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Book Review: TIMOR MORTIS

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TIMOR MORTIS
Siddhartha Mukherjee,
The Emperor of All Maladies
(Scribner 2010)

In the opening pages of *The Emperor of All Maladies*, his narrative history of cancer research and therapy, Mukherjee tells the reader that leukemia “represents a special incarnation of cancer. Its pace, its breathtaking, inexorable arc of growth forces rapid, often drastic decisions; it is terrifying to experience, terrifying to observe, and terrifying to treat.” What Mukherjee says about leukemia could, from the point of view of those afflicted, be said of any cancer. That dark moment arrives, after the physician has given his diagnosis, when all one can think to ask is “should I put my affairs in order?” Up until the 1950s the answer to the question was all too frequently “yes.” However, in the last several decades medical and biological research has achieved significant new understandings of the physiological, chemical, and environmental etiology of tumors. Researchers have developed new therapeutic interventions that have helped mitigate, if not cure, some cancers. Patients afflicted with breast, cervical, prostate and leukemia cancers today have an improved chance of survival. But for those suffering from lung, brain and pancreatic cancers the answer too often remains “no.”

In a PBS Newshour interview (2-24-2011) with Betty Ann Bowser, Mukherjee explains that he used a leukemia patient, whom he calls Carla, as a thread to link his narrative. Prior to meeting Carla in her Mass General Hospital room, he “mentally rehearsed the conversation I would have with her. There was, I noted ruefully, something rehearsed and robotic even about my sympathy.” Mukherjee, ten months into a two-year oncology fellowship notes that he had already seen “dozens of patients” in his care die. “The stories of my patients consumed me, and the decisions I made haunted me.” He also notes that his “day-to-day management of cancer” ultimately gave him a “novice’s hunger for history” and an urgent desire to understand the historical genesis of cancer and how that history shaped the present, more highly developed, but still very incomplete, understanding of the malady. Carla, who faces her leukemia with courage and dignity, benefits from the advances but even so undergoes great physical and mental suffering.

In tracing the history of cancer research, Mukherjee advances some major themes. *The Emperor of All Maladies* examines the distinct (and often opposing) roles played by surgeons, chemotherapists/radiologists and, in more recent decades, genetic/molecular researchers. The most troubling theme looks at the interplay between politics, policy, and scientific research and whether a “war” on cancer devoted to discovering a cure should take precedence over a much broader spectrum of research activities. This brief review cannot hope to cover the broad range of topics Mukherjee introduces; let me focus on the advances in breast cancer research and therapy to engage directly the roles played by surgeons, chemotherapists and biological researchers and, indirectly, the controversies that have arisen out of the research.

Historically, breast cancer had been recognized since pharaonic times; surgical removal of tumors provided the most common method for treating the cancer. Until the discovery of anesthetics, patients underwent almost intolerable suffering. The prevailing practice was to remove not only the tumor but also much of the muscle and sinews proximate—and sometimes not so proximate—to the tumor. “‘The patient was a young lady whom I was loath to disfigure,’” wrote William Halsted, a Johns Hopkins practitioner of radical mastectomy, who applied the term “mistaken kindness” to surgeons who hesitated in the face of metastatic breast cancer to surgically remove pectoral, shoulder, and rib muscles and strip lymph nodes to create clean margins. Gradually, another group of researchers discovered that certain chemicals could shrink tumors and retard their growth. While surgeons as a cohort believed the only way to stop cancer’s spread was surgical removal of the cancerous tissue, chemotherapists believed chemical interventions offered a surer and less physically damaging approach. Since the chemicals destroyed healthy cells as well as cancerous ones, the trick was to develop a chemical tonic whose toxins eliminated the cancerous cells more quickly than they destroyed healthy cells. In many instances it was a near-run race where the cure might present more problems than the disease. The side effects—nausea, vomiting, dehydration, hair loss—meant long term
agonies for many women. For years the prevailing practice was that a wide spectrum of chemical toxins was the most effective therapy and so doses increased in magnitude with a concomitant increase in damaging side effects. More recent discoveries, however, have tended to indicate that the chemical interventions should more narrowly and precisely target tumors which often respond better to specific chemical toxins rather than to a toxic smorgasbord served to them.

Molecular biology and hormonal research has opened new avenues for treating cancer. Hiking in Scottish highlands in the late 1890s, George Beatson, a surgeon “trying to devise new surgical methods to treat breast cancer, had learned from shepherds that the removal of ovaries from cows altered their capacity to lactate and changed the quality of their udders.” Beatson did not understand the basis of this phenomenon. (Edward Doisy’s discovery of the ovarian hormone estrogen lay several decades in the future.) Intrigued by the unexplained connection between ovaries and breasts, Beatson “surgically removed the ovaries of three women with breast cancer… .” To Beatson’s astonishment, his three cases revealed marked responses to the ovarian removal—the breast tumors shrank dramatically.” But why?

Larger patient samples produced mixed and puzzling therapeutic results; a surgical team in London found that only two thirds of breast cancer patients responded to the ovarian removal. Why did some respond and some not? Though Doisy discovered estrogen in 1929, it took until the 1960s for molecular researchers to discover that some breast cancer cells had receptors hungry for estrogen (ER positive) and thus responsive to surgery that cut off the supply of estrogen. Other women, however, had cells lacking receptors (ER negative) which were not estrogen dependent and thus unresponsive to ovarian removal. Moreover, owing to side-effects, most notably osteoporosis, surgically removing a woman’s ovaries became a much less frequent treatment option.

Might there exist a pharmacological therapy to “inhibit estrogen function?” Believing that chemotherapy (which had begun to exert its influence over surgery) offered more promising therapeutic results, pharmaceutical companies had little interest in developing an antiestrogen and were reluctant to embark on an expensive and perhaps unprofitable research program. Once again, one of those serendipitous moments that so often happen in scientific research emerged. A team of British chemists working for the Imperial Chemical Industries filed a patent for ICI 46474, or tamoxifen, originally intended as a birth control pill which, instead of turning on the estrogen receptor necessary for a contraceptive drug, in fact turned it off. In an “aha!” moment, Arthur Walpole, the lead chemist on the tamoxifen project,
wondered whether the drug might provide the answer to one half of Beatson’s puzzle. He arranged for a clinical trial at Manchester’s Christie Hospital where forty-six women suffering from “advanced, metastatic breast cancer,” many of them doomed, were administered the drug. Ten responded almost immediately with shrinking tumors and, while many of the patients did subsequently relapse, trial and error had proved that a drug, “not a cellular poison,” could drive “metastatic tumors into remission.” ER positive cells responded to tamoxifen; ER negative cells didn’t. Mukherjee notes that “for the first time in the history of cancer, a drug, its target, and a cancer cell had been conjoined by a core molecular logic.”

The rediscovery by Axel Ullrich, a researcher at Genentech, of what’s termed an oncogene began to fill in more pieces to the puzzle. An oncogene, if I understand correctly, signals a cell to grow unchecked; the trick was to find some means for rendering the oncogene inactive. One oncogene designated Her-2 turned out to associate itself with aggressive breast cancer. Dennis Slamon, a UCLA oncologist described by one reporter as a “velvet jackhammer,” had heard Ullrich speak about his discovery and realized that the Genentech scientists didn’t know how to proceed with their knowledge. In collaboration with Genentech immunologists, Slamon developed an antibody that inactivated Her-2 in mouse tumors and, in his UCLA lab he treated breast cancer cells with the antibody: they “stopped growing, involuted and died.”

However, by the late 1980’s Genentech had started “abandoning its interest in cancer” for fear that investing millions in a drug that might fail would cripple the company’s finances. Ullrich left the company to work in a German Laboratory. Slamon and a small group of sympathetic Genentech scientists worked tirelessly to keep the project alive. The group ultimately in 1990 “humanized” the mouse antibody into a potential drug which soon took the name Herceptin (Her-2, intercept, and inhibitor). Genentech ultimately agreed to conduct clinical trials. Mukherjee recounts the events of Herceptin’s clinical trials where the drug proved effective in prolonging the lives of women with aggressive metastatic breast cancers. News of the drug’s effectiveness brought advocacy groups to pressure the FDA for rapid approval. Herceptin, marketed as Trastuzumab, is now routinely prescribed. The fact, however, that the prescribed Herceptin regimen is substantially cheaper in Australia than in the US has moved the controversy into a new arena.

The Emperor of All Maladies ranges widely over the history of cancer. Mukherjee understands the paradox of cancer, which “consumes that which it is nourished by”; in his narratives about individual patients like Carla, he never loses sight that those researchers and physicians like himself who consume their lives working in laboratories and clinics are driven to alleviate the human suffering caused by this disease.

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