

# CURRENT SCIENCE

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EDITORIAL

## Cancer: Human Mortality and Cellular Immortality

Cancer is a word used as a metaphor for unchecked malignancies in human societies. Corruption, indiscipline, lawlessness and intolerance spread uncontrollably, like cancers, if left unchecked. But, their advance can be halted by purposeful action, supported by public consensus. Is the disease itself, stoppable? Is the war on cancer, declared almost exactly 40 years ago, going well? In marking the anniversary of the National Cancer Act, signed into US law in 1971, a recent retrospective notes that annual spending by the National Cancer Institute (NCI) has grown from \$233 million to over \$5 billion, in four decades. Thus far, \$90 billion is the estimated amount spent on battling cancer. The 'war', a costly metaphor, has not gone the way researchers and policymakers anticipated in the 1970s. A 1986 critique, appearing 15 years after the battle had begun, noted that 'cancer incidence and mortality had not changed much' (Marshall, E., *Science*, 2011, **331**, 1540). The 25 March issue of *Science* presents a retrospective on the experiences of the 'cancer crusade'. The major forms of the disease, which attack the lung, colon, rectum, breast, prostate, blood (leukemia), pancreas and liver, are still formidable killers, despite the range of weapons thrown at them. Oral cancer, a major public health problem in India as a result of unrestrained tobacco usage, appears less of a concern in the United States. In 2003 the then NCI director optimistically pronounced that victory over cancer was imminent and that the war would be over by 2015. The end does not really seem to be in sight. Churchill's famous exhortation, after one of the early successes of the Allies at El Alamein in the Second World War, may be apt: 'This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.' Churchillian rhetoric may in fact be needed to garner public support for a campaign that is likely to become ever more costly.

Cancer is truly 'the emperor of all maladies', a phrase borrowed from a nineteenth century description by Siddhartha Mukherjee for the title of his compelling, Pulitzer Prize winning 'biography' of the disease. Mukherjee, an oncologist and a writer of rare talent, traces the long history of the disease, presumably as old as human history; a disease that has resisted and, at times, repulsed the enormously powerful attack of twentieth century

science. In Mukherjee's words, his extraordinary account is really 'a military history – one in which the adversary is formless, timeless and pervasive. Here, too, there are victories and losses, campaigns upon campaigns, heroes and hubris, survival and resilience – and inevitably, the wounded, the condemned, the forgotten, the dead'. In fashioning a biography of a subject whose origins are shrouded in a distant past and whose end is not even visible on a distant horizon, Mukherjee weaves a story that must be read by every scientist who believes that modern biomedical research, so firmly founded on advances in molecular biology and genetics, will soon conquer cancer. It must also be read by those who believe technology will trump nature. It must be read by all those who are captivated by good writing, for Mukherjee displays an eloquence in writing about science that is elevating. The broad and scholarly historical approach to cancer allows Mukherjee to emphasise that our understanding of the disease has continually transformed over the centuries and even 'morphed, often radically, from decade to decade' in the turbulent advance of twentieth century science. Cancer is a term used to describe a heterogeneous group of conditions 'caused by the uncontrolled growth of a single cell'. This growth, in lung or liver, in blood or brain, or indeed in any organ of the human body 'is unleashed by mutations – changes in DNA that specifically affect genes that incite unlimited cell growth. In a normal cell, powerful genetic circuits regulate cell division and cell death. In a cancer cell, these circuits have been broken, unleashing a cell that cannot stop growing' (*The Emperor of All Maladies*, Siddhartha Mukherjee, Harper-Collins, London, 2011). What is it that frustrates most efforts to retard this uncontrolled growth? Mukherjee answers: 'Cell division allows us as organisms to grow, to adapt, to recover, to repair – to live. And distorted and unleashed, it allows cancer cells to grow, to flourish, to adapt, to recover, and to repair – to live at the cost of our living. Cancer cells grow faster, adapt better. They are more perfect versions of ourselves.' The difficulty in distinguishing between normal and malignant cells has limited the efficacy of every therapy advanced for cancer. The 'adaptability' of cancer cells lies at the heart of the problem of drug resistance. Mukherjee is eloquent when he views his subject: 'Cancer is built into our

genomes: the genes that unmoor normal cell division are not foreign to our bodies, but rather mutated, distorted versions of the very genes that perform vital cellular functions. And cancer is imprinted in our society: as we extend our life span as a species, we inevitably unleash malignant cell growth ... If we seek immortality, then so, too, in a rather perverse sense, does the cancer cell.' Will science enable a future generation to win the war on cancer? Mukherjee recalls a memorable quote from J. B. S. Haldane: 'The universe is not only queerer than we suppose, but queerer than we can suppose' and adds, 'so is the trajectory of science'.

The origins of surgical excision of tumors go back across the millennia. Mukherjee narrates the tale of Atossa, the queen of Persia in about 500 BC, detecting 'a bleeding lump in her breast'. Her tumor was excised by a Greek slave, providing a reprieve, leading her to persuade the king, Darius, to invade Greece so that her benefactor could return home. Mukherjee wryly notes: 'It was Atossa's tumor, then, that quietly launched a thousand ships.' Surgical intervention made facile by technical advances in surgery is often used to remove accessible tumors. Surgery fails when cancer cells migrate, metastasize, and lodge themselves in other locations in the body, to grow again unchecked. Radiation and chemotherapy are the only other weapons available in the war on cancer. While early detection heightens the chance of limiting the spread of the disease, cancer often strikes silently, announcing its presence only when it is too late. Mukherjee traces the origins of chemotherapy for childhood leukemia to Sidney Farber's transition from being a pediatric pathologist, 'more preoccupied with the dead than the living', to a clinical researcher searching for a new therapeutic strategy. When he began, acute leukemia cases were 'discussed on medical rounds with professional grandiosity and then ... diagnosed, transfused – and sent home to die'. Farber chose his enemy well. Leukemia, characterized by the wild proliferation of white blood cells could be quantitatively measured, counted. The effects of any drug could then be readily assessed. The road to experiment was open. It is at this point that Mukherjee draws attention to an Indian connection. Millworkers in Bombay, struggling in poverty, malnourished and over-worked, suffered from an anemia that could not be reversed by vitamin B-12. Mukherjee describes the discovery of Wills factor, folic acid or folate. Farber turned to folate, a dangerous act of empiricism, in treating leukemia. The disease accelerated in patients administered folic acid – a clinical trial gone awry in the days before regulation. But a new question arose – would antifolates halt the growth of white blood cells? The folate 'antagonists' were indeed available with Yellapragada Subbarao working at the Lederle Labs. The first trial with pteroylaspartic acid began in September 1947, when Farber treated a two-year-old patient, whose immature white blood cells 'were dividing in a frenzy'.

The drug had little effect. A few weeks later a new sample, aminopterin, arrived from Subbarao. The patient, by now, was near death. The response was dramatic. Chemotherapy for leukemia had been launched at a time when no ethical guidelines were in effect for controlling clinical trials. Coincidentally, 'the Nuremberg code for human experimentation, requiring explicit voluntary consent from patients was drafted on 9 August 1947'.

Mukherjee's description of a cancer cell as a 'cell seeking immortality' reminded me of HeLa cells, derived from the biopsy tissue of a patient with a particularly devastating form of cervical cancer. HeLa cells are central to a great deal of biomedical research; a human 'cell line' that can be maintained and multiplied in laboratory culture across the world. The biopsy tissue was obtained from a woman, Henrietta Lacks, almost exactly half a century ago, in early 1951. They first grew in culture in a Johns Hopkins laboratory. Later, they grew and grew, immortal in laboratories across continents. In *The Immortal Life of Henrietta Lacks*, Rebecca Skloot (Crown Publishers, New York, 2010) chronicles the story of a black woman, her family and her cells which have remained alive, dividing and well, in research laboratories, contributing to the advance of modern medical science. Skloot, is a writer immersed in her subject, who weaves a tale of haunting sadness, where a family struggles to comprehend the meaning of cellular immortality, even as they accept, stoically, the stark reality of human mortality. Skloot's portrayal of Henrietta Lacks' daughter, Deborah, is warm and moving, describing her determination, in the midst of great adversity, to understand the biological mystery of her mother's cells. Throughout the book runs the theme of medical ethics, not a critical public issue in the early 1950s, when Henrietta Lacks tumor was excised. While millions upon millions of dollars have been made using research based on HeLa cells, her family, in the 21st century, remains unable to afford health insurance. Do people have ownership over their bodies? Do scraps of tissue which turn into a gold mine, as in the case of Henrietta Lacks, place moral obligations on a society that benefits from research? These and many other troubling questions arise even as a reader moves smoothly through Skloot's captivating narrative.

In reflecting on the cancer wars, Mukherjee notes: '...while the content of medicine is constantly changing, its *form* ... remains astonishingly the same. History repeats, but science reverberates. The tools that we will use to battle cancer in the future will doubtless alter.... But much about this battle will remain the same: the relentlessness, the inventiveness, the resilience, the queasy pivoting between defeatism and hope, the hypnotic drive for universal solutions, the disappointment of defeat, the arrogance and the hubris.' Cancer presents a strange paradox; reminding us starkly of human mortality, even as our cells seek immortality.

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