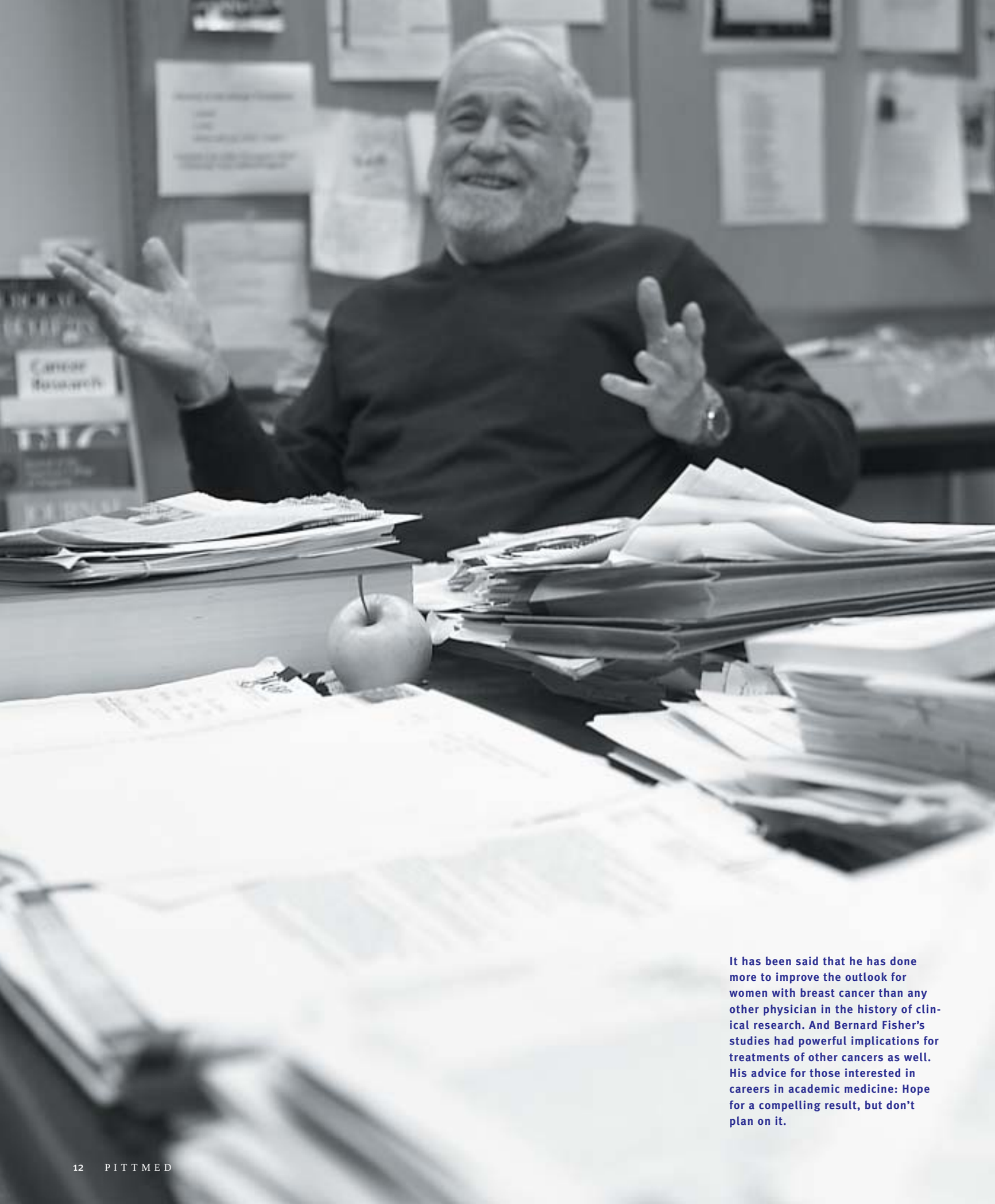

It has been said that he has done more to improve the outlook for women with breast cancer than any other physician in the history of clinical research. And Bernard Fisher's studies had powerful implications for treatments of other cancers as well. His advice for those interested in careers in academic medicine: Hope for a compelling result, but don't plan on it.

IT DOESN'T HAVE TO BE A BLOCKBUSTER

BERNARD FISHER

IN CONVERSATION

A dreamy photo of dancer Betty Bloomer, circa 1945, shows her splayed on the ground, back arched against a grassy lawn, her sweeping skirt in a splendid fan surrounding her. Others show the lithe woman, who performed and studied under Martha Graham's direction, slicing the air with a dramatic lean or whirl, at once a picture of strength and vulnerability. Decades later, in September 1974, First Lady Betty Bloomer Ford had a radical mastectomy, again a dramatic display of strength and vulnerability: Her very public surgery is credited with doing much to advance a vital health issue that Americans had shied away from discussing in anything but whispers.

While the first lady underwent surgery at the Naval Medical Center, across the street, at the National Institutes of Health, Bernard Fisher, MD '43, of the University of Pittsburgh, reported findings from studies that would have a profound effect on the treatment of breast cancer for the next 30 years.

PHOTOGRAPH | ROY ENGELBRECHT

PHOTOS THIS PAGE: COURTESY FISHER

"I felt at an early point in my career that cancer is not a surgical disease any more than is arteriosclerosis a surgical disease," notes Fisher. (LEFT AND ABOVE, circa 1970)

Fisher's report showed that less-extensive surgery was just as effective as radical mastectomy. He also reported findings from the first clinical trial ever carried out to evaluate the value of postoperative chemotherapy, indicating that a single agent (L-PAM) after surgery led to a better outcome. The first lady was prescribed L-PAM as a result of Fisher's findings; it was too late for her to receive the less radical surgery.

The day before Fisher's announcement, radical mastectomy was the *accepted treatment for breast cancer; it involved removing not only the breast but also the chest wall muscles, the nearby lymph nodes, and sometimes even both breasts. This treatment was based on the Halstedian hypothesis, derived from anecdotes and induction. The Halstedians proposed that cancer spreads in an orderly way, progressing from one anatomical site to another: Thus, stopping cancer's progression necessitated extensive surgery. But anecdotes to the contrary were common. Women who'd undergone radical mastectomies were still dying from cancer.*

In a meeting held during the late '50s, Fisher and fellow surgeons from across the country discussed why radical mastectomy so often failed to improve the outcome of patients. To that group, which eventually became the National Surgical Adjuvant Breast and Bowel Project (NSABP), it seemed that, rather than prevent the spread of cancer, surgery might actually stimulate *its progression: "One of the weak links of surgery was that, while you were trying to get a tumor out," Fisher explains, "some tumor cells got disseminated." The spread of those cells, or metastasis, was an understudied field at the time, though the phenomenon intrigued Fisher. With his brother Edwin Fisher, a member of the faculty of medicine and also a School of Medicine graduate (MD '47), he studied the biology of metastasis throughout the next decade. Their laboratory studies showed "dormant" tumor cells exist and altering a host can result in lethal metastases—challenging the then widely accepted notion that cancer was autonomous from its host. Findings coming out of the brothers' lab suggested a thesis that, unlike Halsted's, was biologic, rather than anatomic and mechanistic.*

Fisher proposed that cancer spreads unpredictably, and metastases occur because of the individual characteristics of the tumor cells and of the individual patients in whom they exist.

By 1967, the NSABP needed a new chair and an infusion of energy. Fisher, among the group's founders, certainly had the qualifications, but he resisted because "it didn't look like a very promising thing to devote your life to." His colleagues pressed. The NSABP got a new chair.

Fisher soon realized that members of the NSABP could help him test this new hypothesis and, at the same time, determine the value of less-mutilating surgery. The first clinical trial he designed was to compare radical mastectomy with removal of the breast without removing the muscles or lymph nodes. A second compared the efficacy of removing the tumor by lumpectomy with more radical operations. The operations were all found to be equally effective. In more than 25 clinical trials involving more than 50,000 women, Fisher's group would go on to prove the effectiveness of new therapies and combinations of chemotherapy and tamoxifen. These latter two systemic treatments eliminated tumor cells that circulated in the blood or that remained undetected within organs, out of the reach of the Halstedian's knife.

It turned out that tamoxifen, which became available in the '80s, not only was an effective therapeutic, but could be employed for breast cancer prevention. This 1998 finding is among the more recent Fisher breakthroughs.

Fisher is now 82, and most of the horizontal space in his office is covered by papers and folders relating to his current projects. He indulged us with an interview this spring, during which he reflected on his career (including some 40 years of research at the University), deliberated on the future of breast cancer treatment, and meditated on the academic life. Excerpts follow.

I was a reader as a kid and was fascinated by books such as Paul de Kruif's *Microbe Hunters*. Plus, I had every contagious disease known to mankind: measles, mumps, whooping cough, scarlet fever, you name it. It was a different time, when the public health nurse would come along and put a little sign on the door, and your house was quarantined; nobody came in or went out. It was a rather interesting immersion experience. In retrospect, it gave me an opportunity to read and to fantasize about my future.

A great-uncle of mine, Julius Rogoff, was a very well-known physiologist who started off his career as a surgeon, then became an academic.

"I speak, I write, others tell you what I mean. Prejudice can alter perception more profoundly than hallucinogens."

As chance would have it, in the '40s he came to the University of Pittsburgh, where he became the first research professor of experimental endocrinology. I had an opportunity to work occasionally in his laboratory.

[*In the '50s, Fisher investigated blood vessels, liver regeneration, and hypothermia in his surgical research lab at Pitt.*] In those days, being a clinician and an investigator was an unusual combination. I was difficult to categorize. Clinicians looked upon me as an animal doctor and basic researchers looked upon me as a clinical doctor. As a result, I was often asked, "What are you going to do when you grow up?"

Around 1955, I got a call from Dr. George Moore, who was chief of surgery at Roswell Park in Buffalo. He was creating a cancer institute and asked me if I would be interested in going there as a surgical oncologist. And I said, "Well, I am not really interested in cancer." In 1958, I got a call from Dr. I. S. Ravdin, who had been my mentor at Penn. He said, "We're having a meeting in Washington at the National Institutes of Health, and I want you to be there. We're going to set up a clinical trial involving women with breast cancer." I said, "I'm not in the least bit interested. I'm doing what I want to do in the laboratory here at Pitt." He said, "I'm telling you to be there." Well, you don't refuse a two-star general who . . . had operated on Eisenhower, and who was known the world over.

To me, a clinical trial is like a flow cytometer or an electron microscope. It's where you put something in and get something out. What you get out relates to the quality of what you put in. The chance of obtaining important results from a clinical trial depends upon the strength of the hypothesis being tested.

While the clinical trial mechanism is accepted today, when I began my clinical trials, it was difficult for me to get women and physicians to participate in them. When radical mastectomy was being evaluated, the idea of performing less-extensive operations was considered, in some institutions, to be equivalent to malpractice.

To get a woman to participate in a clinical trial where she was going to have her breast off or have her breast not taken off, that was a pretty difficult thing to do. Not like testing Drug A versus Drug B. In time, as more trials were being done, it became easier to attract participants. Those women who did participate in our studies felt that they were making a contribution that would be of value to their progeny and to other members of their family. The women themselves are the heroes.

Our 1998 report indicating, for the first time, that breast cancer could be prevented with tamoxifen was probably the capstone of my career. Certainly, in 1958, when I began this journey, the idea of using an agent to try to prevent breast cancer was . . . science fiction.

During my scientific life, I have been trying to make a contribution toward bettering the lives of women with breast cancer. Others will have to assess the worth of my accomplishments. Unfortunately, after four decades of investigation, I've recognized that discovery is not always triumphant. There's a sign right there. [*He points to the cabinet across the room, papered with his own maxims.*] It says, "I speak, I write, others tell you what I mean. Prejudice can alter perception more profoundly than hallucinogens."

I have always believed that the research we were doing was not only related to breast cancer but to other cancers like colon or lung cancer, or to all other tumors where unbelievably extensive operations were being done—forequarter, hindquarter amputations, and so on.

The understanding of the disease has changed, and that's the important thing. Now we're entering a new era in which there are molecular or genetic kinds of approaches, which have a great deal of promise. We may have reached the end of what we're going to get with chemotherapy. There are people who are talking about the use of immunologic agents, about finding genetic mechanisms that can be interfered with. Those will be the new systemic therapies of the future. Hopefully that will occur, because, if it doesn't, then we're not making any progress.

I felt at an early point in my career that cancer is not a surgical disease any more than is arteriosclerosis a surgical disease. With regard to the latter, what one does is to use coronary artery bypass, or stents, or to resect aortic aneurysms, but you're not curing arteriosclerosis. You are nowhere near preventing or eradicating that process. And the same thing applies to cancer.

I've recently become interested in the mammography controversy. We can demonstrate from all of our trials that women with small tumors—really small tumors—do better than women with big tumors. Almost all of those small tumors were detected by mammography. Screening is still appropriate. It's not so much how many tumors you find; it's what kind of tumors you're able to detect. Incidentally, in 1974, I established, at Pitt, the first breast cancer detection center in Pittsburgh.

My advice to those who are going into academic medicine is that they should pick something important to work on, something that could make a difference. And then, do it with passion. Hope for a compelling result, but don't plan on it. But even if they make some contribution, that's worthwhile. It doesn't have to be a blockbuster. I think that's the thing that they should aim for, but they should realize that they're going to be disappointed more often than not.

Whatever contribution I have made has only been possible because of both my family, who have been entirely devoted to my career, and the thousands of people who worked with me over the years. They were committed. Totally committed.

It's been an interesting life. And it isn't over yet. I still have a full briefcase! ■

Interview by Leah Kauffman