

# A Toast to Twinned Toes

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Highly complex processes are prone to occasional errors, and human development is no exception, as I should know. I have a condition known as syndactyly—while others have ten toes, I have only nine. Two of my toes are not separate, but joined by a webbing of flesh. Since I was young, I have always wondered—what went wrong? What caused my conjoined toes?

When I grew older, I read the textbooks, and the answer was revealed to me. The key was apoptosis. The developing mouse paw starts off as a rounded blob. Then cells in between would-be digits die off—and only then are the digits revealed, carved out of that unformed lump by the chisel of programmed cell death. Since what's true for mice is also true for the hairless apes that share some



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70% of their genes, my syndactyly was the result of cells in between my toes that refused to die as planned. I was intrigued by this piece of knowledge—but who worked it out? And how did they do it?

Research, of course, is not a masterpiece painted by one artist—but a jigsaw painstakingly pieced together by many, over decades. But the pioneering work done by Dr Sydney Brenner at the MRC Laboratory of Molecular Biology in Cambridge [1], along with that of John Sulston and Robert Horvitz, laid the framework for much of what we know about apoptosis today [2], and in the process, earned the three scientists the 2002 Nobel Prize for Physiology or Medicine [5]. Amazingly, much of this work was not done on mouse paws or human cells—but on a humble, transparent worm called *Caenorhabditis elegans*. Painstakingly counting the cells of *C. elegans*, they concluded that out of the 1090 cells generated during the worm's development, only 959 remained in the adult, while the rest underwent apoptosis.

## References:

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Thus, in terms of development, men, mice and worms all share the use of cellular suicide [3]. These important findings ultimately led to the explanation for my conjoined toes.

Of course, today's understanding of apoptosis has gone far beyond conjoined toes. Less trivially, understanding

“ **Men, mice and worms all share the use of cellular suicide** ”

how cells program their own suicide sheds light on many facets of human disease, especially the causes of cancer. Sometimes cells refuse to obediently swallow their cyanide pills—an insurrection which leads to cancer. A tumour is a mass of rebellious cells that refuses to die, even after orders to do so. After decades of research, scientists today have a better understanding of the signals that trigger apoptosis, and how they can go wrong.

There I would have left things, but my affinity with apoptosis was not at an end. With my interest in cell biology kindled, I took on a high school project under a mentor who studied a few proteins involved in cell death [4]. In a chain of coincidences, my mentor's laboratories were located in the Brenner Centre for Molecular Medicine; and eventually, my project won a prize in Singapore's National Science Talent Search—a prize which was presented by none other than Dr Brenner himself. Dr Brenner, still active at the age of 81, was a key advisor in the development of Singapore's budding biomedical industry, and was awarded Singapore's National Science and Technology Medal in 2006 [6]. I would never have imagined that work done decades ago in a distant country would intertwine with my life in such an intricate way, and would become the catalyst that pushed me into medicine and science.

Apoptosis is a fundamental process. We now know that it applies to all multi-cellular organisms, from plants to animals and from mice to men. But for me, apoptosis is also a personal story, one that demonstrates not just how a simple piece of work can lift the veil on a whole new field of science, but also how science can cross space and time to impact other people's lives. ■

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