

OBITUARY



The power of an idea: Andrew Wyllie

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Andrew H. Wyllie 1944–2022

We have lost a giant. When one mentions apoptosis, one thinks of Andrew Wyllie. And when one thinks of cell death, one thinks of apoptosis. The concept of cell death, and the concept that it was an important biological phenomenon, has a long history, but the image and biology of apoptosis now dominate all previous concepts. Whether one considers death to be programmed, to be an alternate form of death—necroptosis, ferroptosis, and several other variants, apoptosis is the standard by which they are evaluated.

Cell death had been known since the 19th C, attracting the attention of such stellar scientists as August Weissmann, Elie Metchnikoff, Alfred Glüxsmann, and Viktor Hamburger. Rita Levi-Montalcini became interested in dying neurons during the Second World War. Embryologists such as John Saunders saw a “death clock”; and, based on terms from the burgeoning field of computer science, the term “programmed” attracted attention after 1964 [1, 2]. The pathologist John Kerr had since 1965 [3] been calling attention to what he described as “shrinkage necrosis”, referring to the collapse of a dying cell, very unlike the osmotic lysis that would be predicted from a cell’s having lost control of its ion pumps, taking in water, and bursting [4, 5]. These ideas were not ignored, but they hovered quietly, primarily in the thinking of developmental biologists and others aware that cell death was often predictable. Then John Kerr went to the University of Aberdeen on sabbatical leave, where he worked with Alastair Currie and the then junior Andrew Wyllie [6]. The three of them discussed these shrunken cells and, comparing notes and new data, realized how common this type of death could be, frequently appearing in tumors, mild intoxications, and elsewhere. This type of death had been ignored. As Tidball and Albrecht later observed, an entire organ could disappear in 20 days with only 3 or 4 dying cells being visible in any given tissue section. Kerr, Wyllie, and Currie realized that the common sense of turnover as “cells die and then are relaced by cells undergoing mitosis” could be better expressed by emphasizing “cells die”, recognizing that the death itself was a process that could be studied [7]. They called attention to this issue by choosing a name that resembled

“mitosis” and argued this point in a 1972 review [6] emphasizing the commonality of cell death, the flat declaration based in the title of the now-famous publication in the British Journal of Medicine, “Apoptosis: A Basic Biological Phenomenon with Wide- Ranging Implications in Tissue Kinetics”, followed in 1980 by a likewise influential review in *International Reviews of Cytology* entitled, “Cell death. The significance of Apoptosis”, this time by Wyllie, Kerr, and Currie [7]. Even more than their bold and somewhat aggressive statement, it was the choice of a word that stayed in everyone’s mind and ultimately became a shibboleth that defined the field. To quote Kerr, Wyllie, and Currie, ‘We are most grateful to Professor James Cormack of the Department of Greek, University of Aberdeen, for suggesting this term. The word “apoptosis” (αποπτωσις) is used in Greek to describe the “dropping off” or “falling off” of petals from flowers, or leaves from trees. To show the derivation clearly, we propose that the stress should be on the penultimate syllable, the second half of the word being pronounced like “ptosis” (with the “p” silent), which comes from the same root “to fall” and is already used to describe drooping of the upper eyelid’.

Thus, the suggested pronunciation, apo-TO-sis. (Many researchers, particularly in North America, comfortable with neither classic Greek or glottal stops, prefer “a-POP-tosis”). As is often the case, it is the word that catches the imagination and makes the idea memorable. And memorable it became: Well over 700,000 publications, with Andrew Wyllie being cited 42,000 times, including 2800 citations of the 1972 review. This salesmanship characterized Andrew. While continuing to lead the field, for instance being among the first to associate the now-famous DNA ladder with apoptosis, he also acted as the spokesman for the field, presenting the argument and pushing for its acceptance at cancer and hematology meetings and in many other venues.

It was obvious that the idea was important: Andrew wrote the lead chapter in the first modern book on cell death in 1981; he spoke at the first specific meeting on cell death, in 1989; and he was co-chair of the first Gordon Conference on Cell Death, in 1995. However, the field did not really take off until the late 1980’s— by which time the association of bcl-2, Fas/Apo, and p53 with cell death mechanisms in cancers and in the immune system in general combined with the identification of a genetic sequence for embryonic cell death in a worm—particularly once an effector of cell death was identified as a homolog of mammalian genes that were quickly related to apoptosis—attracted the attention of the medical world [8–10]. A major contributor to that attention was the cheap and easily-performed assay for double-stranded breaks in DNA, again highlighted by Wyllie in 1980, which allowed laboratories everywhere to validate the 1972 hypothesis that controlled and patterned cell death, whether in pathology or non-pathological physiology, was a quite common and important process [11, 12].

The first formal international meeting on cell death, convened by Amedeo and Giovanna Columbano in Sardinia in 1989, brought together Kerr, Wyllie, Lockshin, Zakeri, and several others. At that very interesting meeting—it was in honor of the great pathologist,

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Emmanuel Farber, who did not believe in apoptosis— we, among other early recruits to the field, chatted easily, comparing and sharing notes and observations, feeling very much like intimate colleagues rather than rivals. We have kept that sense of comradery ever since. We maintained relaxed contact for many years after that.

Since those days, apoptosis research has expanded into distinct molecular paths, currently under very intense investigation [13–16].

Professor Wyllie was a Fellow of the Royal Society of Edinburgh, the Royal Society, and the Royal College of Pathologists as well as the Academy of Medical Sciences. Professor Wyllie was one of the Founder Member of the British Academy of Medical Science. During his life, he was awarded numerous recognitions including, as an example, the Hans Bloemendal Award, the Bertner Award, the Scheel Award, the Canada Gairdner Foundation International Award. At the personal level, Andrew was a pure gentleman. Andrew trained a number of students, attracting them to the beauty of science. He cared very much, on a personal level, for his staff and his students. He passed away in Cambridge at his home; Hilary, his wife, as well as his three children and a grandchild were at his side.

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