neural symptoms. This is important because leprosy is a neuropathy first than a dermatopathology. So, our detection rating that time holds from 7.4 to 226 per 100,000 citizens, proving that the disease was hidden, not gone.

So, the surveillance [00:19:00] based solely on dermatological signs, misses ~~this~~ these patients, for example. So, we have to think first in neurological and after that in the dermatologic signs in leprosy, maybe in the field to recognize the early diagnosis.

**Camila:** Well, that's very impressive. And, Dr. Vera in the first episode said exactly this, how the training of health professionals can raise, the suspicion and the diagnosis of these patients.

And of course, it helps to eliminate the transmission and reduce the cases. ~~So,~~ it's absolutely very nice paper that can highlight this. So, leprosy of course is not just a medical issue, it's social. And, how should social determinants inform our classification and management? Professor Marco?

**Marco:** Well… I agree with you ~~with~~ [00:20:00] because the social impact of leprosy is so huge, but leprosy affects all social classes, but crowded living and poor sanitation increase the transmission. Still, even those with lower exposure can develop also neuropathy years later. ~~In Private practice In my private practice, for example, I see many cases completely subtle, minor signs appear, late onset neurological case often miss as well.~~

In my private practice, I see subtle late onset neurological cases, often missed as well. We must shift from dermatological to neuro function diagnosis. It's very important mainly to ~~recognize. It's not early diagnosis, but when the~~ [00:21:00] ~~diagnosis went up. We have in this time, we have a nice opportunity to~~ do the diagnosis in the best time to recognize it and also to treat it as soon as possible.

**Camila:** Yeah, of course. Professor Ben?

**Ben:** Well, I fully agree with Marco Andrey. Social determinants can result in the patient coming late with a more advanced disease, and they can come from a higher class because he's so afraid to come and from the lower class. But for this extremely poor, we should organize that getting the medication does not cost them more time nor money. Help them with the shoes and the tools and show understanding that is the most important thing, and visit them at home and ask where you can help with care, not with money. They have to [00:22:00] feel that you care. And for the rich ones you have, just to try to get the understanding, most of them are able to.

**Wilson:** If you could redesign the classification system, integrating clinical, immunological, and social parameters, what would it look like?

**Marco:** Well, I would like to include pure neural leprosy and also the hypocromic borderline cases, explicitly mentioned in the classification. Our studies with high frequency ultrasound, for example, showed us that even in indeterminate forms, for example, we have detectable nerve chains with asymmetry and also many points with focalities.

~~So that's it is the diagnosis of Leprosy.~~ This should be a part of the standard criteria to [00:23:00] define the leprosy case and consequently to notification and treat these cases as soon as possible.

**Wilson:** Professor Naafs?

**Ben:** Well. For the ones who got leprosy, one could classify them along a line from TT to LL by means of an error on the place where they are in the spectrum within and with this all error, whether they go and then and horizon tell to Arrow where they go down or upgrade. And when one may put a Ridley-Joplin classification borderline group. Also ask Marco on, on this line, because I think the criteria of Ridley-Joplin are still the way of finding for them the place in the line [00:24:00]. ~~Concerning social parameters, I'm not a socialist. I would add to the classification, social, weak, be careful, or social. Alright. It was a difficult one for me to answer.~~

**Camila:** ~~So I would like to brought here the paper that Professor Pedro Tomaseli and Professor Wilson published. The study that they made at Universidade do Estado de Sao Paulo – USP - Ribeirao Preto was wonderful. They showed all the pure neural leprosy, how it is frequent in this area and the tools to raise the suspicion about the pure neural leprosy, that's so important to prevent functional damage and neurological damage. Professor Wilson, do you mind to say us a little bit about this study?~~ **Jen, Is it possible to record again this question?**

**~~Wilson:~~** ~~Thank you, [00:25:00] Camila. Well, I think it is a first all a very important study, where we tried to characterize the pure neural leprosy in the early stage of the disease and in the late stage of the disease. Because we have a misdiagnosis in both of them and we were also able to show that the disease is a progressive disease. It starts with a mononeuropathy to a multiple mononeuropathy.~~

~~And I look as my foundry call patient. It's very important to be a patient to use focal areas of loss of sensation talk. Why the, the, the severe disease that we, that the result, if you don't treat these patients at the right time, I think that's the most important clues like from our paper.~~

**~~Camila:~~** ~~So I think this is the idea, , of the suspect, just when you have neurological symptoms and not the skin lesions is very important to neurologists, especially for neuropathy specialists. We still can [00:26:00] have leprosy in patients that doesn't have skin lesions. And of course, we have some tips and signs that we can raise the suspicion.~~

~~We will put this reference here in this episode because it's really important to have this in mind.~~

So, finally, what do you say to young physicians or researchers beginning their journey in leprosy? Why does this disease still matter, professor Andrey?

**Marco:** Well, we still lack a definitive test. More than half part of the case of the Leprosy cases tests are negative. This is important to say. Diagnosis depends on a skilled clinical exam. We have to first to hear and to touch the patient, to recognize leprosy diagnosis.

 We should learn about palpation of nerves, test of the thermo [00:27:00], ~~tatil~~ tactile and pain sensitivities. For example, we have to learn to use the monofilament, the aesthesiometer monofilament. ~~In my opinion, it's looks like a stethoscope for the cardiologist. The ter should be our, our tool, important tool, to recognize the spot of the loss of sensation.~~

~~Properly use when instrument, when~~ we have to measure the loss of sensation in the skin, for example. Also, you have to learn about the autonomic tests. And nowadays, the ultrasound, the peripheral nerve root assault, it's very important to recognize the soon signs of the neuropathy in leprosy.

So it's hard work. But it should be our challenge. If you want to change the [00:28:00] reality of the world in leprosy field, it's essential to change our mind from skin to nerve approach. So we have to think more about neural symptoms ~~then~~ first, then only to focus in the skin lesion in Leprosy field. Nowadays skin lesion of leprosy. ~~I recognized that I came late for this. The diagnosis, unfortunately.~~

**Camila:** So that, that's so important for us, right? Because you are dermatologist, you are specialized in leprosy, and you are telling us that neurologists Yes. Has to be aware about the first signs of leprosy because leprosy starts in the nerve, right?

Professor?

**Marco:** Yes, because I'm here. I'm very glad to participate in this podcast to say for the neurologists to ~~climb, to~~ [00:29:00] ~~cry for the neurologist, to~~ help us in this war about leprosy in the field. So we have to consider the neurology to also, to open their minds to this because leprosy should be consider in the diagnosis, ~~the hypothesis about the neuropathies. So in leprosy is more common that are other neuropathies, so we have to. Maybe it's good idea to start for leprosy after to consider another, , etiological diagnosis from, for this, this neuropathy. Because in nowadays, you have patient treated with, , really with, like prednisolone pulsotherapy and also biological, , ,~~ [00:30:00] ~~treatments before.~~

~~Then think about leprosy. So we have to change this idea firstly, and most of the time it's not a complimentary exam. We'll say us, the diagnosis we have to do a bit more from for these patients to recognize them early.~~

**Camila:** Yeah, it's very important because we still have patients that it's not in the poverty social conditions, but still have the Leprosy neuropathy and we have to think about it.

~~When~~ Of course we have clinical tools and clinical suspicion. So we have as well this migration, in a global world, patients that can have the disease in countries that are considering rich countries, right?

**Marco:** Yes, you are right. And most of them they were not recognized as leprosy [00:31:00] because this social situation.

~~So we have to open our mind for this because, well, the leprosy is related with social determinants, but it's not when diagnosed determinants. So because of this, the majority of my patients from the private clinic. They come with, treated with most of them brought to me because of vu.~~

~~So, for example reference these, these guys, these patients for me, and most of them are in treat under the treatment for a long time, treated the neuropathy and also they. Thought about Leroy diagnosis, but the no diagnosis of Lero was considered when they asked for skin smear examination. Also, PCR and they, these, these [00:32:00] laboratory tests came firstly negative and the complete, the diagnosis of Lepar was completely delight. Delighted then. So. After three, five years treating the neuropathy with this many kinds of medicines, they came again to me. And so I could see the spots the middle signs in the skin, they, they spots and the, the kind of areas when you.~~

~~Find one kind of Iceland with loss of sensation with prosti. We should consider this as a, a diagnosis of leprosy. So this is the, the. The situation that happened, the private, so it's very common for me, treat this kind of patients treated. The neuro [00:33:00] symptoms are very high, and the quality of the life of these patients is completely impaired. So we recognize these sports and sometimes I paint in the skin to, to see the level of the loss of sensation is different in many parts. So when I show this, also the thermal sensation is down. It's decreased, also the pain. And also we can find ultrasound signs in the, the peripheral nerve in, in, is taking it in in many points, for example.~~

~~And we start to treat. And after three and six months, this, the loss of sensation disappeared completely only using the antibiotic, the Multi drug therapy. So this is when. In contest. This is when proved [00:34:00] that we were in the right way to treat it. So this is our, this is very difficult nowadays because, it's common. The, so my message here, my end message is about this. Think about nerve, think about neuro symptoms first, then dermatological sign in Leroy Field. This is one way to recognize this diagnosis early.~~

**Camila:** Professor Ben, I will ask the same question I did to Professor Marco. What do you say to young physicians or researchers in the beginning of this journey in leprosy, and why does the disease still matter?

**Ben:** Leprosy is a disease that has so many phases. When you understand leprosy, you have a model to understand other diseases as well, both on [00:35:00] dermatology and in neurological fields. ~~Therefore, in the time in, in the top of world, immunology came to I and a Ababa in Ethiopia in the 1970s to understand the immunology.~~

~~Also, we tried to follow up the nerve damage and we introduced the nerve conduction. We introduced the sensory testing, the voluntary muscle testing, just to see how much is the nerve involved.~~ It is not only an immunological model, but also genetically and clinically. Of course, many diseases may look like leprosy, and understanding leprosy will make you a better physician and better researchers, and especially in a clinical way, [00:36:00] and it'll make you empathic, because you really have contact with the patient and with the awareness that leprosy is not only the skin, it is certainly most important to nerve. You are capable to make a proper diagnosis and if you give proper treatment for the disease and for the complications, you prevent a lifelong suffering of a patient and his family.

I think leprosy as disease to treat that well is very, very, very rewarding.

**Wilson:** Well, that bring us for the end of today's conversation, we're deeply grateful to our guests Professor Marco Andrey and Professor Ben Naafs, for the insight, generosity and their insight, generosity, and decades of commitment to the field of leprosy~~. patient evolving partners of recognized the neurological manifestation~~ [00:37:00] ~~of this disease.~~

**Camila:** We hope this episode help it illuminate the complexities and the urgent, relevance of classification and immunology in clinical practice. As we've heard today, the science of leprosy, is not just in the lab. It's in the field, in the community, and in the hands of training eyes.

**Wilson:** If you enjoyed this conversation, don't forget to share it to your colleagues, residents, the students, and follow us on your favorite podcast platform.

**Camila:** In our next episode, we will explore the clinical presentation of Leprosy neuropathy I'm sure that you will not miss it.

**Wilson:** you for listening, and until next time, stay curious and stay connect.

**~~Camila:~~** ~~Thank you again, professor Ben and Professor Marco.~~