Published on *Up Close* (http://www.upclose.unimelb.edu.au)

#310: Beyond the tremors: Understanding the impact of Parkinson?s disease

VOICEOVER
This is Up Close, the research talk show from the University of Melbourne, Australia.

SHANE HUNTINGTON
I?m Dr Shane Huntington. Thanks for joining us. Among the many degenerative neurological disorders that can afflict us, Parkinson's disease is one such condition that can radically change the way we live and function. Second only to Alzheimer's disease in prevalence in the ageing West. Many of us have an image of the Parkinson's sufferer with increasingly debilitating tremors. But the symptoms of the disease go well beyond the visible. We don't know the cause, we don't have a cure, yet progress is being made.
Today on Up Close we discuss research into Parkinsons and what the future holds for sufferers and those who support them. With new genetic technologies improving by the day are we are on the verge of cracking this disease? Can we identify the risk factors and try to avoid them?
To answer these questions and more we are joined by Professor Malcolm Horne, Head of the Neurodegeneration Lab at the Florey Institute for Neuroscience and Mental Health, Consultant Neurologist at St Vincent Hospital and Conjoint Professor, Centre for Neurosciences at the University of Melbourne. Welcome to Up Close Mal.

MALCOLM HORNE
Thank you.

SHANE HUNTINGTON
Could you start with a brief description of what Parkinson's disease is like for someone with the condition?

MALCOLM HORNE
It really depends on what stage of the disease. So when people first turn up to the neurologist and say look there's something not quite right here, they're actually talking about problems with movement. Often they come because they've got the tremor. But the factors that cause the disability is not so much the tremor but

slowness of movement, loss of dexterity and as we've come to understand it this is not just a matter of being clumsy, but it's actually about being able to make goal directed and purposeful movements. And so actually carrying tasks with intent become increasingly difficult. But over time the disease progresses into becoming more than just about movement and eventually begins to affect cognitive functions so people find problem solving and this broad area of cognition we call executive function becomes impaired. As well they have disturbance of the parts of the nervous system that control processes such as blood pressure and gut function, swallowing and becoming increasingly affected by that.
And also there's an element of neuropsychiatry which is this process of dealing with thoughts and impulses so that impulsive behaviour such as gambling and overeating become common. People also get hallucinations and become depressed. So it's these latter stages of cognitive and psychiatric disturbances as well as the autonomic disease which really are the devastating components although it's the movement that is most prominent and often receives most of the attention.

SHANE HUNTINGTON
When you describe all of these various symptoms I mean it's quite a swag of things that a person will end up with. But when they're first going through that process how do we go about making a diagnosis? Is there a blood test, a genetic test or is this all based just on looking at some of those movements and so forth and evaluating.

MALCOLM HORNE
Yes unfortunately we're still very much on that stage of ?Trust me. I'm a doctor. I know?, and it's not a very satisfactory position for anyone. And that is that it's really up to the judgement and experience of a clinician who has seen enough Parkinsons to make the call. It's usually relatively straight forward and the complications in the diagnosis are not so much whether or not someone has Parkinsonism which is this broad description of this movement disturbance, it's really more that there are other causes of Parkinsonism other than the what's called idiopathic or the mainstream Parkinson's disease. We're not so good at diagnosing that accurately at the beginning. When I say not so good we probably make mistakes around about 10 to 15 per cent of the time at the onset of disease although it becomes clearer with time.

SHANE HUNTINGTON
When I walk down the street or I hit a cricket ball or I do a variety of things there's some things that are conscious, I'm thinking about it to some degree of detail, and there's other things where I'm not thinking about them at all and they just happen. What's occurring in someone with Parkinsons with regards to these various types of movement? How are they being affected and why are they being affected?

MALCOLM HORNE
So I think this is the interesting aspect of Parkinsons that's become increasingly clear over the last probably 20 years, that the movements and the capacity to make movements are really part of this broader function of the frontal lobes. This area of brain that sits really in front of the ears and occupies a large amount of space in humans and we have a capacity to pay attention to a relatively small number of

things. While I might get some arguments from my expert colleagues we can broadly call this working memory and that's what you can pay attention to at any one time. It's probably around about two or three tasks or six or seven things. So if I'm paying attention to a goal I have to do things automatically to achieve this goal. I can use an example if you like which is say learning to drive a car.
If you recall when you first learnt to drive a car all your attention was getting the gears and the clutch and everything correct. You couldn't pay attention to who you might run over or what you might bump into. But as they became automatic, which is the job of the part of the brain affected by Parkinson's disease is to make that automatic, then you could pay attention to what you were using driving for. And so there are these whole ranges of automated movements which are used underneath to carry out a goal directed or task directed movement. So the reason a musician practices is so that the producing of the notes becomes automatic so the attention can be directed at making music.
When we learn a language we can relatively quickly once we've moved from thinking about how to express ourselves to thinking about what it is we want to say and the purpose of the communication. So there are many, many examples of this and these are the processes affected so that more attention has to be directed to thinking about how to carry out the movement and less time is available to thinking about what am I doing it for. So the movements become slower and clunkier but also our executive function or ability to think about why we're doing something is consumed in doing the task and so we're less efficient at thinking about how to do it or why to do it.

SHANE HUNTINGTON
Obviously this is a progressive disease that develops over a protracted period of time. Are we able to look at the level of difficulty in movement and determine how far along a person is in this disease cycle?

MALCOLM HORNE
We can though it's really more that the involvement of other parts of the nervous system that aren't directed to movement that tells us how far we're involved in the disease cycle. For reasons that are not particularly clear and there's some debate about this, it seems that the nerve cells involved in producing the movement itself and they're in a particular part of the brain and have certain characteristics, are perhaps more susceptible or earlier affected in disease which is why movement comes to the fore and draws attention. But you can tell how far the disease is going when these other aspects of processes such as cognition and balance become affected and they tell you that the disease is actually progressing further because these other parts of the nervous system are involved.

SHANE HUNTINGTON
Now you mentioned before a very specific part of the brain that's involved in movement but when we started you gave us some examples of various issues that people with Parkinsons eventually develop. Are these all problems coming from the same part of the brain or are there a variety of elements of our brain that are being affected over time by the condition?

MALCOLM HORNE
There's a variety of parts to the brain that is affected over time although a significant proportion of the abnormalities are brought about by this one area which produces the chemical dopamine. That role is to actually make these movements automatic which I talked about before and it's also to make other thoughts and habits automatic as well. As they become disturbed then things such as anxiety and impulsive behaviours become more prominent. But the disturbances that are involved with hallucinations and probably the blood pressure control and so on, they are other parts of the nervous system. And there are a couple of theories as to how this might happen.
A prominent Austrian pathologist called Braak has the theory that perhaps the disease might enter through the gut or through the old factory system and then progress through susceptible neurons to other parts of the nervous system. That's why perhaps sleep disorders come early on because they're lower in the brain stem and swallowing and the gut becomes affected earlier and then eventually spreads to the superficial layers of the brain called the cortex and producing cognitive disturbance. However that's a theory and while it's got a lot going for it there are other people who think that perhaps these parts of the nervous system are affected together and it's just that some are more susceptible to others and so they come to prominence earlier in the disease. So it's a little unclear which way it is.

SHANE HUNTINGTON
We commonly associate Parkinson's disease with movement disorders. Is there a reason why these other quite extreme systems are not better known?

MALCOLM HORNE
It's not clear to me why that is. And I think it's perhaps because there's a degree of folklore. I mean compared with Alzheimer's disease Parkinsons is really much the poor cousin and it's seen to be just a tremulous disorder and something that happens to elderly folk and just makes them a bit clumsy with the peas on the fork. I really don't know why it's not clear that this is such a devastating illness. And whether it's because people like me are not very good at articulating how important it is to the rest of the world. But I think even if you ask a lot of the community about Alzheimer's disease they will still think that it's just a matter of forgetfulness. So I think there is a tendency to pick on one or two aspects of a disease and believe that that's all it is and not realise just how devastating it can be.

SHANE HUNTINGTON
I'm Shane Huntington and you're listening to Up Close. We're discussing Parkinson's disease with neurologist Professor Malcolm Horne. Mal when you look inside the brain of someone with advanced Parkinson's disease what would you expect to see.

MALCOLM HORNE
The hallmark, the things that the pathologist will want to see is a process or something you can see under the microscope called the Lewy body. It's a small accretion of protein that sits inside particular neurons and tells us that those neurons

have been affected by the process of Parkinsons. We've now come to understand that it's mainly composed of a molecule called alpha-synuclein which is aggregated in an abnormal way. That's led the community interested in Parkinsons to think that somehow or rather alpha-synuclein's the culprit molecule. You know that it's either at the heart of the matter or it's very close and is almost always a bystander. These inclusion bodies as they're called are clumps of alpha-synuclein and other proteins bound together and we don't know whether they're the cells best effort to sequester them away out of harm. Or whether they are actually indicative of the process themselves but in some way they are closely related to the disease mechanisms. And so that's become a target of research to try and understand how this protein accumulation is occurring.
That's led to a number of theories which are really around the idea that there is a disturbance that either leads to the protein to have an unusual propensity to accumulate. But that probably can only explain a small proportion. Therefore the question is, is this a problem of disposal of the protein appropriately through the normal cellular disposal mechanisms and bearing in mind that neurons, we have them for life, and so housekeeping and disposal of garbage is an important process. And so there is this idea that it's something to do with autophagy which is the cell's process of recycling damaged protein for further use in the cell is somehow or rather affected and the alpha-synuclein in some way is not digestible by the autophagy mechanism. That's probably the most hot focus of the pathology of the disease. But exactly how autophagy is involved and even if it really is autophagy is still unclear but that's probably where most people are thinking at present.

SHANE HUNTINGTON
How do we make the determination when we look at these proteins that they're causing the problem and not a result of the problem? There's always that tension when we look inside the body and we see something, then we ask the question is it caused by the problem or is that is doing the damage itself? I mean how do we determine that for Parkinsons in this case?

MALCOLM HORNE
So we may never be able to do that and I think that comes down to this concept of neurodegeneration as distinct from say infectious diseases. So we have this legacy in medicine where we think of there being an offending process such as a virus and if you don't catch the virus you don't get the disease. You know this leads to this idea of Koch's postulates which was you know if you find the virus you can stop the virus, you stop the disease, you know et cetera. Whereas degenerative diseases such as heart disease is a really good example where 200 years ago people talked about dropsy which is just the accumulation of fluid. That was the best we could say which was the end result of disease and slowly people would track back from that and say well actually dropsy could be caused by heart disease or kidney disease. So then there was the idea that it was heart failure that was the problem.
Then when you look back further you realise that heart failure can come about because of hypertension or heart attack or cardiomyopathy. And so then the idea was well heart attack is the big culprit, we've got to stop that. Then that led to the idea that actually atheroma was the thing that set it going. So how do we stop

atheroma? And in the end you come to the point that there's really no single culprit. You've got hypertension, diabetes, obesity, cholesterols et cetera and it's really a sum of risk factors which reach a tipping point and then a new event is set in motion and that event has a life of its own. So it may be that there is no single culprit but that somehow or rather these processes which involve the mishandling of alpha-synuclein can conspire together and therefore have a number of tipping points.

SHANE HUNTINGTON
Now lets' talk about the neurons briefly. I mean you've got these other materials, the alpha-synuclein is there and you're building this up over time, what is actually happening to the neurons? Are they ceasing to function? Are they dying? Are they unable to transmit the information that they are producing to other parts of the brain? What is going on in the brain itself?

MALCOLM HORNE
We don't really know a lot about that. It looks like alpha-synuclein is a molecule that's involved in vesicles, which are small membranous bags inside the cell, being transported to the surface and dumping chemicals to the outside. Alpha-synuclein is involved in some way in having these molecules dock with their membrane. Now nerve cells have a particularly important function about vesicles because that's how transmitters are packaged up. When one nerve cell talks to another nerve cell the electrical impulse comes to the synapse, which is the end of the nerve terminal, and gives a signal which allows the vesicle containing the neurotransmitter to travel towards the membrane, bind with it and tip its neurotransmitter contents out. And Alpha-synuclein has got something to do with that docking process as well as other vesicle docking. We think therefore the first thing that goes wrong in Parkinsons is that these neurotransmitter functions begin to fail in some way or the terminals misfunction and so the conversation between nerve cells becomes impaired.
With time though it seems that the terminals and the axons or the fibres connecting the terminals from the cell body begin to die back. And eventually the nerve cells - the cells die. One of the views it that the disturbance in the vesicles leads to problems with them trafficking backwards and forwards between the end of the terminal and the cell body or there's something like that that ends up using up a lot of energy and causes the nerve cell to be inefficient. But it's really unclear how that happens.

SHANE HUNTINGTON
When we consider there's a variety of neurons that we have in the brain, are all of them attacked or damaged equally by this process or are particular ones being picked out?

MALCOLM HORNE
They are being picked out and we mentioned before the dopamine ones are particularly important. But it seems that there are cells that have fragile terminal ends and that they're releasing chemicals that are related to dopamine or similar in that respect and don't have the binding sheath of myelin around them that seem to be more susceptible than others. What it is about these cells that make them

susceptible is unclear. There's been a lot of attention to dopamine because it has a high redox potential, that is it likes to exchange electrons, and that means that it's got the capacity to be damaging to other proteins just by being there as a redox molecule. That probably doesn't really explain why it damages cells that don't have dopamine in it though.

SHANE HUNTINGTON
And dopamine is linked to depression so presumably is that where some of those other later stage symptoms are coming from?

MALCOLM HORNE
It may be. We're not clear about that. It's probably one of the factors but it's also that dopamine is particularly involved in making behaviours salient and therefore learning them. One of the other drivers for it is that paradoxically the levels of dopamine fluctuate between being very low in Parkinson's disease and then abnormally high when you give drugs to treat it such as levodopa. In fact the levels get almost as high as if you were going to give someone cocaine. Now we know that on the falling levels of dopamine with cocaine people become very anxious and disturbed and upset. And we wonder whether in fact that's what causes some of the anxiety that's associated and then the progressive anxiety that you can't resolve eventually leads to depression. So whether it's a strictly chemical thing related to mismanagement of serotonin and related molecules or whether it's related to the chemicals we give to treat the Parkinsons is still a little unclear.

SHANE HUNTINGTON
You are listening to Up Close. I'm Shane Huntington and my guest is neurologist Professor Malcolm Horne. We're talking about Parkinson's disease. Mal, do you know how long the Lewy bodies are formed in the brain before symptoms actually start? Can we go looking for them potentially early on? And is it a preventative measure?

MALCOLM HORNE
We'd love to be able to do that. That's a little bit of a holy grail for people to find out. We know that for example the dopamine neurons that are involved in producing movement by the time people turn up probably about 60 per cent of them have been lost. So clearly the disease has been going for a while and there are various estimates about how long the disease has been present in terms of causing cell death and possibly even longer in terms of these abnormal accumulations. We also know that if you biopsy the gut at the time of diagnosis if you're able to look inside the colon at the nerve cells they've got Lewy bodies in them. So presumably they've been there for some time before.
A really important component in terms of research at present is to try and identify molecules that are uniquely present at the time of diagnosis or behaviours that are uniquely present at the time of diagnosis and then try and find those molecules in the so called normal population. That would lead us to be able to study people hopefully who have early forms of the disease. That's important for two reasons. If ever we find a disease modifying drug it's going to work better if you've still got neurons to

save. As well it gives you a better chance of looking at the behaviour of these people or the environment of these people or the characteristics of these people to actually understand what are the risk factors that actually set the process in motion.

SHANE HUNTINGTON
So are there no drugs available at the moment to actually deal with aspects of Parkinsons? I can imagine that there must be something out there to reduce some of the symptoms.

MALCOLM HORNE
There are good symptom modifying drugs particularly for the movement. There are some that are helpful for some of the non-movement components but there are no drugs that have been unequivocally shown to be disease modifying. There is a suspicion that some of the drugs we currently use if we were able to conduct the studies carefully and thoroughly in people with early disease may well actually have some disease modifying capacity. But they have not been proven to actually have that so at present we have to say look hand on heart we haven't got anything that slows the disease down that we really convincingly know. Although we suspect there might be both behaviours as well as drugs that could slow it down.

SHANE HUNTINGTON
In terms of early detection what sort of tests are you looking for at the moment? This is obviously as you said it's the Holy Grail trying to work out when someone is progressing down this path. And presumably not just so you can catch it early if we have a drug but as you mentioned also so that we can try and determine what risk factors are affecting them. What sort of tests are we heading towards?

MALCOLM HORNE
Our approach has been, and you know we're not wanting to say we're unique at this approach, but our approach has been to look within the blood. You might think well that's an odd thing to do. This is a brain disease why look in the blood? There are a couple of reasons for thinking that and that's first of all we do know that alpha-synuclein for example is in blood cells. It's possible that they misbehave in blood cells in the same way as they misbehave in brain cells. And we know that some of the blood cells in people with Parkinsons die faster than in people without Parkinsons suggesting there's something going on there. The second thing is that if Braak is right that the disease begins in the gut or in the nose then that is going to be - being bathed by the blood and we might see molecules there.
So we're trawling through proteins in the blood to see whether we can find ones that are high in people with Parkinsons but not in controlled population.
One of the team in the lab, Blaine Roberts, has been very good at developing a technique which allows us to refine the trawling process so that we can select molecules in a better way. We think we have some targets there that are interesting. We haven't gone through all of the processes of cleaning that up so I can't really tell you exactly what they look like. But we think that's a promising way because as we find that they're high in people with Parkinsons. They're not in the controlled population. They're high in people with early disease. So that then leads us to say

well how do we go about trying to find that in people in the general population and select out those people who have the high protein.
Similarly we've been using a device for measuring movement and it gives us much more accurate movement than my expert eye. We can measure these movements as being clearly abnormal in people with early disease in terms of the asymmetry of the movement and the way they move. If we could put this simple device on people who have got the right age group and find that they had the abnormal type of movement that might give us a group of people who have very early movement disturbances and we would be able to look at. So combining both the blood measurements and the movement measurements you start to get into a population that may be at risk or have already begun to develop early disease.

SHANE HUNTINGTON
Presumably now we have the technology. I mean you see every second person wearing it that monitors our movement day in day out. You see all sorts of exercise bands around people's wrists and the like. Is there any sort of push to utilise that technology in a much broader cohort study to try and collect data over a longer period to perhaps bring to light some of the very early symptoms that people probably won't even know this for the first five or 10 years.

MALCOLM HORNE
Yes that's really the nature of this study that we're working at, what the logistics are of doing it. We've developed a device which is worn on a wrist like a watch. We've developed the algorithm which allows us to distinguish the abnormal movements of Parkinsons from the sorts of movements that the rest of the population might make. And indeed what we found is that the movements are not so much abnormal but that a person with Parkinsons makes more movements as if they were learning a new task. Which is really what I was saying before is that they have to go back and think about the movement more and they make it in a way that looks like someone just learning the task.
And if we use that algorithm that puts higher scores on having movements that look like learning movements then we can pick out people with Parkinsons quite clearly from the normal population and we know we can do that already. Our question then is if we put this wrist watch like device on people who have got the right age group would we be able to detect a group of people who already had the signature abnormalities or trending towards that signature and therefore pick out them in the very early stages of movement.

SHANE HUNTINGTON
The obvious direction a lot of different researchers are going for other conditions and diseases is that of genetic testing. Is this not a viable option for Parkinsons?

MALCOLM HORNE
No it's a very viable option and so far it's revealed about 14 likely gene candidates of a single mutation that explains Parkinsons in that particular cohort. Unfortunately though that probably still only explains about less than 10 per cent of Parkinson's disease and the people who have that form of Parkinsons doesn't look like the typical

form that the rest of the community get. There is also other genetic mutations in specific populations, for example in the Ashkenazi Jewish community there is a mutation in a gene related to Gaucher's disease which is related to this lysosome autophagy process we talked about before. And we know that carriers of that have a much greater risk of getting Parkinson's disease and so it's looking like it's a good risk related gene and there's a couple of other genes now that are falling into that category. Whether we are going to find genes like that that will explain Parkinsons outside of these very specific communities is less clear cut.
The other hope is that it may be something a little bit like diabetes where there isn't probably going to be a single genetic mechanism, a single mutation, but there's probably going to be enabling genes that make it more likely that these risk factors will then come into play if you carry that particular genotype. And that's perhaps another way of saying we're finding the genetic code for the risk factors we were talking about before. There are clues. For example we know that Parkinsons is one of the few conditions where being a non-smoker makes you more likely to get it. Now is that an environmental factor that smoking somehow or rather protects or is it actually a behavioural thing that people who don't smoke have a particular genetic predisposition that makes them more likely to get the disease. So they're the sort of clues that you can see how genetics might actually interact with environment in that way to make someone at risk.

SHANE HUNTINGTON
It all sounds very exciting in terms of these approaches. But I get the feeling many of these are fairly extended longitudinal studies that will take perhaps decades to really get information on as you watch people go from perhaps being non-Parkinsons to Parkinson's sufferers. Is that the case and what time frame are we sort of looking at before we have the sorts of things we would need to put into the average clinic?

MALCOLM HORNE
I think that's right. I think the studies that are going to look at the development of Parkinsons from the early diagnosis or the risk factors into proving that they're the actual disease are probably of the order of five to 10 years even if we began today. On the other hand the likelihood of there being breakthroughs in the sort of - you know everyone cringes when we use that but you know sort of quantum steps in understanding which I think is a better way of thinking about them, is very high. Because I think since probably 1995 when the first gene for Parkinsons was found and then that turned out to be alpha-synuclein and the whole thing snowballed.
I think we're really in a position now where we've moved from not so much wondering what Parkinsons is but actually a fair amount of optimism that it will be understood but it is a matter of time. Those steps come as always unexpectedly and from different quarters. I've been telling you yes the explanation is going to be by looking at these groups of people who have early disease. It just might come out of the blue from somewhere else. But I think there's a far greater optimism that there's something there that will lead to at least a slowing of the disease. It's going to be like heart disease. I'm young enough or old enough to remember the first coronary care unit in Australia and we're really now looking at the stage where cardiac disease is really beginning to tumble.

So it takes a while before these things flow through and you know can we actually say what was the single breakthrough? Well there isn't one. It was accumulation and accretion of many, many steps that have led to that change.

SHANE HUNTINGTON
Mal, thank you very much for being our guest on Up Close today.

MALCOLM HORNE
It's a pleasure.

SHANE HUNTINGTON
Professor Malcolm Horne is head of the Neurodegeneration Lab at the Florey Institute for Neuroscience and Mental Health, consultant neurologist at St Vincent's Hospital and conjoint professor in the Centre for Neurosciences at the University of Melbourne. If you'd like more information or a transcript of this episode head to the Up Close website. Up Close is a production of the University of Melbourne Australia. This episode was recorded on 10 July 2014. Producers were Kelvin Param, Eric van Bemmel and Dr Dyani Lewis. Audio engineering by Gavin Nebauer. Up Close is created by Eric van Bemmel and Kelvin Param. I'm Dr Shane Huntington, until next time, goodbye.

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