

Case Histories of Significant Medical Advances: Tamoxifen

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Tamoxifen (through 2001)

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Abstract: Our case history describes the development of tamoxifen, considered a “gold standard” treatment for millions of breast cancer patients. Specifically, we describe breast cancer treatments prior to tamoxifen’s development; the initial development of tamoxifen from 1960 to 1973; tamoxifen’s adoption as an adjuvant breast cancer treatment between 1973 and 1985; and the extension of tamoxifen’s use to include preventative treatment, between 1986 and 2002.

Note: Tamoxifen, like the others in this series of case-histories, are included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a major impact on patient care. The case histories focus on advances in the 20th century (i.e. before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

Tamoxifen

Tamoxifen is considered a “gold standard” treatment for millions of breast cancer patients. In 1985, twelve years after Imperial Chemical Industries (ICI), had first introduced tamoxifen in the United Kingdom (UK), the World Health Organization (WHO) designated it an essential cancer drug.¹ In 2003 a leading tamoxifen researcher, estimated that “over 400,000 women are alive...as a result of tamoxifen therapy.”² (See **Exhibit 1**)

The drug disrupts estrogen’s promotion of cancerous breast tumors. Estrogen is a hormone produced by the body that normally--and beneficially--regulates reproduction. However, in about 80% of breast cancer cases, estrogen promotes the growth of tumors.³

Doctors prescribe tamoxifen after patients have undergone other treatments, such as surgery and radiation, to remove their initial tumors. Drugs used in this way are often referred to as “adjuvant therapy.” Doctors also prescribe the drug to healthy women who have a high risk of developing breast cancer because of factors such as close relatives with the disease; studies show preventative use reduces women’s chances of developing tumors by about 50%.⁴ And, pricing has kept the drug relatively affordable: tamoxifen has been available, a full course of treatment has been relatively cheap, costing as much as six times less than other adjuvant breast cancer treatments – even when it was under patent protection.⁵

The four main sections of this Note will describe: 1) breast cancer treatments and research before tamoxifen’s development; 2) the initial development of tamoxifen from 1960 to 1973; 3) tamoxifen’s adoption as an adjuvant breast cancer treatment between 1973 and 1985; and 4) the extension of tamoxifen’s use to include preventative treatment, between 1986 and 2001.

1. Prior Treatments and Research (before 1960)

Since ancient times, physicians have treated breast cancer by cutting off all or parts of women’s breasts. In 1894, two American surgeons, William Halsted and Willy Meyer, independently systematized operations that came to be known as “radical mastectomy”: removal of the entire breast and the muscles beneath it. Variants of mastectomy soon became and long remained a standard treatment for breast cancer.⁶

An indirect surgical approach was attempted in 1895 when a Scottish surgeon, George Thomas Beatson, removed the ovaries of women with advanced breast cancer. The traditional practice of dairy farmers of removing cows’ ovaries to increase lactation led Beatson to speculate that, in humans, ovarian activity could influence breast tumor growth. (See **Exhibit 2**) Later, when working as a surgeon at the Glasgow Cancer Hospital,⁷ Beatson removed the ovaries of three women believed to have incurable breast cancers. As he reported in an 1896 article in *The Lancet*, a prestigious British medical journal, the cancer “disappeared” in one woman and shrank significantly in another, reducing their pain and leading to “excellent health.”⁸ However, Beatson turned his attention thereafter to surgical treatments for other cancers and tuberculosis, and few other physicians took on his ovarian removal technique.⁹

Instead, radiation treatments became the main alternative and complement to mastectomies. A year after Wilhelm Roentgen had discovered X-rays in 1895, physicians found they killed cancer cells. Soon physicians routinely used X-rays to treat gastric, skin, and breast cancers.¹⁰

In the 1940s, chemotherapy emerged to “poison” cancer cells. Researchers first developed cancer-killing drugs based on mustard gas (previously used as a chemical weapon in the First World War) to

treat lymphoma in 1942, and shortly after, drugs to treat leukemia. Doctors started to use these “chemotherapeutic” drugs to treat breast cancers in the 1950s.¹¹

Surgery, radiation, and chemotherapy treatments for breast cancer, however, were painful, disfiguring, harmful, and ineffective. They could also cause infertility, birth defects, and blood cancers and problems with the immune system, bone marrow, bladder, and liver functions. And they typically produced only temporary remissions. Breast cancers returned, killing 40-50% of patients within as little as five years.¹²

Meanwhile, researchers were attempting to use sex hormones for cancer treatments. In the 1930s, researchers found that sex hormones that regulate human reproductive systems also had beneficial—and harmful—effects throughout the body. In 1941, Charles Huggins, a Canadian medical researcher working at the University of Chicago, published an article reporting that removing testicles, which produce male sex hormones, helped control prostate cancer. Huggins’s 1941 article also reported the same results by injecting synthetic estrogen.¹³ (Dr. E. Charles Dodds, a researcher at University College London, had first synthesized this hormone in 1933).

By the 1950s, Huggins and other researchers had tried to treat breast cancer by reducing or increasing estrogen levels in the body. Huggins revived and improved George Thomas Beatson’s surgical techniques for removing ovaries, which by then had been shown to produce estrogen. Other researchers however reported that *injecting* high doses of synthetic estrogen temporarily halted growth of or reduced the size of breast tumors.¹⁴

In the 1950s, researchers also synthesized hormones to regulate female reproduction. Researchers at the American pharmaceutical company G.D. Searle synthesized and patented progesterone to treat menstrual disorders in 1952. That year, the company supplied their new hormone to researchers at the Worcester Foundation for Experimental Biology, a private institute that was trying to develop contraceptive drugs. The following year, Searle also provided modest funding to the institution,* supplementing larger grants from individual donors, notably the American heiress Katharine McCormick and the birth control pioneer Margaret Sanger.¹⁵

The Worcester Foundation researchers found that Searle’s progesterone had the contraceptive effect of preventing ovaries from releasing eggs.¹⁶ It could also control menstruation. The results encouraged Searle to market the drug. However, before it could do so, it needed to conduct safety trials required by the U.S. Food and Drug Administration (FDA). Searle relied on the Worcester Foundation to conduct the trials, and, after the drug passed safety trials, Searle obtained FDA approval to market it to treat irregular menstruation in 1957.¹⁷

However, Searle’s drug rapidly became popular for its contraceptive effects. The FDA’S 1957 approval had required a label warning of the drug’s adverse effects on fertility, and by 1959, over 500,000 American women were using the Searle pill for this “adverse” effect. Searle then immediately sought regulatory approval to market its drug for birth control, which the FDA granted in 1960.¹⁸

The success of Searle’s drug encouraged several American and European companies, including ICI, that were already researching and synthesizing hormones for cancer and other treatments to investigate their contraceptive applications.¹⁹

2. Initial Development of Tamoxifen (1960-1973)

ICI (which for most of its history was the largest industrial company in the UK) had been formed in 1926 through a merger of four chemical companies.²⁰ It had started synthesizing chemicals for

* Searle had initially refused to fund the project in 1952 to avoid controversies about contraceptive drugs (which were illegal in twenty-six states at the time.)

potential pharmaceutical uses in 1936, as German chemical companies had been doing since the 19th century. In 1938, the company started research on the use of synthetic estrogen (which, as mentioned, had first been synthesized in 1933) for cancer treatments.²¹

The company added contraception to its estrogen research in 1957 (about five years after Searle had started supporting the Worcester Foundation's research). In 1960, ICI placed contraceptive research in a separate division. Researchers in the division synthesized a series of hormones, including estrogen, and tested them on animals to see if they had contraceptive effects.²²

ICI's newly created division did not, however, focus on just contraception. ICI had placed the division under the direction of Dr. Arthur Walpole, a cancer researcher at ICI since 1938. Because he was principally a cancer researcher, Walpole hoped synthetic estrogens could also lead to new cancer treatments. Therefore, Walpole's team investigated the potential use of their synthetic hormones in cancer treatments, as well as in contraceptives.²³

Animal studies on ICI 46,474, or "tamoxifen," synthesized in 1962, indicated promising—yet puzzling—possibilities. Some studies suggested that like estrogen, it stimulated ovulation. Other studies, however, suggested "anti-estrogen" (or estrogen antagonist) effects, such as preventing pregnancy by disrupting the implantation of fertilized eggs in the uterus. Yet other studies indicated potential for treating high cholesterol and cancer.²⁴

In 1965, ICI patented tamoxifen for all these uses in the UK while preparing to market the drug as a contraceptive to compete with Searle's already successful drug. This required undertaking trials on the gestation of primates (which lasted about six months) to study whether ICI's proposed contraceptive would harm fetuses or mothers. (Regulators had instituted the requirements – which Searle's drug had not faced -- after the thalidomide disaster of 1962. Thalidomide, marketed as a mild sleeping pill, was found to cause thousands of babies to be born with malformed limbs.)²⁵

In 1969, before completing these studies on pregnant primates, ICI also sponsored human trials to test tamoxifen as a treatment for infertility and for relieving the pain and other symptoms of patients with advanced breast cancer. These other uses did not raise concerns about effects on fetal development—nor did they require researchers address potential legal and ethical problems arising from failures of contraceptive use.²⁶

After its primate trials showed tamoxifen did not harm fetuses ICI sponsored human contraceptive trials in 1971. ICI chose a Stockholm research institute – rather than a UK hospital -- in part because Sweden had long legalized abortion, providing options for women in cases where the contraceptive failed. Meanwhile, human trials (in UK hospitals) for treating infertility and breast cancer patients had shown tamoxifen had fewer side effects than synthetic estrogens already on market (to treat, for instance, irregular menstruation). Therefore, ICI also expanded its trials for infertility and breast cancer treatment in UK hospitals.²⁷

The Swedish contraception trials failed -- tamoxifen did not reliably prevent pregnancy. However, the UK trials showed considerable promise in treating infertility and in relieving pain and shrinking tumors in older patients with advanced breast cancer.²⁸

Nonetheless, ICI's Board of Directors nearly stopped tamoxifen development in 1972. The company had already invested £148,000 (equal to about \$2.5 million in 2020) without producing any drugs. Market research had suggested that sales from infertility treatments would not justify further investment. In addition, tamoxifen faced five recently introduced synthetic hormone-based²⁹ breast cancer treatments. ICI's senior management reportedly told its tamoxifen researchers to prepare to end their project.³⁰

Arthur Walpole, the thirty-four-year ICI veteran who led the tamoxifen project from the start, strongly resisted. After threatening to resign, he somehow persuaded his bosses to market tamoxifen³¹

to treat infertility and as a palliative treatment for patients with terminal breast cancer in the UK. ICI introduced the drug in 1973, reportedly at a higher price point than the other synthetic hormones then used as palliative treatments.³² ICI's managers also agreed to sponsor human trials in the United States, where ICI had failed to secure a patent for tamoxifen.³³

3. Adoption as adjuvant treatment (1973-1985)

In the late 1960s, the U.S. patent office had rejected ICI's patent application (made in 1963) because American pharmaceutical company Merrell had already patented a similar drug. ICI had immediately challenged the rejection and in 1975 – while the U.S. courts were still adjudicating the challenge – the company initiated human trials needed to secure regulatory approval from the FDA to market tamoxifen in the United States.³⁴

Unlike UK regulators, who only required studies demonstrating the safety of new drugs at the time, the U.S. FDA required (after 1962) trials demonstrating a drug's effectiveness in treating a specified "indication." ICI's American trials targeted ambitious indications. In the earlier UK hospital trials, tamoxifen had been given to alleviate the pain and other symptoms of terminal patients with inoperable, untreatable tumors. The new trials examined tamoxifen's effects when administered after mastectomy and radiation therapies.³⁵

Favorable results helped ICI secure FDA approval in 1977. Sixty-one percent of patients who took tamoxifen for two years after treatment with surgery and radiation improved: the drug eliminated tumors in four percent, shrank tumors in 35%, and kept tumors from growing larger in 22% of patients. The studies also showed tamoxifen to be exceptionally safe, enabling ICI to market its "minimal, non-life-threatening" side effects.³⁶

Subsequent worldwide trials of tamoxifen's effectiveness validated the U.S. results. Like many cancer trials in the 1970s, the initial trials had enrolled only a few hundred women (because of the difficulty of finding participants). The subsequent trials treated over 3,100 women of all ages with less advanced cases of breast cancer in hospitals in Europe, U.S., and New Zealand. Initial results, published in 1983 in *The Lancet*, reported that tamoxifen helped 10-20% more women over 50 survive disease-free in the two to three years following surgery and radiation. Additional results published in *The Lancet* in 1985, showed six years of tamoxifen treatment reduced death rates by 34% for patients of all ages with the disease.³⁷

In 1985, the U.S. National Institutes of Health held a consensus conference on breast cancer treatments and declared tamoxifen the "treatment of choice" to extend the lives (after surgery and radiation) of women over 50 years of age with tumors promoted by estrogen. (As previously mentioned, tamoxifen does not affect all breast tumors. Its benefits vary according to whether a patient has tumors with estrogen "receptors." Researchers first identified such receptors in studies of the uterus in 1968 and on breast tumors in 1971.)³⁸

ICI then sponsored research that led to the introduction of commercial test kits in 1988 to identify estrogen-sensitive tumors. These kits helped physicians target patients who would respond to treatment with tamoxifen.³⁹

Pharmacologist V. Craig Jordan, a former student of ICI's Arthur Walpole, emerged as a prominent tamoxifen advocate after Walpole's death in 1977. Jordan led American and European studies and published and lectured widely.⁴⁰ (See **Exhibit 1**)

Sales grew along with use. In 1974, sales were £140,000 – about a third of a million U.S. dollars -- predominantly from sales in ICI's home market of Britain. In 1985, ICI's tamoxifen sales in the U.S. alone were more than 150 times that, amounting to \$50 million (about £65 million).⁴¹ The amounts reflected the high volume of sales, however, rather than a high price: by 1986, a two-month supply of

tamoxifen cost \$51 in the U.S., making the recommended two-year course of treatment about \$600 total* – less than half the cost of other adjuvant breast cancer drugs introduced at the time.⁴²

Then in 1985, a U.S. court of appeals granted ICI a U.S. patent for tamoxifen and guaranteed exclusive rights to market the drug through 2002. Even before ICI had succeeded in securing its patent, no other U.S. pharmaceutical company had attempted to introduce the ICI molecule.⁴³ However, pharmaceutical companies did offer alternative adjuvant treatments, such as Pfizer's Provera, Syntex's Masteril, Eli Lilly's Oncovin, and Adria Laboratories' Adriamycin. Notwithstanding its preeminent position, as mentioned, tamoxifen was affordably priced.⁴⁴

ICI's tamoxifen patent in the UK and Europe, which had been obtained in 1965, expired in 1983. By the mid-1980s, twenty companies offered generic alternatives, which according to one account, discouraged ICI from further development.⁴⁵ (See **Exhibit 3**)

4. Extension to preventative treatment (1986-2001)

Animal trials in the 1970s had suggested tamoxifen not only shrank existing tumors but also prevented tumors from growing in other parts of the body. Human trials had also shown that women who took tamoxifen after developing cancer in one breast were less likely to develop a tumor in the other breast. These results prompted researchers to initiate a pilot study of the preventative use of tamoxifen in the UK in 1986. The study included healthy, cancer-free women who had a high risk of developing breast cancer because they had one or more close family members with the disease. Large-scale, multicenter trials of preventative use began in North America, Europe, Australia, and New Zealand in 1992. These trials expanded to include women over 60 years of age and women 35-59 years of age with one or more risk factors, such as: a first period before age 12, childlessness or a first child born after age 25, a history of benign breast biopsies or removal of precancerous growths, and one or more close relatives with breast cancer.⁴⁶

In 1998, North American researchers (but not European ones) discontinued their trials when preliminary American results showed that women who had these risk factors (but were otherwise healthy) and who took tamoxifen were 50% less likely to develop breast tumors than those who did not take the drug. That same year, the FDA did something it had never done before: approve a cancer drug – tamoxifen -- for use on patients deemed high risk but otherwise healthy and cancer-free (as opposed to patients undergoing treatment to eradicate existing tumors).⁴⁷

The FDA's approval for preventative use helped tamoxifen revenues continue to grow in the United States. Between 1985 and 1995, tamoxifen's U.S. sales revenues had increased 6-fold; between 1996 and 1999, they increased again, by almost another 80%. In 1999, tamoxifen dominated the U.S. breast cancer drugs market with about 39% share of the *whole* market -- including all other kinds of chemotherapy.⁴⁸

Tamoxifen's price had increased in the U.S. since the 1980s, from \$51 for a two-month supply to about \$190 for a two-month supply in the late 1990s.[†] However, its cost remained below other adjuvant breast cancer drugs at the time.⁴⁹ For instance, Bristol-Myers Squibb's adjuvant treatment Taxol cost about \$2,600 for a one-month supply[‡] when introduced in the mid-1990s.⁵⁰

European researchers and regulators were skeptical of tamoxifen's preventative use, however. Prevention trials based in Europe (which had continued after U.S. trials had been stopped) had not

* 1986 tamoxifen prices are equivalent to about \$120 for a two-month supply and about \$1,400 for two years in 2020 dollars.

† 1998 tamoxifen prices are equivalent to about \$300 for a two-month supply in 2020 dollars. By that time, the recommended course of treatment had been lengthened to two to five years. In 1998, a two-year course would cost about \$2,300 (or about \$3,600 in 2020) and a five-year course would cost about \$5,700 (or about \$9,000 in 2020).

‡ 1994 Taxol prices are equivalent to about \$4,600 for a one-month supply in 2020 dollars. The recommended twelve-week course of treatment would cost about \$7,800 in 1994 (or \$13,700 in 2020 dollars).

shown similarly significant benefits. In addition, both the European and American trials had found increased risk of uterine cancers, life-threatening blood clots, and cataracts among women who took tamoxifen for five or more years.⁵¹ These concerns prompted researchers to investigate drugs that might have the same benefits as tamoxifen without its risks.⁵²

Meanwhile, ICI had spun out tamoxifen and other pharmaceutical businesses in 1993 into “Zeneca,” an independent, publicly traded company. Using a compound previously synthesized by ICI chemists, Zeneca developed Arimidex, which inhibits estrogen production in the body. In 1995, Zeneca secured FDA approval to market Arimidex as a treatment for older women with advanced breast cancer who no longer responded to treatment with tamoxifen. Sales of Arimidex rapidly took off in the United States: in 1997 alone, they grew by 155%.⁵³

Throughout the 1990s, ICI (and then Zeneca) faced legal challenges from producers of generic drugs. Only one, Barr Laboratories, succeeded, leading to an agreement that stipulated that Barr license *and* source its drug from ICI (Zeneca). Barr sold its generic tamoxifen at a relatively slight discount off the price of ICI’s drug, so it did not present the same competitive challenge as typical low-cost generics did.⁵⁴

The Situation in 2001.

In 1999, Zeneca merged with the longtime Swedish pharmaceutical company Astra to form AstraZeneca.⁵⁵ AstraZeneca’s researchers then developed an adjuvant breast cancer treatment using fulvestrant, an anti-estrogen synthesized at ICI in 1992 that did not increase patients’ risk of cancer of the uterus.⁵⁶ After conducting the requisite trials, AstraZeneca applied to the FDA to market fulvestrant in 2001, the year before tamoxifen’s patent was scheduled to expire.⁵⁷

That same year, in 2001, the FDA had approved a new drug, Herceptin, for adjuvant use. Herceptin had been developed by the California-based biotech company Genentech to treat the up to 20% of breast cancer patients with a mutation in their HER2 gene. It had been initially approved in 1998 to treat advanced breast cancer in women with HER2 gene abnormalities.⁵⁸

Exhibit 1 “Drug’s Champion Defied Skeptics,” published in *The New York Times*, April 14, 1998

TWENTY-FIVE years ago, fellow scientists warned Dr. Craig Jordan that his career would suffer if he did not branch out and study something else besides the obscure compound that he hoped to make into a drug to treat breast cancer. Dr. Jordan ignored the advice.

The compound, which he has worked on ever since, is now known as tamoxifen. It is the most widely used treatment in the world for breast cancer, and last week it was also declared by Federal health officials to be the first drug ever shown to prevent the disease in women at high risk of developing it.

“This is everything I’ve worked for all my life,” said Dr. Jordan, a professor of cancer pharmacology and director of the breast cancer research program at the Lurie Comprehensive Cancer Center at Northwestern University Medical School in Chicago. The reward is not material: Despite his many years of research on tamoxifen, Dr. Jordan said he had no financial interest in the company that makes it. “I’m sort of old-fashioned,” he said.

Originally, tamoxifen was not even considered as a cancer treatment. said Dr. Jordan, who studied the drug as a graduate student from 1969 until 1972, “It was the age of making love and not war, and everybody was looking for more contraceptives.” As a postcoital contraceptive, or morning-after pill, tamoxifen was great -- in rats. In women, it was a flop.

“It went back on the shelf,” Dr. Jordan said.

Tamoxifen belonged to Zeneca Pharmaceuticals, the British company whose scientists had discovered it. The company had no further plans for it. But Dr. Jordan did, and in 1972 when he finished his doctorate and began a research career, he called Dr. Arthur Walpole, one of the Zeneca scientists who had created tamoxifen. “I said I wanted to turn it into a breast-cancer drug,” Dr. Jordan recalled, adding that Dr. Walpole agreed at once.

But other colleagues were skeptical, to say the least. “For the first 10 years everybody thought I was crazy, because chemotherapy was going to cure cancer, and why bother with this?” Dr. Jordan said. “Why would anybody work on a failed contraceptive?”

Several lines of evidence had led him to the idea. Doctors had first noticed around the turn of the century that some women with breast cancer seemed to fare better after removal of their ovaries, which produces the female hormone estrogen. That observation was explained in the 1960’s, when researchers showed that estrogen could fuel the growth of breast cancer: some breast tumors have estrogen receptors, molecules that the hormone locks onto, enabling it to stimulate the growth of cancer cells.

Building on that work, Dr. Jordan and his colleagues showed that tamoxifen can stop estrogen from feeding human breast tumors grown in the laboratory. Like estrogen itself, the drug locks onto estrogen receptors, blocking or displacing the hormone, but without stimulating malignant cells. In addition, the researchers showed that tamoxifen could prevent breast cancer in animals.

By 1974, tamoxifen was being tested in American women with breast cancer, and it was approved by the Food and Drug Administration in 1977 to treat advanced cases of the disease. In the 1980’s, tamoxifen was also approved for use in earlier stages, after surgery. Then, on April 6, researchers reported that tamoxifen was very effective in preventing breast cancer in women who were at high risk for the disease.

But while tamoxifen can prevent breast cancer, it can also increase the risk of uterine cancer. For that reason, Dr. Jordan and other scientists have looked for other drugs that, like tamoxifen, might protect against both breast cancer and bone loss, but without causing uterine cancer. Dr. Jordan said that one possible candidate is raloxifene, a drug approved last year to prevent osteoporosis. That drug will be compared to tamoxifen in another study, limited to postmenopausal women, expected to start next fall, with Dr. Jordan as its scientific chairman.

Source: Grady, Denise “Drug's Champion Defied Skeptics,” *New York Times*, April 14, 1998.

Exhibit 2 Excerpts from “On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases,” published in *The Lancet*, July 11, 1896

“I have no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such causes naturally excite our sympathy, but they also bring home to us the fact that once a case of cancer has passed beyond the reach of the surgeon’s knife our curative measures are practically *nil*.... Of late, owing to my taking up the work of surgeon to the Glasgow Cancer Hospital, I have seen a considerable number of such cases, and an opportunity has been furnished me of working out a line of treatment which I am not aware has yet been tried by others and which is founded on a view of the etiology and nature of cancer which is entirely opposed to the local parasitic theory of the disease and which seems to me to offer a more reasonable explanation of it....

“The first case that I wish to bring under notice is that of a woman who consulted with me on May 11, 1895, at Glasgow Cancer Hospital.... The history she gave me was that she was thirty-three years of age, married, and the mother of two children, the oldest three years of age and the youngest fifteen months. She nursed both her children for from ten to twelve months, chiefly on the left breast, the first child entirely so, as the right breast suppurated for two or three weeks. While nursing her first baby she observed a small, hard lump at the outside of her left breast, and as it was painless and did not increase in size, she took no further notice of it. It was only when her second baby was born twenty months later that she became aware it was increasing.... In January of 1895 she was admitted... and the journal report states that an examination showed the left mammary gland... [had in its center] a large mass, measuring 5 in. across and 3½ in. in vertical diameter [with several other small tumors and an ulcer around it].... The patient appeared to be strong, healthy, active, and robust. On January 25th, 1895, she was operated upon. The hospital journal says the left breast was excised, a large area of skin free of tumour being taken away. The axillary glands were removed, also a considerable part of the pectoral muscle which appeared to be implicated.... About a month after she had gone home – that is, within three months of the operation – she noticed that the wound had opened... [and] she observed that some hardness was developing at the side of the scar, so she returned to the Infirmary for advice. [She was admitted for a few days, then sent home.] On May 11, at the time she presented herself to me, the local condition for which she sought advice was as follows... immediately below and arching over the center of the long scar was a mass of recurrent tumour... about 2½ in. broad at its broadest part, and about 3½ in. in length. ...She looked pale and careworn, and when questioned admitted she felt ill and was quite unable to perform her household duties....

“The question that had to be decided was whether anything further could be done for the case. As regards local removal I was quite at one with the opinion already expressed at the Royal Infirmary that it was unjustifiable.... Failing, then, local measures, could the disease be attacked in any other way and by any other channels? To answer this it is necessary that I should put before you views that I have for some time held as to the etiology or cause of cancer generally, but more particularly of that of the female mamma....

“I shall do so as shortly as I can. It is just twenty years ago that I was asked to take medical charge of a man whose mind was affected, and I went to reside with him at one of his estates in the west of Scotland. My duties were at times exciting, but never onerous, and I had a good deal of leisure to myself. I thought it would be a good opportunity of writing my M.D. thesis, and after consideration I decided I would take up the subject of lactation. What suggested it to me was the weaning of the lambs on a large adjoining sheep farm.... Accordingly I commenced to work at it, getting all the practical information could about it from the farmers and the shepherds round.... I learnt this very remarkable fact, that is the custom in certain countries, to remove the ovaries of the cow after calving if it is wished to keep up the supply of milk, and that if this is done the cow will go on giving milk indefinitely. This fact seemed to me of great interest, for it pointed to one organ holding the control over the secretion of another and separate organ.... I need hardly say that though I temporarily abandoned the subject of

lactation for my thesis, I did not lose sight of the facts above mentioned, for they seemed to me to point to influences at work in the human system that had not as yet been generally reckoned with or recognised. Above all, I was struck with the local proliferation of epithelium seen in lactation. Here was the very thing characteristic of carcinoma of the breast, and, indeed, of the cancerous process everywhere, but differing from it in that it was held in control by another organ, and could be arrested by that organ altogether or continued to a further stage, where the cells become fatty and passed out of the system not only in an innocuous but nourishing fluid – milk.

“Now I think I am correct in saying that the spirit of modern pathology is this – that all pathological changes are merely modified physiological ones... and that a knowledge of the forces controlling the one may sometimes give us a clue to the other. I often asked myself, Is cancer of the mamma due to some ovarian irritation, as from some defective steps in the cycle of ovarian changes; and, if so, would the cell proliferation be brought to a standstill, or would the cells go on to the fatty degeneration seen in lactation were the ovaries to be removed? For an answer to these questions... I obtained at the end of 1878 a license for performing the experiment of removing the ovaries from suckling rabbits.... Space will not allow me to go into them in detail, but I may say that the three cases I tried all confirmed the fact....

“On taking up my work at the Glasgow Cancer Hospital... I felt that the position of matters was that our present state of knowledge has nothing better to offer than the surgeon’s knife for the cases where the tumor was limited and could be thoroughly removed; but that in inoperable cases... it was possible a free admission of thyroid extract might influence the growth work through time a cure. Failing this, I thought I might follow up on my old line of reasoning, and in cases of advanced carcinoma of the breast in young patients see what effects the removal of the tubes and ovaries would have on the progress of the cancerous growth in the way of arresting the cell proliferation and converting the cells into fatty matter. Although the breast had been removed, this was the line of procedure I decided to adopt with the case under notice, and accordingly on May 11th, she was put upon the thyroid tablets. They were pushed until their physiological action was made apparent; but as no appreciable change was seen in the diseased condition at the end of a month I put it to her husband and herself as to whether she should have performed the operation of the removal of the tubes and ovaries. Its nature was fully explained to them both, and also that it was a purely experimental one, but that it could be done without risk to life; and that, if it should have no effect on the cancerous process, it would cause her no increase in suffering. She readily consented that I should do anything that held out any prospect of cure, as she knew and felt her case was hopeless. On June 15th, I operated and removed the tubes and ovaries on both sides.... She made a good recovery and on June 28th was sitting up. ...On July 12th, the administration of the thyroid tablets, three daily, was resumed.... On August 1st it was noted that the local improvement continued and that the measurements of the largest area of disease were length 2½ in.; breadth 1¼ in.; while the depth was hardly appreciable.... [In addition, the ulcer had healed, and the smaller tumors were less numerous.]..

“[E]ight months after my operation all vestiges of her precious cancerous disease had disappeared, ...and that she is apparently in excellent health.”

Source: George Thomas Beatson, “On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases,” *The Lancet*, Originally published as Volume 2, Issue 3803, 148, no. 3803 (July 18, 1896).

Exhibit 3 Excerpt from “Why ICI is dragging its feet on cancer trial,” published in *The Guardian*, June 4, 1986

“Some of Britain’s leading cancer experts believe that [tamoxifen], if used preventatively, could protect millions of high-risk women from developing the disease.

“Yet, ICI, the company which discovered the drug, tamoxifen, appears to be doing little to see that women at risk will be allowed to try the preventative treatment...

“Scientists at the Imperial Cancer Research Fund urged in a *Lancet* article last January that a full-scale trial with tamoxifen, given daily to 4,000 high-risk women, should be set up without delay. But ICI has refused to play any direct role in the trials and seems almost reluctant to see them proceed.

“Pharmaceutical companies normally use their considerable influence to expand the market for their drugs whenever they can. A preventative treatment is particularly lucrative since patients are typically required to take a daily dose of the drug for the rest of their lives. The beta-blocking heart drugs (to reduce the risk of coronaries) and the anti-ulcer agents, Tagamet and Zantac, are all among the most profitable and widely sold medicines in the world.

“So what could explain ICI’s reluctance to encourage the expanded use of tamoxifen – especially when a breakthrough in breast cancer prevention could bring plaudits from a grateful, cancer-fearing public?

“The most plausible, if sadly cynical answer is that ICI’s [UK] patent on tamoxifen expired in 1983. More than 20 generic drug makers now produce it around the world – one might say at ICI’s expense. So if tamoxifen’s sales suddenly soared, ICI’s proportion of the profits would be greatly diluted. Yet risks would remain. If the alleged wonder drug proved subsequently (from unseen side-effects) to be a curse rather than a cure, the company might receive only vilification and lawsuits.”

Source: James Erlichman, “Why ICI Is Dragging Its Feet on Cancer Trial: The Crude Patent Law Is Holding up a New Preventative Treatment,” *The Guardian* (1959-2003); London (UK), June 4, 1986.

Endnotes

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² V. Craig Jordan, "Tamoxifen: A Most Unlikely Pioneering Medicine," *Nature Reviews Drug Discovery* 2, no. 3 (March 2003): 205-13, <https://doi.org/10.1038/nrd1031>.

³ A small percentage of tumors are sensitive to the hormone progesterone. Sometimes tumors are sensitive to both estrogen and progesterone at the same time. Estrogen- and progesterone-sensitive tumors are referred to generally as "hormone-sensitive" tumors. "Hormone Therapy for Breast Cancer," FactSheet, National Cancer Institute, accessed May 9, 2017, <https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet>; See also: "Hormone Therapy for Breast Cancer | American Cancer Society," accessed January 2, 2020, <https://www.cancer.org/cancer/breast-cancer/treatment/hormone-therapy-for-breast-cancer.html>.

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⁶ Dr. Meyer was German-American: he was born and educated in Germany, then moved to the U.S. to practice. Ira M. Rutkow, "MOMENTS IN SURGICAL HISTORY: Willy Meyer's Radical Mastectomy," *Archives of Surgery* 132, no. 12 (December 1, 1997): 1362-1362, <https://doi.org/10.1001/archsurg.1997.01430360108019>; Siddhartha Mukherjee, *The Emperor of All Maladies: A Biography of Cancer*, 1st Scribner hardcover ed., Harvard Library E-Reader Collection (New York: Scribner, 2010), 60-72.

⁷ The hospital was known as Glasgow Cancer and Skin Institution at that time, but changed its name in 1894, a year after Beatson became a surgeon there. In 1953, it was renamed the Royal Beatson Memorial Hospital, and now it is known as the Beatson West of Scotland Cancer Center.

⁸ The second patient reported a significant reduction in pain and increase in mobility after Beatson removed her ovaries. Beatson also reported her tumors shrank in a similar manner to the first patient over the next few weeks. However, once the main tumor was small, another surgeon removed it, and the woman suffered an infection and complications after that surgery, which then led to declining health. The third patient had no change in her tumor at all. George Thomas Beatson, "ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.1," *The Lancet*, Originally published as Volume 2, Issue 3802, 148, no. 3802 (July 11, 1896): 104-7, [https://doi.org/10.1016/S0140-6736\(01\)72307-0](https://doi.org/10.1016/S0140-6736(01)72307-0), page 107; George Thomas Beatson, "ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.," *The Lancet*, Originally published as Volume 2, Issue 3803, 148, no. 3803 (July 18, 1896): 162-65, [https://doi.org/10.1016/S0140-6736\(01\)72384-7](https://doi.org/10.1016/S0140-6736(01)72384-7).

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²⁷ A 1946 law had allowed Swedish women to obtain abortions on "social grounds," and a 1963 amendment allowed for abortions in cases where the fetus had been seriously injured (such as in the case of birth defects caused by thalidomide). However, Swedish women still had to apply to the government for permission to have an abortion through the mid-1970s. Synthetic estrogens were also sometimes prescribed at high doses to treat women with advanced and terminal breast cancers. Quirke, "Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine"; Jordan, "The Development of Tamoxifen for Breast Cancer Therapy"; Jordan, "Tamoxifen," March 2003; "Edward Charles Dodds (1899-1973) | The Embryo Project Encyclopedia"; "How Sweden Got Some of the Most Liberal Abortion Laws in the World - The Local," accessed March 7, 2020, <https://www.thelocal.se/20180524/the-history-of-legal-abortion-in-sweden-liberal-laws/>; "The Pill Hearings - NWHN," accessed February 4, 2020, <https://www.nwhn.org/pill-hearings/>.

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⁴⁴ Quirke, “Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine”; Memorial Sloan Kettering, Bach Center for Health Policy, “Cancer drug costs for a month of treatment at initial Food and Drug Administration approval”; Frost & Sullivan (1987) *Cancer Therapy Products Market in U.S.*, page 50.

⁴⁵ James Erlichman, “Why ICI Is Dragging Its Feet on Cancer Trial: The Crude Patent Law Is Holding up a New Preventative Treatment,” *The Guardian* (1959-2003); *London (UK)*, June 4, 1986; Jordan, “Tamoxifen,” March 2003; Frost & Sullivan. (2000) *U.S. Breast Cancer Therapeutics Markets*. See also: Frost & Sullivan, *Cancer Therapy Products Market in the U.S.* (2 vols—1987), Vol. 1, page xxiii. Frost & Sullivan. (2000) *European Women’s Cancer Pharmaceuticals Markets*, see for example pages 3-27, 3-47, and 4-50. According to another account: “After Dr. Stephen Carter, who had been responsible for ICI’s cancer project on Cell Division and Growth, left the company, taking early retirement in 1979, he was not replaced, and the project on cell growth was terminated. Thus, in 1980, when tamoxifen was bringing in sizeable profits for the company and Zoladex (for prostate cancer) was in the pipeline, ICI had no longer a cancer research programme.” However, Zeneca’s and AstraZeneca’s later development of breast cancer drugs based on ICI molecules suggests ICI maintained other groups that did cancer research. See Quirke, “Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine”.

⁴⁶ The draft protocol for the pilot study was drawn up in July 1985 and the study enrolled its first patients in October 1986. ICI did not sponsor the studies; however, they did donate 64 million Nolvadex tablets to the NCI study. In 1988, two years after the pilot study began to enroll patients, researchers published results of an animal study that suggested that tamoxifen might increase a woman’s risk of uterine cancer. Protocols for the pilots study and subsequent preventive studies were adjusted to include more screening and gynecological examinations for those enrolled. Jordan, “Four Decades of Discovery in Breast Cancer Research and Treatment—an Interview with V. Craig Jordan. Interview by Marc Poirot”; Marco M. Gottardis and V. Craig Jordan, “Development of Tamoxifen-Stimulated Growth of MCF-7 Tumors in Athymic Mice after Long-Term Antiestrogen Administration,” *Cancer Research* 48, no. 18 (September 15, 1988): 5183–87. Maximov, McDaniel, and Jordan, “Adjuvant Therapy”; Philipp Y. Maximov, Russell E. McDaniel, and V. Craig Jordan, “Chemoprevention: Cinderella Waiting for the Ball,” in *Tamoxifen: Pioneering Medicine in Breast Cancer*, ed. Philipp Y. Maximov, Russell E. McDaniel, and V. Craig Jordan, *Milestones in Drug Therapy* (Basel: Springer, 2013), 115–34, https://doi.org/10.1007/978-3-0348-0664-0_7; Jordan, *The Quest for Multi-Functional Medicines*, 2011; V. Craig Jordan, *The Quest for Multi-Functional Medicines: Path for Progress: The SERM Story*, 2011, <http://hstalks.com/t/2048/the-quest-for-multi-functional-medicines-path-for-/>; B. Fisher et al., “Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study,” *Journal of the National Cancer Institute* 90, no. 18 (September 16, 1998): 1371–88, <https://doi.org/10.1093/jnci/90.18.1371>; Jordan et al., “The Evolution of Nonsteroidal Antiestrogens to Become Selective Estrogen Receptor Modulators”; Jordan, “Four Decades of Discovery in Breast Cancer Research and Treatment—an Interview with V. Craig Jordan. Interview by Marc Poirot”; Trevor Powles et al., “Interim Analysis of the Incidence of Breast Cancer in the Royal Marsden Hospital Tamoxifen Randomised Chemoprevention Trial,” *The Lancet* 352, no. 9122 (July 11, 1998): 98–101, [https://doi.org/10.1016/S0140-6736\(98\)85012-5](https://doi.org/10.1016/S0140-6736(98)85012-5); “ICI’s NOLVADEX (TAMOXIFEN) PATENT IS ‘UNENFORCEABLE’ IN FACE OF BARR’S CHALLENGE.”

⁴⁷ Richard Woodman, "FDA Approves Drug for Women at Cancer Risk," *BMJ: British Medical Journal* 317, no. 7168 (1998): 1274-1274; Fisher et al., "Tamoxifen for Prevention of Breast Cancer," September 16, 1998; Jordan, *The Quest for Multi-Functional Medicines*, 2011; "Tamoxifen Clears Hurdle to Preventive Use - ProQuest," accessed April 16, 2020, <http://search.proquest.com/docview/197537856?OpenUrlRefId=info:xri/sid:primo&accountid=11311>.

⁴⁸ Jordan, V. Craig. "Tamoxifen: A Most Unlikely Pioneering Medicine." *Nature Reviews Drug Discovery* 2, no. 3 (March 2003): 205-13. <https://doi.org/10.1038/nrd1031>. Frost & Sullivan. (2000) *U.S. Breast Cancer Therapeutics Markets*. Note that these estimates are based on the overall market figures and tamoxifen's share of sales alone. In the 1990s, both ICI (as AstraZeneca--AZ) and Barr Labs offered tamoxifen. Barr's "generic" version was licensed and sourced from ICI/AZ; it was also priced similarly, so it did not function as a typical generic under their agreement. Frost & Sullivan's report estimates that ICI/AZ had 97% of the hormonal therapies market, in part because of revenue from ICI/AZ's other hormone-based breast cancer drugs, which were developed after tamoxifen (Zolodex, which was originally developed by ICI as a prostate cancer drug, and Arimidex, the first aromatase inhibitor). Frost & Sullivan, *Cancer Therapy Products Market in the U.S. (2 vols—1987)*, Vol. 1, page xxii. Frost & Sullivan. (2000) *European Women's Cancer Pharmaceuticals Markets*, see for example pages 3-27, 3-47, and 4-50; see also: Gardiner Harris, "Group Sues Barr, AstraZeneca, Citing Tamoxifen Price Collusion," *Wall Street Journal, Eastern Edition; New York, N.Y.*, May 10, 2001, sec. Health.

⁴⁹ A full three-month course of paclitaxil (Taxol) in 1994 cost almost \$8,000, and a full year's course of trastuzumab (Herceptin) in 1998 cost about \$38,500. Estimates not adjusted for inflation and based on pricing found in: Memorial Sloan Kettering, Bach Center for Health Policy, "Cancer drug costs for a month of treatment at initial Food and Drug Administration approval"; Frost & Sullivan (1998) *U.S., European and Japanese Cancer Therapeutics Markets*, page 5-15. See also: Alex Berenson, "Hope, at \$4,200 a Dose," *The New York Times*, October 1, 2006, sec. Business, <https://www.nytimes.com/2006/10/01/business/yourmoney/01drug.html>.

⁵⁰ Berenson; Memorial Sloan Kettering, Bach Center for Health Policy, "Cancer drug costs for a month of treatment at initial Food and Drug Administration approval"; See also: Frost & Sullivan (1998) *U.S., European and Japanese Cancer Therapeutics Markets*.

⁵¹ Woodman, "FDA Approves Drug for Women at Cancer Risk"; Jordan et al., "The Evolution of Nonsteroidal Antiestrogens to Become Selective Estrogen Receptor Modulators"; Jordan, "Four Decades of Discovery in Breast Cancer Research and Treatment—an Interview with V. Craig Jordan. Interview by Marc Poirot"; Powles et al., "Interim Analysis of the Incidence of Breast Cancer in the Royal Marsden Hospital Tamoxifen Randomised Chemoprevention Trial"; J Cuzick, "A Brief Review of the Current Breast Cancer Prevention Trials and Proposals for Future Trials," *European Journal of Cancer* 36, no. 10 (June 1, 2000): 1298-1302, [https://doi.org/10.1016/S0959-8049\(00\)00106-4](https://doi.org/10.1016/S0959-8049(00)00106-4); J. Cuzick et al., "First Results from the International Breast Cancer Intervention Study (IBIS-I): A Randomised Prevention Trial," *Lancet (London, England)* 360, no. 9336 (September 14, 2002): 817-24, [https://doi.org/10.1016/s0140-6736\(02\)09962-2](https://doi.org/10.1016/s0140-6736(02)09962-2).

⁵² For instance, researchers at longtime American pharmaceutical company Eli Lilly had developed raloxifene, a synthetic hormone intended to improve bone density. As part of the trials required by the FDA, Lilly's researchers documented the drug's effects on each patient's bones, uterus, and breasts. Results of the trials helped Lilly secure FDA approval to market raloxifene for the prevention of bone loss in older women in 1997. In 1999, the FDA expanded the drug's approval to include treatment of osteoporosis in women over 50 years of age. The studies also laid the groundwork for Lilly to conduct additional trials and secure FDA approval to market raloxifene as a treatment for breast cancer in 2007. Steven R. Cummings et al., "The Effect of Raloxifene on Risk of Breast Cancer in Postmenopausal Women: Results From the MORE Randomized Trial," *JAMA* 281, no. 23 (June 16, 1999): 2189-97, <https://doi.org/10.1001/jama.281.23.2189>; "FDA Approves Raloxifene For Osteoporosis - Pharmaceutical Industry New," accessed April 16, 2020, <https://www.thepharmaletter.com/article/fda-approves-raloxifene-for-osteoporosis>; "FDA Approves Lilly's Osteoporosis Drug EVISTA(R) (Raloxifene HCl) to Reduce The Risk of Invasive Breast Cancer in Two Populations of Postmenopausal Women," Eli Lilly and Company, accessed April 16, 2020, <https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-osteoporosis-drug-evistar-raloxifene-hcl>; "Eli Lilly's Osteoporosis Drug Raloxifene May Also Treat Cancers," accessed April 16, 2020, <https://www.bioprocessonline.com/doc/eli-lilly-s-osteoporosis-drug-raloxifene-may-also-treat-cancers-0001>; Peggy Peck, Managing Editor, and MedPage Today, "FDA Advisers Recommend Raloxifene (Evista) for Prevention of Breast Cancer," July 25, 2007, <http://www.medpagetoday.com/productalert/prescriptions/6258>.

⁵³ "Drugs@FDA: FDA-Approved Drugs," accessed April 23, 2020, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=020541>; Paul V. Plourde, Martin Dyroff, and Michael Dukes, "Arimidex®: A Potent and Selective Fourth-Generation Aromatase Inhibitor," *Breast Cancer Research and Treatment* 30, no. 1 (January 1, 1994): 103-11, <https://doi.org/10.1007/BF00682745>; Paul V. Plourde et al., "ARIMIDEX™: A New Oral, Once-a-Day Aromatase Inhibitor," *The Journal of Steroid Biochemistry and Molecular Biology, Hormonal Steroids*, 53, no. 1 (June 1, 1995): 175-79, [https://doi.org/10.1016/0960-0760\(95\)00045-2](https://doi.org/10.1016/0960-0760(95)00045-2); "Anastrozole," accessed April 23, 2020, <https://www.drugbank.ca/drugs/DB01217>; Frost & Sullivan (1998) *U.S., European and Japanese Cancer Therapeutics Markets*, page 5-28.

⁵⁴ Kollwe and Wearden, "History of ICI"; "ICI's NOLVADEX (TAMOXIFEN) PATENT IS 'UNENFORCEABLE' IN FACE OF BARR'S CHALLENGE"; Gardiner Harris, "Group Sues Barr, AstraZeneca, Citing Tamoxifen Price Collusion," *Wall Street Journal, Eastern Edition; New York, N.Y.*, May 10, 2001, sec. Health; Anonymous, "Tamoxifen Is an Example of a Patent-Settlement Drug"; "Four Firms Get Tamoxifen Marketing OK - MarketWatch," accessed January 13, 2020, <https://www.marketwatch.com/story/four-firms-get-final-fda-nod-for-cancer-drug-tamoxifen>.

⁵⁵ "AstraZeneca," accessed April 16, 2020, <https://www.forbes.com/companies/astrazeneca/#1aa493526866>.

⁵⁶ Faslodex is also effective against tumors that have developed resistance to tamoxifen, so it is often prescribed for patients who had taken tamoxifen but then experienced treatment failure.

⁵⁷ Anthony Howell et al., "ICI 182,780 (Faslodex™)," *Cancer* 89, no. 4 (2000): 817–25, [https://doi.org/10.1002/1097-0142\(20000815\)89:4<817::AID-CNCR14>3.0.CO;2-6](https://doi.org/10.1002/1097-0142(20000815)89:4<817::AID-CNCR14>3.0.CO;2-6); Jean Lynn, "Fulvestrant ('Faslodex')—a New Hormonal Treatment for Advanced Breast Cancer," *European Journal of Oncology Nursing: The Official Journal of European Oncology Nursing Society* 8 Suppl 2 (2004): S83–88, <https://doi.org/10.1016/j.ejon.2004.09.007>; "AstraZeneca Settles Sandoz Patent Fight over Its Top-Selling Cancer Med," FiercePharma, accessed April 16, 2020, <https://www.fiercepharma.com/pharma/astrazeneca-settles-sandoz-patent-fight-over-its-top-selling-cancer-med>; Alan E. Wakeling and Jean Bowler, "ICI 182,780, a New Antioestrogen with Clinical Potential," *The Journal of Steroid Biochemistry and Molecular Biology* 43, no. 1 (September 1, 1992): 780, [https://doi.org/10.1016/0960-0760\(92\)90204-V](https://doi.org/10.1016/0960-0760(92)90204-V).

⁵⁸ In about 10% of all breast cancer cases, tumors are sensitive to both HER2 proteins and estrogen, at the same time. Genentech, founded in 1976, used genetic technologies to develop Herceptin to stimulate the body's immune system to attack HER2 sensitive tumors and disrupt the cancer-promoting capacities of HER2 proteins. Charles L. Sawyers, "Herceptin: A First Assault on Oncogenes That Launched a Revolution," *Cell* 179, no. 1 (September 19, 2019): 8–12, <https://doi.org/10.1016/j.cell.2019.08.027>; "Monoclonal Antibody Drugs for Cancer: How They Work," Mayo Clinic, accessed April 21, 2020, <https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/monoclonal-antibody/art-20047808>; "Herceptin: Biotechnology Breakthrough In Breast Cancer Wins FDA Approval," Drugs.com, accessed April 21, 2020, <https://www.drugs.com/newdrugs/herceptin-biotechnology-breakthrough-breast-cancer-wins-fda-approval-4878.html>; "FDA Approves Herceptin for the Adjuvant Treatment of HER2-Positive Node-Positive Breast Cancer," Drugs.com, accessed April 21, 2020, <https://www.drugs.com/newdrugs/fda-approves-herceptin-adjuvant-her2-positive-node-positive-breast-cancer-4879.html>; Mukherjee, *The Emperor of All Maladies*, pages 412–429; "What to Know about HER2-Positive Breast Cancer," Mayo Clinic, accessed April 28, 2020, <https://www.mayoclinic.org/breast-cancer/expert-answers/faq-20058066>.