Airing Pain Programme 116: Neuropathic Pain Part 2 of 2 – Latest Research

Half a century worth of research exists on neuropathic pain but what are the latest developments?

This edition of **Airing Pain** *is facilitated by the neuropathic pain special interest group (NeuPSIG) of the International Association for the Study of Pain (IASP).*

With the previous edition of **Airing Pain** *focusing on the 'psycho' and 'social' of the bio-psycho-social model, this programme tackles the 'bio' component.*

In this second instalment in a mini-series on neuropathic pain, Paul Evans delves into the latest scientific developments on the condition and the ways in which the gap between research and treatments could be bridged.

Following on from **Airing Pain** *115, which concentrated on targeted Pain Management Programmes, this edition discusses the 'bio' element on dealing with neuropathic pain. Speaking to Professor Srinivasa Raja, Paul discusses what exactly is going on in the brain with neuropathic pain. Professor Raja provides a valuable explanation of the science behind the condition.*

Patrick M. Dougherty, Professor at the Department of Pain Medicine at The University of Texas MD Anderson Cancer Centre then shares with Paul the latest advances in neuropathic pain research. He examines the link between cancer treatments and the condition as well as the potential for treatments such as immunotherapy to combat neuropathic pain in the future.

Issues covered in this programme include: Neuropathic pain, the bio-psychosocial model, allodynia, nerve injury, post-herpetic neuralgia, pain after shingles, pain after amputation, differences between men and women, chemotherapy-related pain, cancer, multidisciplinary pain teams, and personalised pain management therapies.

Paul Evans: This is ***Airing Pain***, a programme brought to you by Pain Concern, the UK charity providing information and support for those of us living with pain, and for healthcare professionals. I'm Paul Evans, and this edition of ***Airing Pain*** has been supported by the International Association for the Study of Pain.

Patrick Dougherty: The idea that you could use immunotherapy for chronic neuropathic pain – that's a completely new vista. This sort of research has only come up now over, like, the last three or four years. So this is a whole new vista.

Paul Evans: This is the second of two editions of ***Airing Pain*** about neuropathic pain, a condition caused by nerve disease or nerve damage. The biopsychosocial model for managing chronic pain recognises that the biological, psychological, and socio-environmental factors all feed into each other and affect the pain. And that's why multi-discipline pain teams made up of psychologists, physiotherapists, occupational therapists, physicians and other disciplines can be so effective in helping people live with their pain.

In the previous edition, we looked at how the psychological and social elements of people's neuropathic pain are addressed at the National Hospital for Neurology and Neurosurgery Pain Management Centre in London, and I recommend you listen to that. In this edition, I want to look at the biological component of the biopsychosocial trinity, and in particular, to the progress or otherwise, that's been made into the understanding of neuropathic pain, and what developments and treatments might be just around the corner.

In May of this year, that's 2019, the International Association for the Study of Pain brought together the world's leading experts on neuropathic pain in London to share experience and knowledge. One of those is Professor Srinivasa Raja of Johns Hopkins School of Medicine, Baltimore, in the United States. He's internationally recognised for his research into neuropathic pain.

Srinivasa Raja: One of the earlier things that we were seeing is that in patients who had nerve injuries, they had chronic pain, they would have pain long after their, quote-unquote, tissue injury healed. And they would come up with this sensation, where they would say, you know: ‘Just touching that area, or even rubbing of things bothered me.’ This phenomenon is called allodynia, or pain to sensations that are normally not painful. So we were wondering, you know, what could be causing this, you know, is it because of change in how the normal pain signalling nerves or pathways change? Or is it something else?

So we brought some of these patients, and a simple experiment we did was we applied a tourniquet around their arms. So, after the tourniquet, the sequence of loss of sensations in nerves of different sizes are variable. So the touch fibres are often lost first, and then the pain fibres. So as soon as these touch fibres were lost, you know, these patients lost the sensation of this hypersensitivity, which told us that what's happened is, there were changes occurring at the level of the central nervous system, such that this touch sensation – which in the spinal cord at higher centres, has a common termination with where the pain fibres go – there were changes in the level of the spinal cord resulting in a phenomenon called central

sensitisation. That is, it's almost like the amplifier or the volume has been increased at the level of the central nervous system, such that now even kind of activating these fibres, which on normal individuals we would call as touch, now those individuals feel that as pain. So, this is one of the clinical aspects of understanding that injury to nerves changes how the central nervous system now perceives different sensations. And this also led to a lot of investigation by numerous investigators, looking specifically at the level of the spinal cord and even the brain, [at] what we now call the neuroplasticity [of the brain], or how these signalling mechanisms change. And now we know the molecular biology, we know a lot about it. And this has led also to possibly identifying targets for treating patients with this type of presentation.

Paul Evans: Let me go back a little bit to see if I understand this: a tourniquet on my arm, and I will lose touch sensation. Lots of us will have experienced that, [for example] when we say: ‘oh my foot has gone to sleep’. At what point do you stop the pain signal?

Srinivasa Raja: These patients, when they lost the sensation of touch, could still feel a pinprick, so their pain was still intact. But what they lost also was that hypersensitivity phenomenon where their touch resulted in the sensation of pain. And this is something we commonly see, particularly with patients with post-herpetic neuralgia or pain after shingles. You know, the common site for shingles is often the chest wall. And women are much more prone – two-to-one, almost – [to experience this] than men. And the common complaint that they'll present to us is that [they] can't wear a bra, you know, clothes are very uncomfortable. That rubbing of the clothes on that skin is very uncomfortable.

Paul Evans: Explain to me now – we've gone through the putting the tourniquet on and losing touch. What is going on in the brain with neuropathic pain?

Srinivasa Raja: This is a challenging question, because we're talking about half the pain research community, working for almost half a century trying to understand this. The good news is that we have made enormous progress in understanding the science, the molecular biology, the neuro-physiology or the changes in the nervous system. The unfortunate sad news is, it hasn't been translated into new treatments for patients with neuropathic pain. So there's a big gap between the advances in research versus what we call translating that into new treatments for patients. A significant new area of research is to try to understand why this gap [exists] and what may be causing it. But to go back to answering your question, what we have understood is that changes occur at every level of the pain signalling pathway. In certain cases, this occurs at the level of the periphery at the site of injury itself. Again, I'll come back to the amputation example, where a nerve is often cut at the time of the amputation. And these cut nerves form what's called a neuroma, which is a nerve trying to

grow back to its original site. And these neuromas are very sensitive, they are active, and they fire spontaneously, almost like seizure activity of a peripheral nerve. And these signals, [which are] constantly going from the periphery to the nervous system, are sending signals to the brain saying [that] there is a problem somewhere in the periphery. So the first thing – and this phenomena is called peripheral sensitisation, or changes in the peripheral nervous system. These, kind of, ongoing signals in turn cause changes at multiple levels in the central nervous system, at the level of the spinal cord, the level of the thalamus in the brain and the cortical levels, where this constant barrage of signals changes how the central nervous system perceives the signals. And it's altered in a number of ways, which globally is called a central sensitisation. So this combination of peripheral and central sensitisation in various degrees can occur at different brain states.

Paul Evans: So with an amputation, those nerves [which are] firing off at the amputation, [are] looking for where they were, presumably, and [are] maybe overloading circuits in the brain?

Srinivasa Raja: You said that better than I explained. It is overloading the system in some ways, resulting in changes. Some of these changes seem to be more persistent than others. So, the struggle has been to see how we can revert this process, how we can reverse these changes occurring at the level of the central nervous system, and that's been a significant area for research.

Paul Evans: That's Professor Srinivasa Raja of Johns Hopkins School of Medicine in the United States. Professor Patrick Dougherty is professor of pain research at the MD Anderson Cancer Institute in Houston in the United States.

Patrick Dougherty: I've been interested in neuropathic pain, basically, ever since I was a postdoc or graduate student. And I was really very interested in how activation of the immune system impacts us in such a dramatic fashion. So imagine the last time you were really sick, how just godawful you felt, and that biology to me was extremely fascinating. Well, that carries straight over then into what happens to the nervous system following peripheral injury. And so, ultimately, that leads to what we know now is neuropathic pain. Any type of injury that either leads to some sort of a chronic maladaptive response in the nervous system, or direct injury to the nervous system that then leads to maladaptive responses, resulting in pain. Any of those would fit the category of what we call now neuropathic pain. And so, initially, our work was focused on trying to tie [in] specifically what we call psychophysics. Psychophysics means what people report when you apply energy to skin. And we want to model how human psychophysics is reflected in the activity of specific neurons within the central nervous system. And that was very successful, then led to an

appointment at Johns Hopkins University, where I became interested there in changes in neurons in the brain related then to neuropathic pain.

That group of patients, now imagine the type of patient you're looking at, they have neuropathic pain that has been inadequately treated to the point where they're willing now to have a hole drilled in the top of their head, and put instrumentation inside their brain to try to treat this pain. This is how far down the road they've suffered, basically, and what they're now willing to try. And [when] I'm looking at that I'm thinking, you know, these folks are so complicated, we're never going to be able to figure out mechanisms in this condition. That then led me to think [about] neuropathic pain, [in which] we know the patient starts off basically normal, as far as pain goes, and then we cause neuropathic pain. And that's those folks that are getting cancer treatments. Those people are basically neurologically fine. They had cancer, obviously, but they don't have neuropathic pain. We know exactly what the insult is, it's the cancer treatment. So the thought was, we could basically follow those people from before they get treatment, all the way to the end, [and then] we'll be able to profile a whole natural history of neuropathic pain. Then we can start to come back to other folks that have neuropathic pain, we can stage them in and apply rational therapies. That was the idea.

Paul Evans: So you're going down a known route, [which is] people with cancer, who've had treatment for their cancer. Some get neuropathic pain and some don't. And you're backtracking, then, for people who get neuropathic pain, and you don't know where it started.

Patrick Dougherty: That's basically the idea. It doesn't really work out all that well. Because even cancer treatment-related neuropathic pain becomes very heterogeneous very quickly. In other words, there's a lot of branch points in the road. And so again, to try to back up to anybody becomes complicated, but in any case, we can gain a lot of insights to the underlying mechanisms. And there's been a particular advancement here lately, that is really exciting to us. And that is, we found that you have a group of neurons that innervate your skin, those are called primary efferent neurons. And those primary efferent neurons have cell bodies that basically are what give them sustenance, and metabolic support, and those are called dorsal root ganglion neurons. So the dorsal ganglion neurons are those that send their axons out to every tissue in your body.

What we discovered is that in basically every model of neuropathic pain now – and so this is where the road seems to converge – [in] every model of neuropathic pain that we've looked at so far, these dorsal root ganglion neurons become spontaneously active. They shouldn't be spontaneously active, particularly if they're a pain fibre. Pain fibres should be quiet,

unless you're having pain. To find out that if we give animals chemotherapy drugs, and we go in and deliberately injure nerves to try to produce a neuropathic condition, these dorsal root ganglion neurons become spontaneously active in animal models. Lo and behold, in the course of just simply talking to people at MD Anderson, it turns out that there's a cohort of patients where their dorsal root ganglion neurons are going to be taken out in the course of trying to treat their cancer, so they get cancer into the spine, which is where near where the dorsal root ganglion lives, and sometimes to treat that cancer in the spine, those dorsal root ganglion neurons are taken out in order to get to the tumour.

What we found out is that if those ganglion neurons in human beings come from a part of the body where that patient is experiencing neuropathic pain, lo and behold, they are also spontaneously active. So now we can take animal models of the spontaneous activity, and we can directly line them up to the spontaneous activity that occurs in human neurons, and move back and forth, looking at those mechanisms that are shared or different between humans and the animals. This is really exciting, and a number of different labs now have confirmed that finding, and this is probably one of the biggest new movements in the field.

Paul Evans: Let me see if I can understand, ‘dorsal root ganglion’ – explain to me again what that is.

Patrick Dougherty: You may also hear it called, particularly in the UK, ‘posterior root ganglion’. The posterior root ganglion and the dorsal root ganglion are what are called the cell bodies; the centre of the neuron that leads to all of the peripheral endings that innervate your skin. So, when you move a hair on the back of your hand, there's a neuron that's back along your spinal cord that's being activated by that. It has an axon that goes out and it wraps around the bottom of that hair cell, you move the hair, that causes that axon to discharge, that action potential goes back past the ganglion neuron and then into your spinal cord, [it] makes a synapse, [which is] a connection to another neuron. That then eventually sends that information to your brain and you realise: ‘Aha, a hair’s moving on the back of my hand, something's happened!’ And then every sensation you can think of, for every part of your body, has a separate dorsal root ganglion neuron that has an ending in that part of the skin, muscle, bone, tendon, etc.

Paul Evans: So for cancer patients having treatment, that pathway was broken?

Patrick Dougherty: Not broken – let's describe what happens to cancer patients when they get chemotherapy drugs. There's a number of chemotherapy drugs, not every chemotherapy drug [results in neuropathic pain], but there's many chemotherapy drugs. So for example, those used to treat breast cancer, prostate cancer, most every cancer of a solid tissue and some blood cancers, get sets of drugs that ultimately result in what's called neuropathic

pain. And what happens for all of these classes of drugs, and many people out there can attest to this. They probably will be nodding their head: ‘Yes, that's me.’

You get these drugs, first, it leads to numbness in their hands, that progresses to tingling. That's probably three quarters of patients [who] get those sensations as they get those drugs. And that's fine. Again, mostly everybody's going to get that, [and] mostly everybody that gets better. But [for] some of those patients, that numbness and tingling progresses to the point where their hands and feet feel like they're on fire. Unfortunately, in about one-fifth of patients, that burning sensation, that numbness, that horrible pins and needles feeling, persists long after the cancer treatment’s over and now they would fall into the category of neuropathic pain patient.

Paul Evans: So you follow that track with certain patients having cancer treatment, and you try and replicate that.

Patrick Dougherty: Right, we can give animals chemotherapy drugs, though, we have to change our measurements a little bit, because obviously, the animals can't tell us that they have ongoing pain, but there's different behavioural measurements that we can put the animal in. So for example, folks that have gotten Taxol, often what they'll tell you is that cold applied to their skin feels like it's burning. So you can give animals Taxol, now put them in a little room, and you [make] part of the floor cold, and part of the floor [not cold], and what you'll see is that the animal won't go over to the cold floor, it'll stay over on the warm floor. But since again, [with] the behaviour in the animal, you're always kind of guessing what that means. I'm always really interested in what we can objectively measure. And that's why I say when we find that you get this ectopic spontaneous activity of the neurons that otherwise should be quiet. And you can see the same thing in people. That's what I like to zero in on, we don't have to guess what it means: either that cell is discharging, it's on, or it's off. And then [with] people it's either on or it's off. And if we can figure out how to take the cells that are on and make them shut off, then the idea is that that's what's going to relieve their symptoms.

Paul Evans: Go on, then, can you?

Patrick Dougherty: We are making a lot of interesting progress. So the physiology gets to be really complicated really fast. But there are a number of potential therapeutic avenues that have been uncovered, that now we need to figure out how can we operationalize. There's questions that have arisen that are very surprising. So there's a paper we published a month ago or so, where what we did in that paper – we had these human neurons. In my lab, we did the physiology, and we determined which of these ganglion neurons that we had were in samples associated with pain and with the spontaneous activity. The human

ganglion is big enough that we could divide it, and we can share part of that tissue with another laboratory in Dallas, headed by a fellow named Ted Price. Ted's group broke those ganglion neurons apart and started looking at what we call their transcriptome. And the transcriptome is basically an output from their DNA. In other words, what part of the DNA were those cells activating, that we think would be related to the generation of the spontaneous activity. So we wanted to know, then what sorts of proteins are being made that either weren't made before, or that used to be made that aren't any longer being made. Again, the idea that we can reveal potential new therapeutic targets. And so, Ted did all this analysis. And what we did initially is we took all the ganglion neurons that we had from dermatomes, or segments of the body where patients had pain. And we compared the genetic information coming from all of the neurons from dermatomes without pain. And we run the analysis, and lo and behold, we got almost nothing, we couldn't believe that – that couldn't possibly be the right answer. Finally, we decided, you know, let's just go ahead and we'll pull all the women out, we'll just separate men from women.

Then what we did was, we ran all of the neurons from men, segment pain; men segment no pain, and voila, we got a huge number of results. What that tells us is that men and women are actually changing different gene signals differentially with pain. So in other words, men are from Mars, and women are from Venus. In fact, we have quite distinct mechanisms by which our bodies, in this case, our neurons, respond to this insult – the toxic chemotherapy drug that then results in different ways of expressing pain. Now, what [does] that therapeutically mean? Well, that means that if you give a given drug to a man, that might work, [but] that same drug given to a woman may not. And then if you further follow the logic to that, even for a given man, there's going to be variability within the male cohort. So even a drug that works in man number one may not work in man number two. It's leading to the prospect that what we're really going to need to do is come up with sets of what we call biomarkers, and these gene signals are a type of biomarker, there's others. But we're going to probably need to get sets of biomarkers for each person, and then thereby come up with specific therapeutics for each individual person.

Paul Evans: Wow, how or when will that impact on people with neuropathic pain?

Patrick Dougherty: That's a hugely convoluted question, I think, you know. So number one, there are numbers of compounds that are out there that are available now. Most pain clinics have a set of drugs, and they try different sets for different patients. Some folks respond to one type of agent, others respond to another. So the pain clinics already understand that you have to tailor each pain therapy specifically to each patient. So that concept is already in place. What our research is showing is that we need a broader palette of therapeutics to

address given folks, my lab is not alone in this approach. So there are a number of labs here in the UK that also are doing very similar work to us, in that they've got the same tissues, they're also doing these same kinds of analyses. And one of the other things that we've discovered in these ganglion neurons that's really important is that part of what causes these neurons to become active, is that when the ganglion becomes damaged, becomes inflamed, you get immune cells that go in there – and this is kind of funny, because it closes the loop on my whole career – that's what it began with: how immune cells impact the brain.

It turns out that these ganglion become infiltrated by sets of immune cells, some are your angry uncle, and others are your soothing grandmother. And you can actually train the grandmother cells to go in and quiet everything down. And so with that idea being that you have immune cells that actually get into the ganglion that can either make things worse or better with one potential biomarker, and there's other labs that are doing this, you could take a blood test, and from what's in your blood – the immune cells that are in your blood – you may be able to get a picture of what potentially has gone into your ganglion that's either driving that disease or that we can manipulate to try to make that disease go away. So the idea that you could use immunotherapy for chronic neuropathic pain, that's a completely new vista that again, has been revealed by these new studies on ganglia and what's going on in those ganglia.

So this sort of research has only come up now over like the last three or four years. So this is a whole new vista and what we simply need to do now is build up the sample sizes, I would say, you know, optimistically, as rapidly as biotech and the rest is advanced, let's say five years, we can start actually having some real insights of what may be really good players to follow. And then it will be up to the pharma outfits and the new biotech outfits to operationalize those targets and come up with therapeutics. My side of the ledger is what's called target identification. Once you get targets that are well validated, then you get into the legalistic part of bringing a drug to market. And so, I can't tell you how long that might take based on which government you're working with. If it's in the US, it can be very slow, other countries move faster. So it's hard to predict once you get into the actual regulatory process for each place, but I think as far as target identification goes, I would say within five years, we are going to have a very good idea of some promising new targets. I would say today, you know, our data says that a number of those that we could follow, but we need to validate the targets that we've identified. Other labs are identifying other targets, those should be mature enough, within five years, that you could start to operationalize those into therapeutics, and then you get into the therapeutic regulatory process, so that I can’t give you a handle on.

Paul Evans: That sounds very exciting, very positive. I guess it shouldn't really come as a surprise that the same drug will work differently on different individuals. When we open our tablets, we see the list of the side effects, which could be diarrhoea, it could be constipation, it could be one of a hundred things, you know. Personalising designer drugs sounds really exciting.

Patrick Dougherty: Yeah, and it goes beyond just drugs, right? People need to be aware that pain, particularly a chronic pain condition, is not probably going to be treated by any magic-bullet drug. I mean, you're going to need to go into whatever you can possibly do, that might work for you. Is that walking? Is it swimming? Is it yoga? Is it meditation? You know, there's a whole number of different – both medical or drug – therapies and then non-medical therapies.

So MD Anderson, that is one of the pain treatment centres – what's called a multidisciplinary pain centre – where basically whatever works for a given patient is what you're going to try. And it's probably not going to be one thing, there's probably not one magic bullet. Number one, the patient has to decide they want to get better. It's all about patient buy in: if you give up, the chances of being fixed are small. So you have to be focused, that you are going to get better, this is a disease you're going to overcome. Then you find the combination of medications that work, the combination of exercise, the combination of nutrition, etc., that works for you to get you back, so that you're in the game and you're functional again.

Paul Evans: That's Professor Patrick Dougherty, of MD Anderson Cancer Institute in Houston. And I was speaking to him and Professor Srinivasa Raja, at the International Association for the Study of Pain Neuropathic Pain Special Interest Group conference earlier this year, in London. I will just remind you that whilst we in Pain Concern believe the information and opinions on ***Airing Pain*** are accurate and sound, based on the best judgments available, you should always consult your health professional on any matter relating to your health and wellbeing. He or she is the only person who knows you and your circumstances and, therefore, the appropriate action to take on your behalf.

Well, in this edition of ***Airing Pain***, we've been focusing on the 'bio': the biological elements of the biopsychosocial model for chronic pain. And please do listen to the previous edition of ***Airing Pain*** to learn more about these psychological and social elements.

Patrick Dougherty: They're crucial. They're absolutely crucial. If a person has chronic pain, and they become socially withdrawn, isolated, that quickly leads to depression, and an erosion of the spirit. And that person then is going to suffer even more. You have to get yourself back engaged into social environments, working as hard as you can to get yourself back to a normal level of activity. Meanwhile, we'll be in the lab trying to come up with as

many magic bullets as we can come up with. But I would be very surprised if we find anything that I say is the golden ticket, so to speak. It's going to be a combination of things. Everyone's going to have to sort out what specifically is going on with them in concert with their medical providers. What we're hoping to do is come up with the tools and resources that, number one, we can [use to] better ascertain for that particular person what's going on with them. And then, again, have the agents that can be then implemented.

Contributors:

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- Professor Srinivasa Raja (John Hopkins School of Medicine, USA).

More information:

- Neuropathic pain fact sheets and support, IASP https://www.iasp-pain.org/GlobalYear/NeuropathicPain
- News, information and support at RELIEF, IASP Pain Research Forum https://relief.news/
- The University of Texas MD Anderson Cancer Centre https://www.mdanderson.org/?_ga=2.205594646.486343381.1563359882-181156349.1563359882
- Neuropathic Pain information, National Institute for Health and Care Excellence (NICE), https://www.nice.org.uk/search?q=Neuropathic+pain
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