

INVITED EDITORIAL

My wonderful, exciting, and serendipitous journey in brain research, culminating in the establishment of the Centre for Brain Research — A dream come true!

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I am the fifth generation descendent of a Taranaki pioneer family who immigrated from Plymouth, England, to New Zealand (NZ) on the first immigrant boat (“The William Bryan”) to New Plymouth in 1941. On my Māori side, we proudly whakapapa to *Te Āti Awa, Ngāti Rāhiri*.

Together with my four brothers, I had the great fortune and privilege of growing up in the late 1940s through to the 1960s in rural Taranaki — a place called Tikorangi. Our parents owned the General Store (“Faull’s Foodmarket”). They were very community-minded, and in our formative years, they instilled in us wonderful rural community values: “Look after the people and serve the community.” Those “Tikorangi” values have served us all well and have been the essence and ethos of our various careers in education, business, the church, healthcare, and medicine.

I first saw the human brain as a young, naïve third-year medical student in 1966 at the Otago Medical School. I immediately fell in love with its simple, yet stark complexity. I couldn’t believe that within its beautiful folds on the outside and its deeper recesses lay over 100 billion microscopic brain cells — over ten times the number of people on Earth, and greater than the number of stars in the Milky Way. It was tantalizingly, overwhelmingly complex, and unbelievable to realise that these brain cells were interconnected in the most intricate and incredible way to give us our conscious existence: our personality and behavioural profile; our passion, vision, enthusiasm, and love for life and each other; our conscious sensation of seeing, feeling, hearing, smelling; our ability to move, read and write; the secrets which make each of us wonderfully unique human individuals. I was compelled to explore and unravel those secrets.

At the end of my third year, I interrupted my medical studies to undertake a year of experimental research on the brain. Since it was not possible to undertake experiments on the human brain, I instead undertook research on the rat brain. That was the most incredible and exciting year of my life. I discovered new pathways in the rat brain that controlled motor functions. I presented my findings at an Australasian conference and published them in a top neurology journal of the day.¹ My mind was on fire, and it was at this stage that I knew I was destined to a life of exploring the secrets of the brain.

On the completion of my medical studies in 1970, I briefly “flirted” with neurosurgery as a young house surgeon. I was captivated by the wonders and marvels of brain surgery, but soon realised that we could only do surgery on the outside of the brain and knew so very little about what was going on inside the brain. So, I returned to brain

research, and undertook an unexpectedly exciting and challenging Doctor of Philosophy (PhD) at the newly established University of Auckland Medical School, and was the first PhD graduate in neuroscience in the fledging medical school. During my PhD, I found new pathways from the cerebellum to the rest of the brain, which play a critical role in our movement functions. These landmark findings led me to postdoctoral studies from 1975–1978 in the United States of America (USA) — learning new experimental techniques for tracing connections in the basal ganglia of the rat brain under the mentorship of two of the world’s leading neuroscientists — Dr William Mehler at the National Aeronautical Space Administration (NASA) Ames Research Center in San Francisco, and Professor WJH Nauta at the Massachusetts Institute of Technology in Boston. We discovered additional new pathways and established lifelong brain research collaborations which have flourished for over 40 years and still continue today.

On my return to the Auckland Medical School in 1978, I established my own experimental rat brain research laboratory studying the basal ganglia pathways which are involved with Parkinson’s disease and Huntington’s disease (HD). Then, unexpectedly, in 1980 my life changed forever. Professor Arthur Veale, the then Professor of Genetics at The University of Auckland, and world-leading authority on HD, came to see me and said: “Richard, I look after the 400 families in NZ with HD. This is the most tragic genetic brain disease and is autosomal dominant — if the mum or dad in a family have the gene, then each child will have a 50% chance of getting the gene, and if they do, they will die prematurely in their 40s or 50s. Unfortunately, we do not yet know what the gene is and can’t test for it. Because the symptoms can be confused with other motor neurological diseases, a clinical diagnosis is not definitive. The pathology is definitive — it causes a very specific pattern of brain cell death in the basal ganglia. Since you are an expert on the basal ganglia, the families would like you to look at their loved one’s brain after death to determine if they really do have HD in the family. Would you do this for the families?” Of course, I said yes!

Every few months, Professor Veale would arrive with a brain fixed in formalin from a family somewhere in NZ. After a detailed pathological study in consultation with a brain pathologist, Dr Beth Synek, I could give a definitive diagnosis to the family. I would phone, write, and talk to the families and tell them our findings. Unfortunately, in 90% of cases, it was yes, but very occasionally it was no — which was fantastic news for the family. All of the families were very grateful.

Unexpectedly, they gave me a wonderful gift and a challenge: “Keep mum’s brain and do research on it; please find out why the brain cells are dying and find a cure for our children!” The donation of the brain of their loved one after death to research was the most wonderful and generous gift that families could ever make to brain research. It was just incredible. I was blown away. I was committed to giving hope to families through research. I was reminded of the values instilled to me in my youth by my Mum and Dad at Tikorangi — “Look after the people and serve the community.”

We received the first brain in 1981, and from that day, I changed my research from the rat to the human brain. My mission in life was to unlock the secrets of HD to help the NZ families and their children. Over the years, we have received more than 160 brains from families with HD, and we have made unexpected world-leading findings on the human brain, which have contributed to a better scientific understanding of the cell death and the development of new treatments in HD. All this is because of the extraordinary gift and support from families and whānau. By the mid-1990s, our studies on the first 50 HD brains had unexpectedly found that the pattern of cell death in the basal ganglia and cortex in the human brain with HD varied markedly from one brain to another. This was against all the textbooks and research, which stated that the brain cell death in HD was homogeneous. Why was the cell death so variable? I was totally perplexed. Finally, I talked with expert HD psychologist at The University of Auckland, Associate Professor Lynette Tippett, who, with a stroke of genius, suggested that we talk with all the families and their neurologists to collect detailed clinical symptoms from each HD case. Remarkably, after ten years of detailed studies with the expert assistance of the whānau and the neurologists, we unexpectedly found new and exciting findings: variations in cell death in the basal ganglia and cortex correlated with the variable symptom profiles of patients with HD. That is, in HD cases with mainly motor symptoms, the cell death predominated in mainly motor regions of the basal ganglia and cortex, while in cases with mainly mood and behavioural changes, cell death was especially prominent in the mood regions of the basal ganglia and cortex. These major, and quite revolutionary, findings were published in a series of papers in leading neurological and neuroscience journals — *Brain*, *Annals of Neurology*, and *Journal of Huntington’s Disease*.²⁻⁷ Together, these landmark articles powerfully demonstrated the great benefit in multidisciplinary collaborative research between neuroscientists in the university, neurologists in the hospitals, and patients and whānau in the community.

In other exciting studies on the human HD brain, we showed for the very first time that the adult human brain still contained stem cells which had the potential to proliferate, multiply, and generate new brain cells (i.e., neurogenesis) in an attempt to replace the lost brain cells in HD. These findings were quite unexpected and controversial, because they showed for the very first time that the human brain could make new brain cells throughout life, and debunked the old adage that as we get older, we lose brain cells and do not have the capacity to make new ones. We supported these new findings by showing that the human brain had a pathway (or “motorway”) for neurogenesis comparable to the neurogenesis pathway in other, less complex mammalian brains (i.e. rat, cat, and monkey). These revolutionary findings were published in the leading international scientific journals, *Proceedings of the National Academy of Science USA* (PNAS) and *Science*, and dramatically, they were featured on the front cover of *Science*.⁸⁻⁹ All these wonderful new discoveries on the human brain were only possible through the generosity of families who donated the brain of their loved one to advance scientific research and understanding on the human brain. What an extraordinary legacy to our research and to the advancement of knowledge on the brain.

Furthermore, in the early 1990s, and into 2000 and beyond, when our HD collaborative brain research was becoming so very exciting, we extended our human brain studies to also include Parkinson’s disease, Alzheimer’s disease, epilepsy, Motor Neurone Disease, frontotemporal dementia, brain cancer, and other neurological diseases.

This was only possible through the generous post-mortem donation of brains from families who were touched by these diseases. Our collection of human brain tissue was becoming very extensive; we soon realised that we were establishing a world-leading human brain bank which, with the wonderful financial support from the Neurological Foundation of NZ, we called the “Neurological Foundation Human Brain Bank.” Today, our human brain bank contains tissue from over 1000 brains. We also send brain samples to other world-leading brain researchers in NZ and overseas, to undertake collaborative brain research which we are unable to undertake with our current resources and expertise in Auckland. When we asked the families if they were happy for us to send small samples of their loved one’s brain to other leading international researchers overseas, they were totally enthusiastic and were unequivocal in their consent. Families commented by saying: “It’s like Dad lives on forever, contributing to world class research to help our children,” and others said, “Mum is getting the travel in death that she never had in life.”

By the early 2000s, our collaborative research on human brain diseases expanded to include an increasing number of brain researchers across the university (i.e. geneticists, psychologists, biochemists, physiologists, pharmacologists) and clinicians in the hospitals (i.e. neurologists, neurosurgeons, neuroradiologists, psychiatrists, geriatricians), together with families and community organisations who were committed to improving our human brain donor programme. The power and strength of this collaborative “team” of brain research linking the triad of 1) neuroscientists across the university, 2) doctors in the hospital, and 3) the community, iwi, hapū, and whānau was becoming more and more evident. This was demonstrated through innovative and ground-breaking scientific discoveries, new treatments for brain diseases, and as a vehicle for keeping whānau and the community informed of novel breakthroughs in brain research and treatments. We decided that the time was ripe to formalise and create a very special umbrella organisation linking all these groups together — a sort of “All Blacks for Brain Research” — which we called the “Centre for Brain Research” or the “CBR”.

The CBR was launched in November 2009, and comprised around 25 research groups across the university, 25 clinicians in the hospitals, and around 13 community-based organisations. Today, 12 years later, it comprises over 80 brain research groups across the university (including about 450 people), over 40 clinicians in the hospitals, and over 30 community organisations. It is recognised internationally as a world-leading collaborative research team and centre, which over the last 12 years has attracted philanthropic funding of over \$60 million. This has been used to establish new research platforms; such as the CBR Hugh Green Biobank for culturing human brain cells to trial new drug treatments in the lab, and the Catwalk Spinal Cord Injury Unit to develop new treatments for spinal cord injury; and new professorships in translational neuroscience and brain research to accelerate our research on the human brain and the discovery of new treatments for brain diseases. The establishment of the CBR was also pivotal in gaining Centre of Research Excellence funding from the NZ Government in 2015–2021. This funding was used to establish an exciting national research partnership which was co-hosted with the University of Otago and has flourished over the last six years in promoting innovative collaborative research on the ageing brain between neuroscientists, clinicians and the community across the Universities of Auckland, Otago, Canterbury and the Auckland University of Technology.

Looking back over the years, I could never have predicted such a diverse, wonderful, and exciting journey in brain research, which culminated in the establishment of the CBR flagship. The human brain is the last frontier, and to this day, I still find it wonderfully challenging and exciting. There is so much more to come.

Conclusion

My life in medicine and brain research has taught me the great virtue and value of seeking a research experience early in your career, ideally during your time as a medical student. Research is the foundation of

advancement in medicine, and an experience in research will help make you a well-rounded physician for the challenges ahead, no matter what branch of medicine you ultimately pursue.

My 40 years' experience in research have taught me that collaboration is the vital foundation of success in research, healthcare, and indeed in life. There is a well know African proverb which says it all: "If you want to go somewhere fast, go alone. If you want to go far, go together." Working together as a team is critical for advancing knowledge and looking after people. All our major successes in research and the development of new treatments for people with brain disease have been the result of multidisciplinary collaborative team research — working together with scientists across the university, doctors in the hospital, and most importantly, with people, whānau, and families in the community. Listen to the people and never lose sight of the fact that we are all on this earth to help people — he tangata, he tangata, he tangata. The patient in your room is your focus — listen and respect what they tell you.

At a personal level — always be visionary, do what you love, dream big dreams, and never ever give up on your dreams. You may never get to the mountain top, but always aim for the top. If you aim any lower, you will achieve less.

Most importantly, enjoy life and never stop learning. Hold true to your values, be true to yourself, be honest, do your very best, strive for excellence, and show dignity and love to all. Above all else, serve the community and the people.

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*All authors have been recognised in the reference list of this Invited Editorial, based on the lead author's request.

About the author

> Sir Richard L.M. Faull, KNZM, FRSNZ, BMedSc, MBChB, PhD, DSc, (*Te Āti Awa, Ngāti Rāhiri*) is the Director of the Centre for Brain Research at The University of Auckland. He fell in love with the human brain as a third-year medical student. Subsequently, over the last 40 years, he has pursued exciting research in the United States of America (USA) (NASA Ames Research Centre, Massachusetts Institute of Technology) and The University of Auckland, unravelling the marvels and secrets of the human brain. He has established an international reputation for his research studies on human neurodegenerative diseases — Huntington's, Parkinson's, Alzheimer's, epilepsy, motor neurone dis-

eases, and others — which was made possible through the establishment of a human brain bank in partnership with families, the community, and the Neurological Foundation. He has published over 400 research publications on the brain, which have been cited over 34,000 times, and has an H-index of 99. He established the Centre for Brain Research at The University of Auckland in 2009 to facilitate world-class collaborative brain research between researchers across the university, neurologists and neurosurgeons in Auckland hospitals, and whānau/community organizations across New Zealand (NZ).

He is passionately committed to helping and giving hope, through research, to whānau and people who are touched by brain disorders.

Several awards have recognized his research achievements, including: Fellow of the Royal Society of New Zealand; the Rutherford Medal, New Zealand's highest scientific award; the Supreme Award in the World Class New Zealand Awards; Distinguished Professor at the University of Auckland; and a Knight Companion of the New Zealand Order of Merit (KNZM) for services to medical research.

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