

Fisher's Respect for Scientific Methods Propelled Landmark Advances

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Bernard Fisher, MD

When Bernard Fisher, MD, first became involved in breast cancer research, the only treatment option available to patients was the radical mastectomy, a horribly disfiguring surgery that had been the undisputed standard of care since the late 1800s. In 1894, William Halsted developed the procedure for the radical mastectomy, which involved removing the entire breast, the underlying chest wall muscles, and all of the underarm lymph nodes. At that time, cancer was widely thought to be a local disease that spread in a predictable way, and so it was believed that extensive surgery could theoretically remove all of the cancer cells and cure the patient. Despite a lack of reproducible data to prove this theory or the success of the radical mastectomy, Halsted's procedure remained the unequivocal treatment for breast cancer for nearly 100 years. The only thing physicians disagreed about was whether or not the surgery was

sufficiently radical.

In the 1960s, Fisher and his brother, Edwin Fisher, MD, a worldrenowned breast cancer pathologist, conducted laboratory experiments that questioned the Halstedian view of metastasis. Through these experiments, which were conducted on animals, they discovered that tumor cells spread via the lymph nodes and the bloodstream, indicating that breast cancer is a systemic disease, not a local one as had always been theorized.

Over the next several decades, Fisher conducted laboratory investigations and prospective clinical trials that systematically advanced the understanding of tumor biology, resulting in an improvement in the standard of care for women with breast cancer. Fisher's research proved that radical mastectomy is no more effective than the less extensive total (simple) mastectomy, which limits the surgical procedure to removal of the breast only.

Fisher's subsequent investigations showed that lumpectomy followed by breast irradiation is as effective as modified radical mastectomy (total mastectomy plus the removal of the underarm lymph nodes). Then, in the early 1970s, his research revealed that adjuvant chemotherapy administered after surgery can improve the survival of women with early-stage breast cancer. In another study, he demonstrated that the oral hormonal therapy tamoxifen could reduce the risk of breast cancer recurrence and improve survival, and also that tamoxifen could reduce the incidence of breast cancer by nearly 50% when given to healthy women at high risk for developing the disease.

Step by step, Fisher's research launched the breast cancer community into the modern era of new, promising treatment strategies that improved patient outcomes. The most important aspect to remember, though, is that each of these advancements was supported by laboratory research and clinical evidence.

In Data We Trust

Something that may not be readily understandable to the modern reader is that clinical trials as we know them today have not always been the answer to clinical questions. The first randomized clinical trial, conducted by Austin Bradford Hill on the use of streptomycin for tuberculosis, took place more recently than one might think, in 1948. Before then, anecdotes were the main source of information informing treatment strategies. According to Norman Wolmark, MD, current chairman of the National Surgical Adjuvant Breast and Bowel Project (NSABP), who was a protégé of Fisher's for decades, "Clinical trials were not yet in the mainstream, so Bernie was certainly a pioneer."

Early on in his medical career, Fisher's interest in research was initiated by his work in the late 1940s with Julius M. Rogoff, MD, who was professor of Endocrine Research at the University of Pittsburgh, Pennsylvania, and then from 1950 to 1952, when he was under the tutelage of Isidor S. Ravdin, MD, chairman of the Department of Surgery and director of the Harrison Department of Surgical Research at the University of Pennsylvania. When the first clinical trial was being conducted, Fisher was studying liver regeneration, hypothermia, transplantation biology, and biology of metastasis in the laboratory setting. He was invited in 1957 to discuss the creation of the organization that would become the NSABP. As a result of his laboratory experience, Fisher was familiar with the scientific method, and he consequently viewed clinical trials with proper controls, statistics, and other elements as the appropriate venue for evaluating alternative hypotheses such as the worth of radical mastectomy, and then the worth of lumpectomy.

According to Daniel A. Osman, MD, who just recently retired from his 30-year tenure as the director of the Miami Breast Cancer Conference—a conference organized in large part due to Fisher's groundbreaking data—Fisher had a credo, "In God we trust; all others require data," which was a radically new viewpoint then.

Driven by Truth

Not only was Fisher challenging the status quo, but he was also admitting that surgeons did not have all the answers for treating breast cancer. Another of his colleagues, Jay R. Harris, MD, chair of the Department of Radiation Oncology at the Dana-Farber Cancer Institute, said that "One of his [Fisher's] fundamental contributions globally was [that] he was an American surgeon who got up at meetings and said, 'We don't know the answer to this question. We need to do a clinical trial to answer it.' Even to this day, surgeons are not prone to saying, 'We don't know the answer.' And in the 1960s, it was unheard of."

Bernard Fisher, MD

Career Highlights

As one can imagine, this practice did not make him

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- 2006** — American Association of Cancer Research Lifetime Achievement Award
 - 1993** — Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research
 - General Motors Cancer Research Foundation Kettering Prize
 - 1992** — Elected President of the American Society of Clinical Oncology
 - 1986** — American Cancer Society Medal of Honor
 - Appointed to President Reagan's National Cancer Advisory Board
 - 1985** — Albert Lasker Clinical Research Award
 - 1979** — Appointed to President Carter's Cancer Panel
 - 1965** — Fulbright Commission Award, Appointee to Peru as Visiting Professor
 - 1953-1958** — Appointed a Markle Scholar in Medical Science

particularly popular among his colleagues. Harris said, “He was practically vilified by his specialty initially.” Osman also recalled, “When he started with lumpectomies, the surgeons of the United States hated him for it.” Luckily for the breast cancer community, Fisher was not to be dissuaded by the negative feedback. According to Wolmark, Fisher “was driven by applying the scientific method to clinical problem solving. He was driven by the truth. He was driven by the value of the data rather than by the value of opinion.”

It was his devotion to discovering the scientific truth that made it possible to persevere with cuttingedge research, which takes a special kind of personality. “There’s no doubt he has a big personality, and that’s what was required. He made such fundamental changes in the thinking of American physicians in getting them to do clinical trials. The ego strength that he had to have to face all that pushback and rejection, to keep on going...I could see somebody calling him brash, but that’s not the part of it that I think is key to the man. He had a vision for advancing care for breast cancer patients, and he was relentless in pursuing it,” recalled Wolmark.

In addition to a drive for truth, a facet of Fisher’s personality that has enabled him to succeed as a clinical scientist is the ability to reformulate his own hypotheses when needed. Wolmark reflected that “No matter

how enamored he was of a hypothesis, the minute the data indicated that the hypothesis was not supported, it was abandoned, which is absolutely remarkable. No matter how much time and effort and intellectual commitment there was, if the data showed that the hypothesis was not supported, Fisher abandoned the research.” Anyone who has devoted hours and energy to a difficult cause knows how hard it is to let go of a theory when it is proved to be incorrect, and it is rare indeed to find someone who has the strength to relinquish that intellectual attachment and move on.

Setting the Stage for Change

Fisher also challenged his colleagues to be objective. According to Wolmark, “His standard admonition to the membership of the NSABP was, ‘When you cross the threshold into this room, you cease to be a medical oncologist or a surgeon or a radiotherapist. You become a clinical investigator, and you leave your biases outside.’” It may have been a difficult expectation to live up to, but Fisher gave this NSABP membership all of the tools they needed for success. “Bernie provided a unique environment. Aside from the clinical trials, we had a very active bench research lab, and there was a seamless interface between the lab and the clinical trial process, where hypotheses developed in the lab could be tested globally in a clinical trial. We weren’t certain where this was leading, but we knew that, wherever it was going, that the treatment of breast cancer would be inexorably and irreversibly changed,” continued Wolmark.

Decorated for Service

Fisher’s tenure at the NSABP spanned 47 years, as a founding member in 1958 and as chairman from 1967 to 1994.

He is currently a Distinguished Service Professor of Surgery at the University of Pittsburgh. He lectures occasionally and is writing a historical account of his 50-plus years of laboratory and clinical research related to cancer. Throughout his medical career to date, his contributions have been recognized by countless awards, chairs, and appointments, including appointments by Presidents Carter and Reagan, and he has participated in both national and international committees and panels devoted to furthering the science and treatment of breast cancer.

The breast cancer community is very fortunate to have such a living legend as a champion of its cause, and perhaps owes a thank you to his wife, three children, and five grandchildren for their willingness to share him with this cause. His clinical trials have provided the evidence to transform the way breast cancer is viewed, treated, and how it can be prevented, and Fisher has provided a legacy whereby alternative hypotheses can be formed and rigorously tested. As Wolmark asked, “How many of us can say that we left the state of the art in far better shape than we found it?” Fisher may be one of the few.