IN MEMORIAM

Mark A. Smith, PhD: Renegade Scientist and Visionary

In the recorded history of science, the prominent are often said to have died quietly, long after their important work had been completed, the specific date and circumstances of their death obscured by achievements during life, and the slow decay of time. The same cannot be said for Mark A. Smith, PhD, who died at the young age of 45 on December 19, 2010, 95 years to the day, as it would happen, after the death of Alois Alzheimer, the namesake for the condition that Mark would ultimately redefine.

Mark differed from many of the other great scientists in history, however, in that his prominence was not an accident of pedigree or privilege, but rather the product of the virtues he bore witness to and developed as a working-class Brit. The proud son of a coal miner and homemaker, Mark learned to embrace hard work, self-sacrifice, and determination. Long walks to school throughout his youth—3 miles each way rain or shine—were a reality for him, in an era when such things were an anachronism on the other side of the Atlantic. It was perhaps not without reason that Mark developed an affinity for expensive English shoes later in life. Nor did it surprise anyone close to him that he would be walking a short distance toward home in his final minutes on December 19. Yet he faced his challenges from the beginning with an energy, charisma, and love of life that would never be blunted by station or hardship, and even as he gained in international prominence, Mark would never lose a sense of humility.

Mark graduated from Bushloe High School in Wigston Magna, Leicester, where he was a football (soccer) standout, and would later become the first in his family to attend college after receiving a scholarship to Durham University. His athletic prowess continued on the football field at Durham where he earned the nickname “Animal”, owing to his aggressive and tireless style of play. He graduated with honors in 1986 with a bachelor of science degree in biochemistry and molecular biology and then matriculated at Nottingham University, obtaining a PhD in biochemistry in 1990 under Michael Landon.

After a brief immersion in a big pharmaceutical company as a postdoctoral biochemist under Carolyn A. Foster at Sandoz Forschungsinstitut (now Novartis) in Vienna, Austria, Mark sought and obtained a position as research associate in 1992, under the guidance and mentorship of Dr George Perry, at Case Western Reserve University (Ohio), beginning in earnest his trajectory in neuroscience.

Mark’s meteoric rise in the mid 1990s was marked by his innovative ideas, exceptional enthusiasm, and communication skills, as well as an unlimited giving to collaborators and coworkers, which worked in concert to revolutionize the field and earned him the loyalty and respect of innumerable colleagues. While he is best known for questioning the amyloid β cascade hypothesis, fundamentally he had a distrust of any mechanism that did not rely on evolutionary adaptation for successful aging. Oxidative stress figured prominently in his early studies, with the discovery and characterization of the first oxidative modification of Alzheimer disease’s pathology, and the first in situ demonstration of oxidative response induction. These studies cleared the way for direct application to human brain and away from poorly defined changes that were only tangentially related to oxidative modification.

He also understood that oxidative stress was not an end but an opening into the beginning of Alzheimer disease. As such, Mark was also the first to crystallize the role of cell cycle activation as a basic mechanism of cellular pathophysiology within the brain and the 2-hit hypothesis involving oxidative injury and cell cycle reentry as an upstream occurrence. Pioneering investigations into gonadotropins and a relatively recent interest in mitochondria were among other areas of his active contribution.

Mark’s efforts were aimed, in essence, at understanding Alzheimer disease biology and the pleiotropic threshold between pathology and physiology as a means to reverse the disease, while all other theories were tied to long-known structural lesions. It was not long after Mark arrived at Case when he proposed that amyloid β, tau, and numerous other...
changes were critical homeostatic responses to Alzheimer disease rather than the cause. Heretical and even ridiculed at the time, the concept of amyloid β as a downstream productive response to a more basic biology has since been borne out in immunotherapeutic clinical trials, which Mark predicted over a decade ago were ill fated.

In short, Mark was a visionary. Yet completely apart from this quality was an overcommitment to those around him that was nothing short of legendary. Mark simply could not say “no.” The shear numbers are staggering. In a period that was all too short, Mark directly mentored or trained some 44 undergraduate students, 32 graduate students, and 13 high school students. He hosted 24 medical or graduate student lab rotations, directed 8 postdoctoral fellows, hosted 12 sabbaticals, and was the mentor for 4 faculty members. He sat on 17 National Institutes of Health study sections and 48 other national and international granting agencies. He delivered close to 300 invited lectures and served as keynote speaker for 4 major international meetings. Mark served as editor in chief of the Journal of Alzheimer’s Disease, was the review editor of the Journal of Neurochemistry, and sat on the editorial board of more than 200 scientific journals, including Science Translational Medicine, the American Journal of Pathology, and the Journal of Neuropathology and Experimental Neurology.

Generosity and commitment to the development of students in particular were remarkable and among Mark’s defining qualities. At any given time of year, his laboratory would be bustling with 3, 4, sometimes 5 students, each working separately and relatively autonomously on important projects. Even a casual visit to the Smith laboratory would reveal an unmistakable aura of enthusiasm that simply does not exist in other laboratories, as Mark was able to create in his student trainees a laboratory environment that was an extension of his personality—passion, determination, love of life, freedom of thought, and all with a sense of humor and a sense of humility. Mark, for his part, valued his students’ insights and fresh perspectives. He saw in students what few others genuinely see—limitless potential and an ability to contribute, regardless of educational level. In recognition of his exceptional devotion to students, Mark was honored with the J. Brooks Jackson Undergraduate Award for Excellence in Mentoring in 2009, a singular award given annually across all schools at Case. One student comment uncovered during the selection process summed it up best: “I have never met a professor who is more personally invested in the success and best interest of his students.”

Mark also had an unparalleled gift of collaboration, accumulating literally dozens of collaborators across the United States and beyond, ultimately spanning all but 2 continents, which in turn allowed him to publish at a rate that would seem obscene to the uninformed, with more than 800 peer-reviewed articles, reviews, and chapters at the time of his death. Yet, Mark himself viewed simple numbers of publications as a superficial measure of contribution and instead valued citations, or recognition of one’s work by others, as the better measure of scholarship. In this respect, Mark had an H factor of 73 with more than 21,000 citations at just the age of only 45. In the last year alone, his work was cited more than 3,000 times. In this year, ISI named him the top Alzheimer disease researcher of the last 10 years and the fifth most cited Alzheimer disease researcher in history. At Case Western Reserve University, Mark was the most prolific and most cited faculty member on campus, where his work alone accounted for more than 1% of the publications and 4% of the citations, in a recent survey. Remarkably, Mark achieved full professor with tenure at the age of just 36, among the youngest in the history of Case to achieve this distinction.

His many honors included the Jordi Folch-Pi Award from the American Society for Neurochemistry, the ASIP Outstanding Investigator Award from the American Society for Investigative Pathology, and the Denham Harman Research Award. He was elected as Fellow of the Royal College of Pathologists, Fellow of the American Aging Association, and Fellow of the American Association for the Advancement of Science (the world’s largest scientific organization). He had recently been awarded the Goudie Lecture and Medal of the Pathological Society, but died before he could deliver the lecture.

Mark’s promise for continued progress in science and perhaps the development of a cure for a devastating illness will be sorely missed by humankind, and yet, the magnitude of the loss of Mark Smith, the human being, irrespective of his place in science, is still greater. Among his qualities that are impossible to sum, Mark had a sidesplitting wit, a magnetic personality, and a disarming ear-to-ear grin. He greeted everyone as though it was his privilege to see them, always with a smile, always with an earnest enthusiasm, and always with a laudatory phrase that set a tone of friendliness and levity. One can scarcely recall even a single conversation with Mark that was not accompanied by laughter. His energy and love of life were palpable and extended well beyond the workplace. In a very real sense, the world was his laboratory, and every fellow human being, his collaborator.

Mark leaves behind the love of his life in Gemma Casadesus, an accomplished behavioral neurobiologist in her own right, whose strength and courage in the aftermath of Mark’s loss was, and is, an inspiration to everyone. Mark’s son William, 7 years old, shares Mark’s enthusiasm for life, the thoughtful, deliberate qualities of his mother, and the intelligence of both. His son Luke, who turned 6 years on Christmas day, ever at his father’s side while he tinkered in the yard or in the garage, is so like Mark in appearance and mannerism; there can be little doubt that Mark is alive and well. Mark’s father John (Jack), now in his 70s and retired to Spain, would occupy his “down time” during visits with Mark and Gemma by rebuilding entire sections of their house. In a moment’s interaction with Jack, with his straightforward manner and baritone voice, Mark’s heritage becomes immediately clear. Mark is also survived by his older sister Tina (Wakeling) of the United Kingdom. His mother, Rita, who always maintained that Mark “is a good lad,” died in 2004.

It is perhaps of some comfort to those closest to Mark that he would occasionally comment on the circle of life and the likelihood of his reaching old age. Whether he sensed something in time and space that inspired him to live every
day as though it were his last or whether losing his life 95 years to the day after Alois Alzheimer died is evidence of some larger plan will remain an unanswered question. The certainties we are left with are Mark’s footprints in the annals of science, which will only grow over time; the fact that Mark’s contributions to science, while timeless and virtually without parallel, still pale in comparison to Mark Smith the man; and the fact that no language of mortals could provide proper summation or describe the depth and span of void and disbelief, at the passing of such an embodiment of life into the Hereafter.

Yet we are energized still by Mark himself, by images of an enthusiasm for life so vivid and clear that it is simply not possible to think of him in the past tense alone. A thought of the past brings a smile to the present and a purpose for the future. Such will be his legacy above all others, for many years to come.

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