Brenner, the worm and the prize

Sir Raymond Hoffenberg

ABSTRACT – The recent award of a Nobel Prize to Sydney Brenner crowns an astonishingly distinguished scientific career. He must have come very close to winning it several times in the past. A colleague described him as 'a visionary who sees further into the future than anyone'. This is borne out by his decision – made 40 years ago – to study a one-millimetre long worm in detail to define the biochemical and genetic control of its development and differentiation. The impact of these studies has been so profound, with a significant bearing on human physiology and disease, that over 400 laboratories worldwide have now adopted the worm as a research tool. In this article, a brief outline is given of his work on the worm and of some of the highlights of his brilliant career.

KEY WORDS: Brenner, *caenorhabditis elegans*, development, differentiation, Nobel Prize

The award of a Nobel Prize last year to Sydney Brenner puts an end to the frequent comment that he was the brightest person never to have won it. On a couple of occasions he must have come very close; many feel he should have got it for establishing the existence of messenger RNA in 1961. There is a sense of relief that he has finally made it.

Since the award was announced many people, mistakenly suspecting that as a fellow South African I would know all about these things, have asked me why on earth anyone should receive the prize for working on an obscure small worm. To explain it, one has to go back 40 years. At that time, after critical analysis of where the new biology was heading, Brenner concluded that most of molecular biology had become 'inevitable' and the 'new mysterious and exciting' fields were development and the nervous system. In 1963, in a proposal to the Medical Research Council, he outlined his intention to study development, using *Caenorhabditis elegans* as a model system in which to follow cell division and differentiation from the fertilised egg to the adult form. His inspired choice of this nematode was a reflection of his detailed and profound knowledge of biology.

Choosing the worm

Why did Brenner choose this particular worm? His experiments on aberrant development in bacterial mutants encouraged him to expand the analysis of cellular development into a more complex organism. It had to be small enough to be manageable, but complex enough to provide information about both development and differentiation. *C elegans* seemed to fit the bill. The one-millimetre long adult worm was known to have about a thousand cells differentiated into epidermis, intestine, excretory system, nerve and muscle cells. It was the right size, and its differentiated systems were few in number but sufficient to be interesting. Above all, it was easy to propagate in the laboratory and study under the microscope.

It seemed feasible to identify each of its cells and trace their lineages back to the fertilised egg, and to define the genetic and biochemical control of their development and differentiation. The worm turned out to consist of a constant 1,090 cells, precisely 131 of which were specifically programmed to die (apoptosis), which resulted in an adult of 959 cells. The constancy of this process and the ability to induce mutants in the worm genome allowed analysis of the genetic control of cell death, as well as development and differentiation. An important derivative was the recognition of specific genes that controlled cell death, and of others that protected against it. Horvitz, who had worked with Brenner in Cambridge and shared the prize, showed that most of the genes have their counterparts in humans. The fact that these pathways are so well preserved evolutionarily underlines their importance for the study of human physiology and disease, including some forms of cancer and leukaemia.

About 300 of the cells are neurons, and the neural structures and muscle cells allow movement by flexing and relaxation. Study of their development and decay may be relevant to many neurodegenerative disorders. Almost all of the worms are self-fertilising hermaphrodites; about 0.1% are male. They produce sperm and ova and reproduce, so that meiosis can be studied as well as mitosis.

Today, more than 400 laboratories and thousands of researchers all over the world are exploring the biological secrets that *C elegans* has to offer. Brenner's vision that established it as a system for investigation has only just begun to pay dividends.

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Making the man

I first heard of Sydney Brenner shortly after I returned to the University of Cape Town to resume medical studies after the war. He was then a medical student at the University of Witwatersrand (Wits) in Johannesburg, and his formidable reputation had spread a thousand miles across country to the southern coast. He had completed an MSc by the age of 20, was lecturing in biochemistry and physiology while studying medicine, and was said to be the cleverest student anyone had ever seen. A year or two after I qualified he sat his final examinations, and to everyone's astonishment he failed. (I shamefacedly admit to a moment of schadenfreude.) Frank Forman, Professor of Medicine in Cape Town, for whom I was working at the time, was his external examiner and told me he had no choice – Brenner was quite hopeless at clinical examination. Years later I asked Sydney about this and he confessed he had not wanted to do medicine but had been persuaded on the (seriously mistaken) grounds that he would have no chance of success in biological science unless he held a medical degree. Very reluctantly, he proceeded with the course, spending as much time as he could in the laboratory and totally neglecting the wards. He admitted he had no idea how to conduct a physical examination, adding rather mischievously that he had managed to pass surgery and obstetrics and gynaecology on book knowledge without having seen patients in either. It was medicine that tripped him up. Needless to say, he rapidly corrected this deficiency, passed the examination – and never saw another patient!

Wits was an exciting place in the 1940s. The Medical School in Cape Town concentrated on clinical research and had very little interest in basic science. Wits was quite different. It offered a medical science degree which students could take midstream. Raymond Dart, an internationally acclaimed anthropologist, was head of the anatomy department; under his influence Sydney took part in student research expeditions with Phillip Tobias, who was to become Dart's renowned successor. Joseph Gillman was an eccentric but inspiring scientist, who introduced Sydney to the excitement and rigour of scientific experiment. On Brenner's 75th birthday Tobias wrote about the extraordinary promise he showed in his student days: 'Although not yet out of his teens ... he could argue knowledgeably and persuasively about chromosomes and genes, DNA, and Caspersson's ultraviolet absorption spectromicro-photometry, Bernal and his X-ray diffraction, heterochromatin, Soviet genetics and where Lysenko got it wrong'. He also found time to serve as President of the Students' Representative Council at Wits and became a leading light in the National Union of South African Students (Nusas), both organisations fiercely opposed to the incipient apartheid policy being introduced by the newly elected National Party. The power of his intellect, his grasp of such a wide range of subjects and his formidable memory clearly marked him out for greatness.

A fellowship to Oxford to complete a D Phil convinced him that he had to get out of South Africa into the larger world of science. He had met and impressed Francis Crick who managed to recruit him to what was then the Cavendish Laboratory in Cambridge, and they shared an office for about 20 years. The atmosphere in this office and in the coffee room must have been electric. Crick and Brenner were both talkers, so ideas gushed out and were discussed seriously however speculative they might have seemed. Nothing was too absurd; people were encouraged to come up with wacky ideas but, of course, most had enough science behind them to ensure that they were not too wacky.

During this time Brenner made a number of highly important observations. In a devastating paper, he demolished the overlapping coding system proposed by George Gamow; he coined the term 'codon' for the coding triplet; he identified two of the three nonsense triplets; he suggested the existence of transfer RNAs, and went on to produce a seminal paper identifying and naming messenger RNA. His overarching mastery of so many fields and the contributions he made led to descriptions of him as 'a giant of twentieth century biology' and 'a visionary who sees further into the future than anyone'.

No comment on Sydney would be complete without reference to his somewhat zany sense of humour. I particularly like the comment he made when he received his second Albert Lasker Award. The first in 1971, he said, was 'for science'; the second in 2000 was 'for surviving'. And when the commercial possibilities of the genome spawned a generation of biotech companies, he recited the mantra 'DNA makes RNA makes protein makes money'.

He and I served on the Medical Research Council together. One morning Lord Shepherd, our Chairman, was late and Sydney started intoning 'The Shepherd is our Lord, we shall not want'. As one might have anticipated, Shepherd walked in as we were in mid-song. It took some time before he could lead us back to the quiet waters of Council business.

The last fifty years has probably been the golden age of biology and few have played as important a part in it as Sydney Brenner. We, at the College, take pride in our latest Nobel winner and wish him continued success.