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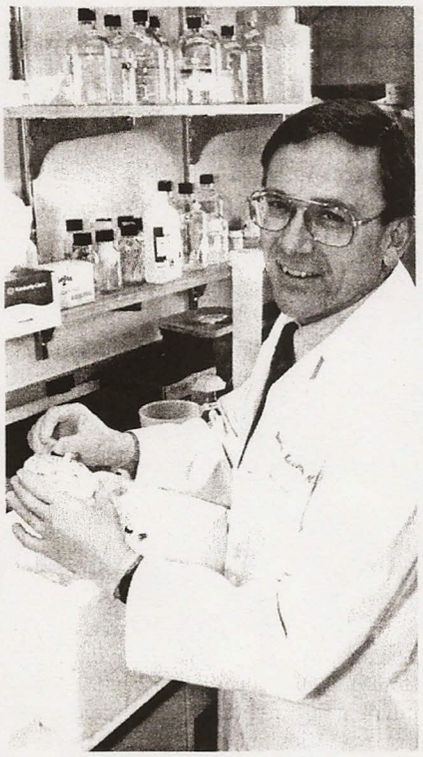
Stanley J. Korsmeyer (1950–2005)

When Stan Korsmeyer was in the eighth grade and looking forward to playing high-school sports, he was told by the school coach that he would have to grow six inches before he would be allowed on any of the teams. Being determined but nonetheless pragmatic, Korsmeyer decided to focus his energies in an alternative direction — raising hogs. Raise hogs he did, and at age 14 Korsmeyer became the youngest person in the history of the Illinois State Fair to show the Grand Champion pair of Hampshire hogs. Two old-time Illinois farmers were heard discussing the competition. One asked, "Who showed the Grand Champions this year?" The other replied, "Just some kid." It was not "just some kid". It was Stan Korsmeyer, who even then dedicated himself to and excelled at whatever he did.

Korsmeyer was born on 8 June 1950, on a farm among the cornfields of southern Illinois, and he planned to be a veterinarian. However, as an undergraduate at the University of Illinois Urbana, he became interested in curing people instead of livestock. In 1976 he earned an MD at the University of Illinois in Chicago. A move to the University of California, San Francisco, allowed him to continue his medical training and to meet his wife-to-be Susan, an oncology nurse. This move also introduced Korsmeyer to sailing and fishing, two passions that continued throughout his life.

Korsmeyer's next move was to the opposite coast (in part to continue his proximity to an ocean), to the National Cancer Institute in Bethesda, Maryland, where, as a fellow in molecular oncology, he trained with leading cancer researchers Thomas Waldmann and Philip Leder. Korsmeyer continued his career as an independent researcher at the NCI, and then as an investigator of the Howard Hughes Medical Institute, first at Washington University in St Louis and later at the Dana-Farber Cancer Institute and Harvard Medical School in Boston.

Korsmeyer opened new doors to the understanding and treatment of cancer. He co-discovered the oncogene *Bcl-2*, which when overexpressed can lead to follicular lymphoma. His studies provided evidence that *Bcl-2* was the first member of a new category of cancer-causing genes — genes that work not by driving cells to proliferate, but rather by preventing them from dying via a process known as programmed cell death, or apoptosis. By causing cells that normally die to survive instead, elevated expression of *Bcl-2* can allow those cells to accumulate additional mutations and become cancerous.



DANA-FARBER CANCER INST.

Trailblazer in the understanding and treatment of cancer

Korsmeyer also discovered other members of the *Bcl-2* gene family and found that they too regulate cell death. Whereas members such as *Bcl-2* protect cells from dying, others, including *Bax*, *Bad* and *Bid*, cause cells to die. Korsmeyer proposed a rheostat model for the regulation of cell death, in which the crucial 'life versus death' decision made by each cell is determined by the balance between the activities of antagonistic survival and killer genes. He also discovered that *Bcl-2* family members are associated with mitochondria, the power plants of cells, and thus implicated mitochondria in the process of apoptosis.

Korsmeyer's studies helped to establish that many human disorders — including lymphomas and other cancers — can be caused by a misregulation of apoptosis. In short, he made crucial contributions to the elucidation of the molecular-genetic pathway that controls cell survival and cell death and to the discovery that the misregulation of cell death has a major role in human disease.

That a deficit in apoptosis can cause tumours implied that cancers might be treated by reactivating apoptosis and causing tumour cells to self-destruct. Korsmeyer's research elegantly demonstrated that cancer cells can be induced to die either by blocking anti-cell-death genes such as *Bcl-2*, or by activating pro-cell-death genes such as *Bax*. As a consequence, the *Bcl-2* family has become a promising target for anticancer drugs. Korsmeyer himself worked directly to develop new treatments for cancer based on his knowledge of apoptosis. Although we met frequently at scientific meetings, it was in the context of our serving as consultants to a start-up biotechnology company focused on apoptosis that I got to know Korsmeyer best. His science and advice helped to make *Bcl-2* a major target, and as a consequence a drug that blocks *Bcl-2* action is currently under development at a major pharmaceutical company.

Korsmeyer's drive to develop an anticancer drug and to cure cancer patients was tempered by his concern about the risks of clinical trials. "I would never want to be involved in the trial of a drug that I wouldn't be willing to test on my own sons," he once told me. Those sons, Evan and Jason, as well as his wife Susan, were at the centre of his life, and his statement about drug trials reflected Korsmeyer's deep empathy for others.

Korsmeyer had a farm boy's work ethic, dedication, energy and modesty. He also had an unshakeable determination, as well as a great sense of humour, a joyous and immediately recognizable laugh, enormous personal warmth, an optimism about people, and an infectious and constantly upbeat approach to life. I never knew anyone who did not like him. He cared enormously about the young scientists who trained with him; he was a superb mentor and seeded the biomedical world with his scientific offspring. He received many well-deserved prizes and honours for his discoveries.

Stan Korsmeyer, a non-smoker, died on 31 March of lung cancer. His death is a tragic loss to science, medicine and humanity. He may never have grown the six inches demanded by his high-school coach, but he was nonetheless a giant — as a scientist, a mentor, a friend and a human being.

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