

The protein pioneer

PROFESSOR ROBIN CARRELL DIDN'T START OUT WANTING TO BE A PATHOLOGIST, BUT SINCE TAKING THAT ROAD, HE HAS BECOME A LEADING EXPERT ON PROTEIN MALFORMATIONS LINKED TO A HOST OF DISEASES, WRITES MICHELLE GRIFFIN.

PHOTOGRAPHER: PAUL JONES

Professor Robin Carrell, emeritus professor of haematology at Cambridge University and one of the world's foremost experts on the stability of human proteins, describes his decision to become a pathologist as "one of those unexpected and spontaneous turning points in life".

Raised in Christchurch, New Zealand, Professor Carrell studied medicine at the University of Otago, and intended to become an orthopaedic surgeon. But shortly after he graduated from medicine

in 1959, he realised that he wanted to learn more about the origins of disease. So he returned to university to do an undergraduate degree in science.

"It was a feeling that I wanted to understand, at a fundamental level, the processes that caused disease," Professor Carrell says. "And much though I enjoyed orthopaedics and thought it was worthwhile, I really wanted to find out what the processes were that underlay disease. That involved studies at the molecular level."

When Professor Carrell went to Cambridge in 1965 to do his PhD, molecular medicine was just beginning to open up as a field of study.

"We were carrying out some of the first analyses to determine the abnormalities in haemoglobin that resulted in familial, or inherited, diseases," he says. "This involved quite simple apparatus but techniques that dissected the very long protein molecules into their individual parts in order to detect where the abnormalities lay."

“There is now a great deal of work going on throughout the world with respect to preventing the same sort of process occurring in Alzheimer's disease. Many people, and numbers of pharmaceutical companies, are working on this. And the field is confident that there will be eventual success.

One of the key abnormalities Professor Carrell detected in his pioneering research at Cambridge, as part of his PhD, was the changes that had minor effects on the way haemoglobin molecules folded and unfolded.

“The consequences were that the molecules became entangled, which led to breakdown of red blood cells, with consequent anaemia. It was later realised that the same process was occurring with different proteins in a number of diseases. For example, the entanglement of the protein in the blood that controls clotting, antithrombin, resulted in the sudden onset of severe thrombosis, whereas the same abnormality in a closely related protein in the liver resulted in the eventual development of cirrhosis.”

One of the first protein abnormalities Professor Carrell analysed was in a haemoglobin sample found in a patient in Sydney who had a genetic condition that triggered episodic haemolytic anaemia (periodically the patients blood cells break down). The sample, identified by Dr Eva Raik (a senior Australian haematologist and past President of the RCPA) and colleagues, was referred on to Cambridge, where the solving of its molecular abnormality gave key information about the ways proteins entangle. In 1967, Professor Carrell's findings were published in the journal *Nature* to wide acclaim. “It made quite a splash at the time,” he admits.

In 1968, he returned to New Zealand, where he took up a post in charge of clinical biochemistry at Christchurch Hospital, the largest tertiary hospital on the South Island.

Over the next decade, he followed up, with a group of colleagues, the findings of a biochemist in Sweden who had noted the absence of one of the proteins (alpha-1-antitrypsin) in the blood of patients who also had emphysema.

“We could see the same pattern of abnormalities in a number of proteins,” says Professor Carrell. “The most readily understood examples are those where there is a genetic defect, but the same sort of changes can often be induced by environmental stresses.”

Although he did not have access to all the technology available at the Cambridge laboratories, Professor Carrell says he felt few constraints on research carried out in New Zealand in the 1970s and 1980s.

“There was a certain freedom in working in New Zealand because you weren't subject to the competitive pressures that are so evident on the east coast of the United States or in Cambridge or London.”

But in 1986, the opportunity came to return to England in a senior position. “I got a telephone call at 2am in the morning some 20 years ago from Cambridge asking if I would come back to a post there, and eventually to a professorship of haematology.”

As the chair of haematology at Cambridge, and a fellow of the Royal Society, Professor Carrell has also been involved in several public health roles.

In 1999, he became a member of SEAC, the Spongiform Encephalopathy Advisory Committee, a body established to advise the British government about bovine spongiform encephalopathy (“mad cow disease”), Creutzfeldt Jakob disease (a fatal brain disorder in humans), and the worrying incidence of variant CJD, which has been linked to BSE.

Early last year, Professor Carrell made the news with his 10-year study into how the anti-clotting drug heparin worked. Heparin, used to stop clotting after major operations, is currently made from the byproducts of animals, and can only be injected for short periods to minimise the risk of haemorrhage.

Scientists led by Professor Carrell analysed the way heparin activated antithrombin, the natural anticoagulant protein in blood, and hoped the findings could lead to ways to administer more precise therapies using synthetic anticoagulants.

While technological advances have revolutionised molecular biology in the 40 years since Professor Carrell first went to Cambridge, increased levels of bureaucracy over the years have made research more frustrating, he says.

“Sadly, restrictions have been developed for the use of clinical material, and greatly diminish opportunities to look back at previous samples when a new observation is made,” he says. “Samples which no longer have any bearings on individual patients are being discarded because the bureaucracy involved in documenting stored samples is so great that it is difficult to justify the time required to set up tissue repositories, which in the past have been an extraordinary resource in medical research.”

Professor Carrell's work on unstable protein molecules has also shed light on the process occurring in a protein in the brain that results in the onset of dementia late in life.

“There is now a great deal of work going on throughout the world with respect to preventing the same sort of process occurring in Alzheimer's disease. Many people, and numbers of pharmaceutical companies, are working on this. And the field is confident that there will be eventual success.

“But the finding of effective treatments requires a bit of luck as well as science, so my guess is that will be 15 years away. However, I am confident the breadth of work will be sufficient, and that a preventive cure for Alzheimer's disease will be available for future generations”. 🔥