"IMAGINE TOMORROW'S WORLD"

The Sir Paul Reeve's Lecture, Holy Trinity Cathedral , Auckland
12 September 2013
Richard Faull

Tena koutou, tena koutou, tena koutou, katoa.

Lady Beverley Reeves and family, distinguished guests, ladies and gentlemen.

Thank you for your kind and generous introduction.

It is a unique and humbling invitation to give the 2013 Sir Paul Reeves Lecture.

I was privileged to know Sir Paul for over 15 years – he was a very generous mentor, a close colleague and friend who always provided sound wisdom and guidance during challenging times.

Sir Paul Reeves was a visionary and great leader. An extraordinary person in every respect. Like so many great leaders, he was a humble man who never forgot his roots. His mission in life was to simply help people. In the Mandela fashion, he led in a quiet and compelling way – he wanted no fuss, but just got on with the challenge at hand to make a difference for Aotearoa New Zealand. He was a man for all people, in all seasons.

I am a humble Taranaki farm boy at heart. I grew up in a family of 5 boys in a tiny North Taranaki farming community called Tikorangi. My Mum and Dad owned the general store. They never completed secondary schooling and we didn't have much money, but they gave us the vital ingredients of life. They taught us to believe in yourself, be true to yourself, be honest, be humble, do your very best, strive for excellence, and show dignity and love to all. My Mother was the eternal optimist – she gave us a boundless enthusiasm and passion for life – our cup was always half full. Above all else: they taught us to "serve the community and the people". So - the bottom line of my lecture tonight: is that people matter. Science is all about people.

"Imagine tomorrows world" if scientists in the University worked collaboratively with doctors in the hospitals, and people affected by brain disease in the community. We could move mountains!!

Tonight I want to take you on a voyage of discovery; tell you a story of the excitement of science in the human brain, the excitement of discovery in science, how finding things out in an unexpected, serendipitous way is at the very core of science discovery; how, discovery in science involves collaboration – people working together. How discovery is the ultimate excitement. Above all – I want to tell you about the Challenges of the Human Brain.

This is a real human brain especially bequeathed by a family for teaching and research.
I first saw the human brain as a young third year medical student; that's when I fell in love with the brain, It has a myriad of folds on the outside. It is tantalizingly beautiful. It is the most marvellous and complex organ in the human body. It is responsible for who we are, and what we are; it determines out potential in life. It is the most vital, the most valuable, the most critical asset we will ever possess and we got it free. That's incredible!

Compared with animal brains, the human brain is so incredibly complex. For example, the rat brain is a basic, prototype mammalian brain. It is small, has a smooth outer forebrain – brilliant for a rat, but they don't make computers or build libraries - I call it the "Ford Model T".

The Human brain - by contrast – is the Rolls Royce. It has a massively enlarged, highly developed forebrain which is divided into 2 halves: a right hemisphere controlling the left side of the body and a left hemisphere controlling the right side of the body. Each Hemisphere consists of a series of beautiful folds.

Marvellously, each fold has quite different and unique functions. The fold in the middle of the hemisphere controls the movement of muscles on the opposite side of the body. Just behind the movement area is the sensory area where you consciously feel touch and pressure on the skin, the passionate kiss on the lips, the tender touch on your hand, the brick on your foot. In the most complex fashion which we still do not comprehend, you feel with your brain and project that feeling to the relevant region of your body.

Vision is located in the folds at the back of your brain; that's where you see the pictures, upside down: the right half of the picture on the left side of the brain, the left half of the picture on the right side of the brain. Your brain turns the images right-side up and seamlessly combines the two separate images together in a precise non-overlapping way to give you 3D vision, in technicolour. Isn't that magic!

All your conscious functions are appreciated in specific parts of your brain. Other complex functions like memory, emotion, behaviour, personality and intelligence are located in other widespread parts of the hemispheres in such complex ways that scientifically we are still trying to unravel. All of these areas of the brain work together in the most marvellous way to give us our conscious existence. When we wake up each day, we take for granted we are the same person we were when we went to sleep.

When these different areas of the brain are affected by a stroke, you lose these functions. For example, if a blood vessel supplying your movement area on the right side of your brain gets blocked you are paralysed on the left side of the body, or if a tumour involves the front of your brain, this results in behaviour and personality changes. Inside the brain, all these functions are provided by the most magic cells which we call neurons. There are over 100 billion neurons in the brain, more than the number of stars in the Milky Way.

The neurons show great diversity in their shape, size, chemicals and functional characteristics. Just like the vehicles on the road - trucks, sports cars, graders, tractors, bulldozers – they are all modified to do different functions. Cells in the movement area are big triangular cells with massive branches - pyramidal cells – which project to the spinal cord on the opposite side to control the muscles. In the vision area of the brain, the cells are small rounded, dandelion like cells; they look like sunbursts, so delicate and beautiful. They turn light rays hitting the retina into pictures in your brain. The memory area contains specialised large and small, rhomboid and pyramidal shaped cells; they are the store-house of memory and knowledge. Amazing.

The brain cells are beautiful in their diversity and their complexity. I told Diana my wife that we should have them on our wall paper at home. Each neuron gets inputs from at least 10,000 to 120,000 other brain cells. All these brain cells work together in the most complex way to give us a unique, individual conscious experience - that's incredible. We are all different and are experts in our own special worlds. No two people are exactly the same. For each of us the human brain is unique – is both scientifically and artistically beautiful.

The limitation is that we try to understand the complexity of the human brain with our own human brain; we actually need a super brain to understand our brain.

The great tragedy is that the human brain is affected by diseases. Diseases like Alzheimer's and dementia. This is a tragic disease which affects memory, personality and behaviour and results in a deterioration of the mind; dementia literally means "without mind". There is progressive brain cell death in those regions which control these critical functions.
Ultimately there is extensive cell death. Instead of the brain weighing 1500 gm, at the time of death it may weigh 900 gm or less. Over one-third of the brain is lost. Over the years in Alzheimer's disease brain cells die in their millions. Under the microscope, the cells are clogged up with toxic proteins called plaques and tangles. Many scientists therefore conclude that it is these toxic proteins which cause brain cell death. But, we know, that is too simple an explanation; it is like going to the cemetery and saying everyone died because of the concrete covering their graves. Alzheimer's disease is more complex than that. We need to find out why the very first brain cell dies if we are going to solve this tragic disease.

Just to give you a hint of the challenge of Alzheimer's disease, today 45,000 New Zealanders are affected by this tragic disease. Tomorrow, with the ageing population, the numbers will increase dramatically; double by 2030 and more than treble by 2050 to over 140,000. The latest World Alzheimers Report calculated that the world wide costs of dementia exceed 1% of the global GDP in 2010; if dementia care were a country - it would be the world's 18th largest economy, equivalent to the economies of Switzerland or the Netherlands. What a huge challenge for the future!

There is hope. It would be fantastic to discover a cure. Realistically, that is a long way off
but if we could delay the onset of the disease by 5 years, we would cut the prevalence of Alzheimer's disease in New Zealand by 50%. That would be a huge step forward and we are working on that.

1 in 5 New Zealanders will be affected by a brain disease in their lifetime; diseases like stroke, Parkinson's, Huntington's, motor neuron disease, epilepsy, multiple sclerosis – the list goes on. Neurological disorders are among the top 5 most common causes of death and longterm disability. The challenge is huge - that is the Challenge of the Human Brain.

My passion as a third year medical student was to undertake research on the brain. Since it is not possible to do experiments on humans, experimental brain research must be undertaken on animal brains, like rats. As a third year medical student at Otago University I undertook a years research on the rat brain, studying the basal ganglia, the region deep inside the brain which controls movement and is affected in Huntington's and Parkinson's disease. That year was one of the most exciting years of my life. Unexpectedly I found a new pathway, published my first research paper, and presented my findings at an international conference. Wow, it doesn't get much better than that! That year was incredible and I knew that I wanted to specialise on the brain.

I completed medicine and then tried neurosurgery; that was really fascinating and so rewarding but I suddenly realised how little we knew about how the brain functions. So I went back to University and started a career in brain research. A PhD at Auckland University on the cerebellum and basal ganglia in the rat brain; more new unexpected pathways – exciting stuff – I was hooked! Three years postdoctoral research studies on a Harkness Fellowship in the USA studying with two world experts on the basal ganglia. First, at the NASA Ames Research Centre at San Francisco where they were researching problems involved with the basal ganglia and space travel - absolutely fascinating research. I had to get a CIA clearance to work there; that's how cutting edge the research was. Then, I studied at MIT and Harvard in Boston where I learnt

the latest brain research techniques for studying pathways in the rat brain at the hands of the "masters." What an incredible opportunity for a Taranaki boy. I then returned to Auckland University in 1978. Set up my very own rat brain research laboratory; just me. More exciting studies on the basal ganglia in the rat.

Then in 1980, something happened which changed my life forever. Professor Arthur Veale, Professor of Genetics came and talked to me about Huntington's disease. He was the New Zealand expert on Huntington's and looked after all the affected families in New Zealand. He told me how Huntington's Disease was caused by dominant gene that affected the basal ganglia. The gene was unknown and there was no definitive gene test available at that time.The tragedy is that each child of an affected parent had a 50% chance of getting the gene and that it was difficult to diagnose exactly from the symptoms. So he asked me if I would help the families by examining the brain of their loved ones after death to determine if they had the disease. He told me how critical this was for the families. So every few months, Professor Veale arrived with the most precious gift, the "brain" from a family for us to study. In most cases, our pathological studies unfortunately confirmed the diagnosis. But in some cases they clearly didn't have Huntington's disease; that was fantastic news for the family. But what was special, the families made the most generous gesture you could ever imagine; they said, keep the brain of our Mum or Dad; use the tissue for research on the brain and find out why the brain cells die and give hope to our children. Their generosity was over whelming.

Over the next few years our research on Huntington's disease on these donated brains showed unexpected findings which were so different from the textbooks. The patterns of the cells dying varied markedly from one brain to another. Why is this? We were perplexed. How can we solve this?

So we talked to the families to find out more details on the clinical history of the disease.
We involved expert clinical psychologists to help in the research and to talk to the families.
The families were so enthusiastic that they were actively involved in our research. Our team grew; we had families, psychologists and the research team on board. The outcome of this combined research was unexpectedly exciting.

We showed that the variation in the pathology in the brain which we saw in the research laboratory correlated with the variation in the pattern of motor and mood symptoms which the families saw in their Mum or Dad. These findings were novel and so important. They helped us to not only unravel the complexities of Huntington's disease, but they have also showed how the basal ganglia functions in the normal brain. These and our ongoing studies have pushed back the frontiers of knowledge on the human brain. All this exciting science because the families had given the greatest gift to science - the brain of their loved one after death. I realised that we had established a special and unique partnership with families

All of these studies emphasised that in order to understand the human brain, you must look at the human brain as well as animal brains. The human brain is the Rolls Royce – it is the ultimate model. Over the years, with growing family and community support, we extended our human brain studies to include Alzheimer's disease, Parkinson's disease, epilepsy and motor neuron disease. In the early 1990's we realised we had unconsciously established something truly special at the University of Auckland in partnership with the community - a Human Brain Bank. We are so grateful that the Human Brain Bank has been generously supported by the Neurological Foundation since 1993; that has been a critical factor in this exciting journey.
We had really established a special 'boutique' Human Brain Bank; it is quite different to any brain bank overseas. It is a partnership between families, doctors and our research groups. The families were so committed; it was their drive and interest in research which was critical to establishing the Brain Bank. They provide vital ongoing information on the disease symptoms.

The families are the experts because they live with the disease 24 hours a day. One of our families said they are so proud to be part of our research – “it seems like Dad lives forever”.

Our collaboration with the doctors, neurologists and neurosurgeons is essential: they provide the clinical details of the cases we are studying and they give us ideas for new research opportunities. Most important are our collaborations with other brain research groups in the University of Auckland, throughout New Zealand, and overseas. These research groups extend the boundaries of our studies and include pharmacologists, psychologists, pathologists, geneticists, physiologists, psychiatrists – the list goes on. With the families permission we send tissue overseas to the leading research groups; the families have always been so enthusiastic for us to share the tissue of their loved one with other top research groups. One family said: “Mum always wanted to travel – in death, she is not only having the travel that she didn’t have in life, but she is also contributing to vital international research for the future health of our family. That is very special to us and is the fulfilment of her dream.”

These multidisciplinary research studies on the human brain have enabled us to push back the boundaries of brain research. For example, working with our leading pharmacologists we have pushed back the boundaries and developed techniques to culture human brain cells and to test new drugs and therapies for Alzheimer’s, Huntington’s, Parkinson’s, epilepsy, motor neuron disease and other brain diseases. Also, by working with our leading geneticists and scientists in New Zealand, Australia, the USA and Cambridge University we have put the human gene for Huntington’s disease into sheep so that we can begin to develop new techniques for turning off the Huntington’s gene and perhaps stop or slow down the disease. That would be a dream come true.

Furthermore, these research studies have enabled us to make quite unexpected new findings on stem cells and the human brain. One of the most exciting findings from animal studies over the last 50 years is the discovery that stem cells are still present in the adult rat, cat and monkey brains and that they multiply to make new brain cells throughout their adult life – that’s called neurogenesis. Furthermore, in the animal brain these new brain cells travel down a special motorway – the rostral migratory stream - extending through the forebrain from “Auckland to Wellington” to provide vital new replacement brain cells for the adult animal brain,

However, as a medical student, I was told that the adult human brain didn’t have stem cells and it was far too complex to make new brain cells. The dogma was that once you have reached maturity in your 20’s you had all the brain cells for life; that was it, and all you could look forward to was losing brain cells as you got older! However, our studies on the human brain over the last 10 years have told us something quite different and very exciting.

In 2003 we showed that, against all dogma, the adult human brain did in fact contain stem cells, and that these magic cells could make new brain cells in an attempt to replace those lost in diseases like Huntington’s disease. That was unexpected and fantastic. Then we asked the critical question: do we have a “motorway” for new brain cells just like the rat? The overseas experts all said no – because they could never find it, and in fact they published papers stating in the title that “there is no pathway for neurogenesis in the human brain.”

We didn’t believe them because we had seen tantalizing hints of this elusive pathway in our human brain studies. After a long challenging search over a number of years, we finally found the “motorway” – the rostral migratory stream - for these new brain cells in the human brain. It was more complex than in the rat brain because of the huge development of the human forebrain. It didn’t go directly from Auckland to Wellington, as it does in the rat; instead, it travelled via Taranaki, around Mt Taranaki, that is, around the basal ganglia. When we submitted these exciting findings to the top English science journal “Nature” – they were questioned and rejected

out-of-hand by the “expert” referees who clearly were non-believers. However, we persisted, adding further data and proof, and then submitted it to the other top rival US journal “Science”. The referees this time were “open minded” and it was not only accepted, but we also got top billing on the front cover! That was incredible.

These findings showing that the adult human brain can make new brain cells throughout life, and that the human brain has a motorway for new brain cells were groundbreaking. It gives us a completely new approach to fight brain disease – that’s fantastic! Furthermore, since we have shown that the human brain has stem cells and a pathway for neurogenesis just like the rat brain, we can now extrapolate the findings from animal studies to the human. In this respect, it is very interesting that if you put rats into stimulating and enhanced environments – and give them lots of things to do and “think about” - like rat mazes, rat “jungle gyms”, running wheels etc –they make lots more new brain cells. Relating these animal findings to the human, it is tempting to speculate that just like rats, stimulation, intellectual excitement and exercise may produce more new brain cells for us. Also, our very latest research by scientists in our Centre has shown that you can take skin cells from a live person and turn them back into stem cells, which could then theoretically be placed in the person’s brain to treat their brain disease. That is still a long way off – but now we can dream the impossible dreams to help people with brain disease. That’s the “Challenge of the human brain.”

We couldn’t have achieved any of this research without the generosity of families, and without the support of our research collaborators in the University and the clinicians in the hospitals.
So, the pathway to success in research is to develop team research.

1. Collaborate with other scientists – that’s multidisciplinary research
2. Work with doctors in the hospitals
3. And, above all, maintain close links with the community.

If we are going to win the “World Cup” for Brain Research and develop new treatments we need to form a brain research club, the “All Blacks” of brain research; a “Team New Zealand” to bring all these partners together. That’s exactly what we have done at Auckland University. We have established the Centre for Brain Research (CBR). It consists of 3 pillars: researchers at the University of Auckland, doctors in the Auckland Hospitals and the Community

The researchers comprise 55 different research groups across the University in the medical and science faculties who are studying brain disease - pharmacologists, physiologists, anatomists, geneticists, psychologists, biochemists, audiologists, clinical scientists and many others. In all there are over 300 people involved in brain research at the University. What a diverse club of experts.

The doctors in the hospitals are vital to the team. They form the second pillar of the Centre and comprise of expert neurologists, neurosurgeons, psychiatrists, radiologists, geriatricians and pathologists in the Auckland Hospitals. They treat and care for the patients on a daily basis. They are involved in drug trials, use exciting new treatments for brain disease like deep brain stimulation for Parkinson’s disease. They are working with clinical scientists developing new methods for rehabilitation, like trans-cranial magnetic stimulation for stroke recovery. They know the vital ingredients of brain disease. They have great ideas for new treatments. By working with them we can trial and undertake research on these new treatments in the research laboratory.

Finally, the community partners are central to our efforts. They form the third pillar. They are the families and patients with brain disease. They are the people we want to help. The community organisations that support the families are critical for supporting the families on a daily basis; they need to know all about our research success. Organisations dedicated to families affected by Alzheimer's, stroke, Parkinson's, Huntington's, epilepsy, motor neuron disease, multiple sclerosis, muscular dystrophy and others. They link with the people and the families affected by brain disease. We exist to give them hope and a brighter future tomorrow.

So we have a virtual army across the University of Auckland, the Auckland Hospitals, and the community. The membership is unique, they are all committed to a common purpose. But our army is not yet complete. We still do not have all the big guns we need to fight brain disease. Our next critical dream is to get a professor of brain surgery. We currently have 6 fulltime world class neurosurgeons at Auckland City and Starship Hospitals. They are all fully employed 24/7 doing over 1500 life saving brain surgery operations per year. They just don't have time for research

We desperately need a University Professor of Neurosurgery who is halftime surgeon and half time researcher, who has one foot in the hospital and the other in the University and is supported by an expert research team. A professor would enable us to maximise brain surgery research for tumours, stroke, Parkinson's & other diseases. That requires an investment fund of $8 million dollars. We are launching that campaign next Tuesday. So watch this space!

Furthermore, we are currently working with the leading brain scientists and clinicians in other regions of New Zealand; at the Brain Health Research Centre at the University of Otago, at Canterbury University and at the Auckland University of Technology to extend this exciting network over the whole of New Zealand.

"Imagine Tomorrows World" if we can get our researchers across New Zealand working more closely together with brain surgeons and neurologists, and with the patients and families. We could make a difference for people with brain disease throughout the Nation. We could develop new therapies, new drugs, new "packages of care" all tailored to patients' specific needs.

In conclusion, our mission is to work together to improve lives and to identify and develop new treatments for Brain Disease. Our lofty and ambitious goals are to unlock the secrets of the brain, develop new therapies for brain disease and engage with communities and people affected by brain disease.

One of our imaginative new treatment packages in the CBR is the establishment of a therapeutic choir which you had the privilege to hear at the beginning of this evening. The CeleBRation Choir helps people who have speech problems because of stroke, Parkinson's and other diseases. It is amazing that speech is controlled by the left side of the brain and music by the right side of the brain, so people who have problems speaking can still sing and singing can help them to recover speech. So this marvellous choir promotes brain recovery by helping people who have problems speaking sing their way back to Brain Health. Isn't that magic.

So, this is your incredible brain. It has changed over the last 45 minutes. Maybe you have been stimulated and made new brain cells. Use it to it's maximum to fulfil your dreams and passion in life and to expand your mind.

Science is about People. He tangata, he tangata, he tangata.
Science is about dreaming. We want to make a difference – to give HOPE to the future for people with brain disease in New Zealand.

That's our passion - IMAGINE TOMORROW'S WORLD.

That's the challenge and the excitement of the human brain

Thank you.