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#280: Deferring dementia: Research efforts to keep Alzheimer?s at bay

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. Our individual identities, along with our ability to interact effectively with those around us are crucial to our sense of self and our place in society. Diseases that impact on our cognitive function, such as Alzheimer?s disease strike at these attributes that we hold most dear. Of course, the impact of Alzheimer?s is not only felt by sufferers, but also by family members and friends who must grapple with the eroding identities of their loved ones. With the advent of high resolution imaging systems and molecular tools to probe the brain?s biology, we are today able to study the intricacies of diseases like Alzheimer?s at new levels of detail.Still, outright cures remain elusive. So what do we know and what treatments currently exist? Is Alzheimer?s yet another lifestyle disease that we can avoid, like type two diabetes? Or are some of us genetically predisposed to this shocking condition? Today in Up Close, we put these questions to an international leader in Alzheimer?s research. Professor Colin Masters is Executive Director of the Mental Health Research Institute, Senior Deputy Director at The Florey Institute of Neuroscience and Mental Health and a Laureate Professor of Neuroscience at the University of Melbourne. Welcome to Up Close, Colin.

COLIN MASTERS
Thanks, Shane. Great to be here.

SHANE HUNTINGTON
Could you start with a brief description of what Alzheimer?s disease involves for someone who has the condition?

COLIN MASTERS
For someone who has got Alzheimer?s disease, it?s principally a disorder of spatial orientation and memory. So what happens is that those parts of the brain which are responsible for orientation in time and place are slowly destroyed. So the person loses their bearings. They can?t remember what time of the day it is or where they are and where they?ve been, who their friends are. Things like that. And it?s the

most recent memories which are lost first. So the memories which are laid down in childhood, for example, are relatively well preserved. It?s like going back in time, reverting to being a child almost.

SHANE HUNTINGTON
So Colin, when we talk about these difficulties with memory, are we talking about an access problem or are we talking about the memory itself eroding? Which part of the process of remembering things is gone?

COLIN MASTERS
Well, the problem is that the synapses in the brain degenerate. So there?s a general malfunction of all neuronal communications within the brain. Certain areas of the brain are affected first. That is in the temporal lobe and the frontal lobe. Those areas of the brains are the ones that are principally affecting memory and orientation. So it?s difficult to answer that question precisely, because it?s a total breakdown in all forms of intercommunication within the brain and it?s progressive.

SHANE HUNTINGTON
We often hear these stories about patients with the condition having these moments of clarity, where all of a sudden, they will be visited by a relative and everything seems back to normal. Is there an understanding of that happening? Or is it...

COLIN MASTERS
There certain is day-to-day fluctuation in the degree of impairment. But looked at over a period of a month or so, there?s clearly a deterioration occurring. It may take many months to deteriorate. Certainly, there?s day-to-day fluctuation, as there is in normal people.

SHANE HUNTINGTON
When you look inside the brain of a person with Alzheimer?s, how does that compare to an unaffected brain? What sort of things do you see?

COLIN MASTERS
Well, we?ve been working on this disease for nearly 30 years. And a hundred years ago, Dr Alzheimer himself was in the same position that I?m in at the moment, where he is seeing patients alive and then they?ve passed away. Then they?ve taken out the brain and looked at the brain. And under a microscope, what you see is the build up of a protein which is called the amyloid-beta protein, a-beta is the way that we refer to it. This is a small molecule which assembles into plaques. And these little plaques sit between the nerve cells and the small protein seems to damage the nerve cells. There?s are two basic types of Alzheimer?s disease. One is where this protein is made in excess. And the other type is where it?s not cleared.So in familial Alzheimer?s disease, where there?s genetic mutations, which we?ll talk about later, it?s very rare ? less than five per cent of all cases, but there?s too much protein being made of this particular protein. But in sporadic Alzheimer?s disease, which is the common form of the disease, more than 95 per cent of all cases are sporadic. There?s a failure to clear this protein out of the brain. And so over a period of time,

it builds up very slowly. We?ve now got precise estimates of how long it takes to build up in both of these types of illness. So in the familial disease, the genetic forms of the disease, the mean age at onset is about 45, whereas in the sporadic forms of the disease, common garden variety, the mean age at onset is about 80. It?s all to do with the kinetics, the rates at which this protein is either made or cleared from the brain.

SHANE HUNTINGTON
Do we have an understanding of whether this particular protein is a cause or effect in this scenario? It?s obviously there with Alzheimer?s patients, but is it a result of the disease itself or is it what?s causing the problem?

COLIN MASTERS
It?s causing the disease and we can say that with confidence, because we know that the genetics of this illness tells us precisely that if you have a mutation, either in the protein itself or the machinery of the cell that makes the protein, you will get the disease. So in other words, the genetics points the way to the absolute cause of the illness. Now, there are proximal causes and there are distal causes. And so we know what the proximal cause is. That is the cause closest to the actual degeneration of the brain is the build up of this protein. But what causes the build up of the protein is a separate question. We?re only just beginning to understand some of these factors.

SHANE HUNTINGTON
Presumably, we all have this protein in our brain at some levels, anyway. What is its normal functional role?

COLIN MASTERS
Well, it doesn?t have a normal function. It?s part of a much larger molecule, which does have a signalling function in the brain. But this part of the molecule that builds up is stuck in the cell in a part that it doesn?t have any function. So normally, after the parent molecule is subserved its function, this part of the molecule is normally cleared and this is where the problems arise. Because in most cases of Alzheimer?s, this protein is not being properly cleared from the brain.

SHANE HUNTINGTON
You mentioned earlier that in past we?ve always had to examine deceased disease carriers to look at this sort of material in the brain. Is that still the case now or are we able to image it in different ways?

COLIN MASTERS
Well, no. We?ve moved on a lot. Up until about 10 years ago, we were totally reliant on making the diagnosis through post mortem analysis. But today, there?s been a revolution in the field. We now have tests of brain imaging that can be conducted during life, which give us a measure of the amount of this protein building up. We can actually see it using either a PET scan, a positron emission tomograph, using a ligand that binds to this protein. We can actually see it during life. Or we can take a

sample of the cerebrospinal fluid by doing a lumbar puncture. That means putting a needle into the membrane surrounding the brain and spinal cord, taking out a bit of the fluid and measuring this protein in that fluid. And as the disease progresses, because it?s been trapped in the brain, the levels decrease in the fluid. So we have two principal measures. And we can see it going down in the spinal fluid or we can see it going up in the brain itself using the PET scan. We can do this with a great degree of accuracy now. And we can follow people over the trajectory of the illness, from the time it starts to the time it finishes. We now know that it takes approximately 30 years from the first signs of it beginning to build up to the time when it?s full blown disease. So this means that in the familial cases with a peak age of onset of 45, it starts at the age of 15. However, in a person with sporadic disease, where the peak age at onset is 80, that means that it?s beginning at the age of 50 in people like you and me, who don?t have a strong family history, we could probably say that by the time you turn 50, if you?re going to get the disease, you will start to see it from the age of 50 onwards.

SHANE HUNTINGTON
Will you be able to see the aspects of the brain that are changing at the same time as when you start seeing symptoms? Or is that happening much earlier on that we?d be capable of measuring those?

COLIN MASTERS
Right. So for the first 20 years of the build up of this protein, very few symptoms exist at all. It?s asymptomatic. It?s only in the last 10 years of the illness that the symptoms and signs of cognitive impairment, memory loss become apparent.

SHANE HUNTINGTON
I?m Shane Huntington and you?re listening to Up Close. Today we?re talking to Professor Colin Masters, a neurobiologist , about Alzheimer?s disease. Colin, in many diseases that we find around the world, both genes and environment play a significant role. What do we know about this interaction for Alzheimer?s?

COLIN MASTERS
So at the moment, most of the evidence is pointing towards genetic factors being much more important than environmental factors. It?s not to say that there are no environmental factors. There probably are some. It?s just that we haven?t really identified them yet. Now, in the lay press, there?s a lot of talk about factors such as the standard cardiovascular risk factors, like high blood pressure, diabetes, overweight, lack of physical activity, prior intelligence, meaning surrogate for the amount of education. All of these, so called, environmental factors are claimed to be having an effect on the incidents of dementia, as opposed to the specific diagnosis of Alzheimer?s disease. But you don?t want to get caught in that trap. Alzheimer?s, as we currently understand it, has very little to do with those environmental factors. What those environmental factors have a major role in is the health of the cerebrovascular elements in the brain; in other words, the amount of blood that is delivered to your brain over your lifetime. If you don?t look after your cardiovascular health, what happens as you get older is that the small blood vessels feeding the

brain can also run into major problems, as they do in the heart. So that?s why it?s very important to look after the cerebrovascular risk factors, which are largely environmentally determined. But the actual root causes of Alzheimer?s disease do not appear to be related directly to these cardiovascular risk factors.

SHANE HUNTINGTON
One interesting area, of course, where I think there have been recent reports is with type two diabetes and many of the things that you just spoke about with regards to cardiovascular function and blood delivery is a significant problem in these patients. How do people with type two diabetes link in with Alzheimer?s? Is there risk associated?

COLIN MASTERS
Well, there isn?t. There is not any direct association of type two diabetes with Alzheimer?s disease. There?s certainly a risk of type two diabetes causing cerebrovascular disease. High blood pressure, small blood vessel disease and so on. However, having said all that, there are people and many researchers around the world who are still investigating the effect of insulin and its effect on the metabolism of nerve cells. And this is slightly different from asking what is the effect of type two diabetes where there is a general lack of insulin or an insulin resistance caused by the loss of beta cells in the pancreas. So it?s a complex area. But the simple answer right now is that there isn?t a direct relationship between type two diabetes and Alzheimer?s disease.

SHANE HUNTINGTON
Do we have an understanding or are we getting close to an understanding of why the brain is starting to make this error at a certain age in our lives? Do we have a clarity as to what potential that might have for us? Is it a malfunction just pure and simple? A genetic variant that?s not supposed to be there? Or is it something our bodies are trying to do and just getting it wrong?

COLIN MASTERS
Yeah. It seems as that we get older, there is a failure of the clearance of this protein out of the brain. So as you can imagine, that the brain evolutionary was not designed to live past 50 years, because most of our reproductive energies go into the first 50 years and not the second 50 years of life. So what?s happened is that in the second 50 years of your life, between 50 and 100, we have not evolved our clearance mechanisms, particularly in the brain. Now, these clearance mechanisms probably are related to small cells in the brain, which we call microglia, whose normal function is to take discarded proteins and chew them up and get them out of the brain. So for some reasons, and we don?t understand the full mechanisms of this yet, this clearance mechanism is impaired.But whatever the clearance mechanism is, it?s deeply connected to the genetics of an individual. So in other words, depending on which genes that you inherit from your mother and your father will have a very large part to play and where this clearance mechanism is successful or fails.

SHANE HUNTINGTON

Do we see any consistency between things like Alzheimer?s and other diseases of the brain, of which there are many, of course?

COLIN MASTERS
Not directly. It?s a very specific disease. It?s very common and it?s not associated with any of the other multitude of diseases that can go on in the brain. So I mean, often we see concurrent of two or more diseases associated with aging. This is not unusual at all.

SHANE HUNTINGTON
Colin, you?re having a look at the early stages of Alzheimer?s disease. What is important in terms of determining what stage a person is in, how far they?ve progressed and how fast they?re progressing?

COLIN MASTERS
So as I was saying, the genetics determines, to a very large extent, the rate of progression and the age at onset. There?s one particular gene called the ApoE gene, which has a very dominant effect in this area. Again, it?s probably related to the clearance mechanisms. But what we?re all on about now is coming up with an effective therapy. So we have spent the last 10, 20 years dissecting these molecular pathways and trying to understand them in the most fine level, so we can then develop drugs which can be used to intervene in this process and help the body clear this protein out of the brain. So there are many therapeutic strategies now being tested in humans. Over the last five years or so, the pharmaceutical industry has poured billions of dollars into this.And unfortunately, to date, many of these studies have not proven very successful. There is one study, however, which we are hopeful will lead the way for the next five or 10 years. That?s one particular antibody that is seeing one particular form of this protein in the brain. When it?s administered over a 12 month period, it?s been shown to have a significant effect at slowing down the rate of progression in people with the mildest forms of this illness. So what we hope now in the future going forward is that we will be able to design clinical trials of administering this type of therapy at the very earliest stage and maybe even at the pre-clinical stage, the asymptomatic stage of Alzheimer?s.In other words, we?ll be recruiting individuals in their late sixties, early seventies who are absolutely cognitively intact, and yet we know that they have this build up of this protein, as we can see with a PET scan or a test of the lumbar puncture fluid. We?ll start these people on this type of drug at the earliest possible stage and see if we can then delay the onset of Alzheimer?s disease. What the holy grail in this field at the moment is to delay onset by about five years. So remember I told you that the peak age at onset in sporadic disease is about 80? If we can shift that to 85, just a five year delay of onset, that?ll have a fantastic important effect on the prevalence of this disorder in our community.It will, in effect, hold the current prevalence levels to the current levels. It we fail to deliver on this type of intervention, the actual prevalence of Alzheimer?s disease is just going to go through the roof. The epidemic of Alzheimer?s, we will have to live with it and deal with it.

SHANE HUNTINGTON

So the strategy then clearly is to slow it down and then push it back in our lives. As our lifespan is changing and the average life expectancy is going up and up, it seems, every decade, how hard does that become? You mentioned five years. Will the new goal in 10 years time be 10 years and what...

COLIN MASTERS
Absolutely.

SHANE HUNTINGTON
Yeah. So...

COLIN MASTERS
As we learn more and more about this illness, we will become more sophisticated in the way that we can deal with it. It?s unrealistic at this stage to think that we will have a magic bullet, one drug that will cure it. It?s just unrealistic right now, because we still don?t understand enough. However, like many complex disorders, it?s not going to be just one drug. There?ll be a combination of therapeutic interventions, possibly combined with environmental lifestyle modulation, as well. Being healthier, getting all those cardiovascular and cerebrovascular risk factors under control, in conjunction with a drug or a combination or drugs that targets the build up of this protein in the brain at the same time.What we can see in a demographic sense on a worldwide population is that we?ve never been healthier. We?re living longer and longer. Every year that goes by now, we are adding three months or so to the average life expectancy. Those life expectancy curves are just going through the roof. A child born today can expect to live to 90, which is a remarkable phenomenon. A child born in 10 years from now can probably expect to live for another five years or so on top of that.

SHANE HUNTINGTON
You?re listening to Up Close. I?m Shane Huntington. Today, I?m speaking with Professor Colin Masters, a neurobiologist who works on Alzheimer?s disease. Colin, when we look around the world at various populations, are there any interesting features there in different countries with regards to the prevalence of Alzheimer?s? Or is it pretty consistent across the board?

COLIN MASTERS
As far as we can tell at the moment, it occurs - the incidents, as opposed to prevalence, so the incidents, the number of new cases per X number of humans is about the same around the world. It differs a little bit from country to country and we don?t know yet whether that?s an ascertainment problem or whether it?s a true incidence problem. But we would very much like to know, because if there are significant differences say, between the Han Chinese and Caucasians, we would like to know about it. And we?re beginning to do these studies now where we can actually measure the amount of build up of the protein during life and we will sooner or later get an answer to that question.

SHANE HUNTINGTON

I understand you?re also looking at a longitudinal study at the moment where you?re trying to track the progress of the disease in early stages. Tell us about how that study is progressing.

COLIN MASTERS
So this is a longitudinal cohort study in which we, in Australia, have enrolled approximately a thousand individuals and we follow them over - every 18 months, we bring them back in and we do measurements of their cognition and their blood tests. We measure the brain scans and the build up of this protein. At the same time, there are similar studies going on in the US, in Japan and Europe and we?re beginning, for the first time, to really understand the natural history of Alzheimer?s as opposed to the natural history of just getting older. It may come as no surprise to you that if you are perfectly healthy and you don?t have the build up of this protein in the brain, your brain functions absolutely normally and barring other forms of diseases, your brain should keep going till you reach 100 or even 120. It?s only when these concurrent diseases start to kick in that your brain starts to fail. So through these longitudinal studies, we?re beginning to tackle some of these fundamental questions about what is normal cognitive aging. What is the brain? What is its real capacities for longevity and so on.

SHANE HUNTINGTON
When you bring the patients in, what sort of cognitive tests are you doing? Are they just around memory, or are they also around critical thinking and other areas of cognition?

COLIN MASTERS
Yeah. There?s a whole battery of neuropsychometric analyses that cover calculation, recall speeds and executive function and your typical episodic memory and that sort of thing.

SHANE HUNTINGTON
Presumably, these are, sort of, different in all the patients anyway, to some degree.

COLIN MASTERS
Yes.

SHANE HUNTINGTON
So are you tracking them relative to the individual?

COLIN MASTERS
Yes. And what happens in Alzheimer?s is that in different individuals, different parts of the brain tend to be affected at different rates. So there will be a variation of the symptomatology of the illness, depending on which parts of the brain are first affected.

SHANE HUNTINGTON
Colin, as we head into the future and we look at the possible ways of treating

Alzheimer?s and, perhaps, holding it back. What do you think will be the most likely approaches we will take? Will they be genetically based or otherwise in the future?

COLIN MASTERS
Well, yeah. Sure. For the - what we call the autosomal dominantly inherited forms, that five per cent of pure genetic Alzheimer?s disease, it?s possible today to do genetic testing in utero or at conception and it is possible to have a child who does not carry the mutation. So that?s one possibility. For people who are unfortunate enough to carry these genes, we hope that there will be specific therapies available in the not too distance future, which again will slow the disease down. But the same applies also for the sporadic forms of the disease. The same sorts of therapies that should affect and benefit people with the genetic forms of the disorder should probably also work in the sporadic forms of the disease.

SHANE HUNTINGTON
Colin, you mentioned a specific antibody that?s being trialled as a therapy. If this is a natural antibody that we find in the body anyway, does that mean the side effects potentially from it are minimised.

COLIN MASTERS
So there are many generations of antibody trials that have been conducted. The first series of antibody studies was active immunisation with the amyloid protein itself, to get the body to make its own antibodies against the protein. That ended in disaster, because what happened is that the body made too much response and caused significant damage in the brain. Subsequently, we are undergoing trials now with what?s called passive antibodies and there has been many attempts to define the particular epitope, the particular shape of the molecule that needs to be recognised by an antibody. The current one that?s showing the best response is directed at what we call the mid region of this amyloid protein.And what seems to happen is that you give the antibody peripherally through a vein, systemic administration, and it circulates in a small proportion that actually gets over the blood brain barrier. One per cent of it. But that?s enough for it to be bind to the amyloid protein and to neutralise it and stop its toxic action in the brain. Then what happens is that the body has a chance to get it out of the brain by its normal clearance mechanisms. But there are many other antibodies in trial. Some of the antibodies have failed, because they either miss the target or they?re provoking too much immune reaction. So it?s just a matter of finding the right antibody to do the job.So at the same time as we?re developing antibodies to clear this material out of the brain, we are developing small compounds, which can cross the blood brain barrier. These are not biologicals. These are straight drugs. The idea is that these drugs will bind to the amyloid and also stabilise it, neutralise it and get it out of the brain.

SHANE HUNTINGTON
Colin, when we consider some of the lifestyle potential interventions that people on occasion talk about, have there been any specific studies to eliminate them as possible pathways?

COLIN MASTERS
Most of the studies fail to discriminate precisely between the symptoms of dementia, which can be caused by many different factors, such as cerebrovascular disease and concurrent Alzheimer?s disease from pure underlying Alzheimer?s. This is one of the big gaps in our knowledge right now. We still don?t understand whether there?s any major effect of lifestyle, environmental factors on the underlying neurodegeneration of Alzheimer?s disease. So much more work is needed to really pin this down and answer the fundamental question, if I get out there and I exercise and lower my blood pressure, does that have any effect on Alzheimer?s disease? At the moment, the evidence is not there.

SHANE HUNTINGTON
You see on the news and so forth all these new games and so forth that apparently keep these things away. Is this all just marketing nonsense at the moment, or is there any truth in it?

COLIN MASTERS
I wouldn?t call it nonsense. I?d call it the lack of scientific evidence.

SHANE HUNTINGTON
Colin, thank you for being our guest on Up Close today and talking with us about Alzheimer?s disease.

COLIN MASTER
It?s my pleasure. Thank you very much.

SHANE HUNTINGTON
Professor Colin Masters is Executive Director of the Mental Health Research Institute and Senior Deputy Director at The Florey Institute of Neuroscience and Mental Health. And he is a Laureate Professor of Neuroscience at the University of Melbourne. If you would like more information on this episode, visit the Up Close website, where you?ll also find a full transcript. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 12 December 2013. Producers were Eric van Bemmel, Kelvin Param and Dr Dyani Lewis. Audio engineering by Jeremy Taylor. Up Close is created by Kelvin Param and Eric van Bemmel. I?m Dr Shane Huntington. Until next time, goodbye.

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